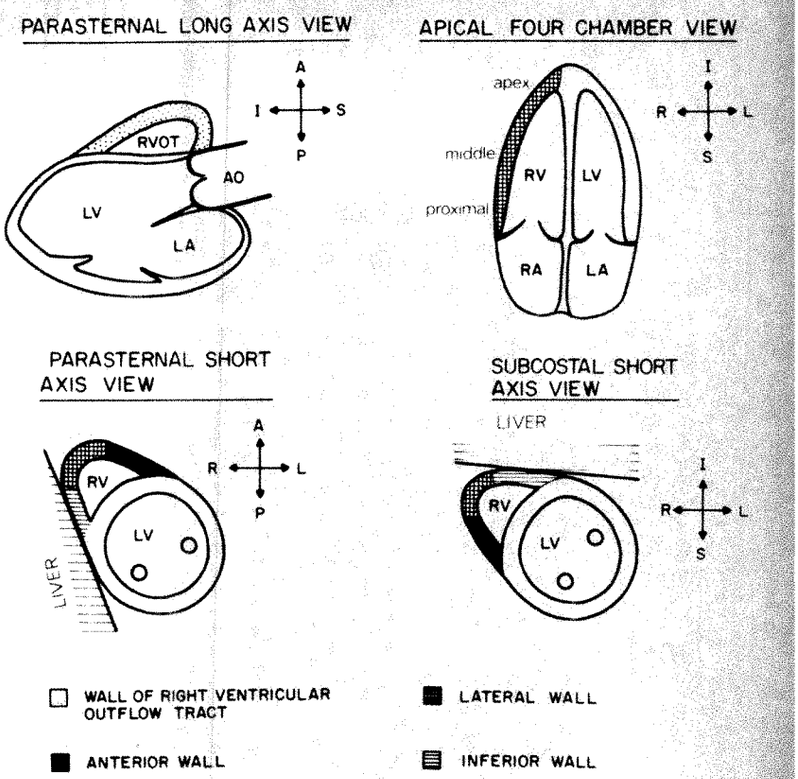



**FIGURE 1.** Schematic representation of the different echocardiographic views studied. A = anterior; AO = aorta; I = inferior; L = left; LA = left atrium; LV = left ventricle; P = posterior; R = right; RA = right atrium; RV = right ventricle; RVOT = right ventricular outflow tract; S = superior.

and aVF. "Anterior" MI was defined by the presence of abnormal Q waves in 2 or more adjacent precordial leads ($V_1$-$V_6$).

The study was initially begun including only those patients with acute posterior MI in whom hemodynamic monitoring had been performed. However, because 2 patients with acute anterior MI were found to have hemodynamic criteria of ischemic RV dysfunction, a group of 5 additional unselected patients with acute anterior MI were included.

Patients with acute MI without hemodynamic monitoring were not included. Patients with previously known MI, chronic congestive failure, pericardial disease, valvular heart disease, or chronic obstructive lung disease were not included. Of the initial 70 patients, 7 were excluded because of failure to obtain satisfactory 2-D echocardiograms of the right ventricle in at least 1 transversal plane (parasternal or subcostal short-axis views). Thus, a total of 63 patients (52 men, and 11 women, aged 36 to 78 years) were included.

**Hemodynamic monitoring:** Hemodynamic monitoring was performed in all patients. Right atrial, pulmonary artery, and pulmonary capillary wedge pressures were recorded in millimeters of mercury with a Hewlett-Packard 1280 transducer on a Siemens Elema Mingograph 34 through a Swan-Ganz thermodilution catheter.

Hemodynamic determinations were made at least every 8 hours. Monitoring was begun at admission and maintained for 3 to 5 days, being discontinued when the condition of the patient was considered as stable (subset I or II according to Forrester[10]) and had no hemodynamic variations for at least 24 hours.

**Criteria of RV dysfunction:** The diagnosis of ischemic RV dysfunction was made when the relation between right atrial and pulmonary capillary pressure was indicative of primary RV dysfunction, according to the results of a previous study.[11] Although this relation varies according to the level of pulmonary capillary pressure, for practical purposes right atrial mean pressure must be >10 mm Hg and either greater than, equal to, or not more than 5 mm Hg less than pulmonary capillary pressure. This criterion was found sensitive (73%) and very specific (100%) for the diagnosis of acute RV MI.[11] In patients with a right atrial pressure <10 mm Hg in the absence of pulmonary congestion, a volume loading test with dextran 40 was performed to identify ischemic RV dysfunction not present in basal conditions.[11,12]

**Echocardiographic examination:** Real-time 2-D echocardiographic examination was performed with the patient in the supine position or 30° to 60° left lateral decubitus using a wide angle (90°) mechanical sector scanner (Mark III, Advanced Technology Laboratory) and a 3 MHz transducer. Echocardiograms were obtained 3 to 12 hours after the last hemodynamic determination. In this period of time, the clinical condition of the patients included in the study was considered stable, without episodes of pain, dyspnea, arrhythmias, or variations in blood pressure.

Visualization of the ventricles and the ventricular septum in the long-axis, 4-chamber, and short-axis planes was obtained from parasternal, apical, and subcostal positions. Transverse planes were obtained from both parasternal and subcostal positions. All echocardiographic recordings were obtained in normal (90°) and amplified (45°) dimensions, and stored on a Sanyo VJC 7100 tape recording system. Individual frames selected for the figures were photographed using a Polaroid® film from the videotape. There was significant degradation of the stop frame image because only 1 of the 2 fields could be visualized.

A simultaneous electrocardiogram was recorded. The initiation of the QRS complex was used as an end-diastolic marker, and the end of systole was assumed to correspond to the end of the T wave. Imaging of the endocardial outline was obtained by playing through preceding and succeeding beats, using both real-time and slow motion playback.

Only RV free wall and ventricular septal motion were considered. The RV wall was divided into several segments (Fig. 1), and each was analyzed for wall motion abnormalities. Wall motion was qualitatively classified as *normal* (inward motion of the endocardium during systole) (Fig. 2), *akinetic* (absence of motion) (Fig. 3), or *dyskinetic* (outward motion of the endocardium during systole) (Fig. 4 and 5). Ventricular septal motion was considered as normal when the septum was displaced toward the left ventricular cavity in systole, akinetic when no septal movement could be appreciated, and dyskinetic or paradoxical when both sides of the septum were displaced toward the RV cavity during systole (Fig. 4 and 5).

All echocardiograms were interpreted independently by 2 observers, without previous knowledge of the hemodynamic data of each patient. In case of discrepancy, the studies were reviewed and an agreement was reached.

**Groups:** The patients were classified into 2 groups: *Group A* included 32 patients with definite ischemic RV dysfunction in at least 1 hemodynamic determination during the monitoring period. Nineteen of the 32 patients had a relation between right atrial and pulmonary capillary pressures indicative of ischemic RV dysfunction at the time of the echocardiographic examination (Group AI); The 13 remaining patients had transient ischemic RV dysfunction with a normal pressure relation at the time of the echocardiographic study (Group AII). Twenty-two patients had electrocardiographic evidence of posterior MI, 2 of anterior MI, and 8 of posterior plus anterior MI. *Group B* included 31 patients without hemodynamic criteria of ischemic RV dysfunction during the entire period of hemodynamic monitoring. Acute MI was posterior in 20 patients, anterior in 5, and posterior plus anterior in 6.

**Statistical analysis:** All statistical analyses were performed using nonparametric tests: chi-square test and Fisher's exact test. Significant values were considered those corresponding to $p < 0.05$. Only hemodynamic data corresponding to the last hemodynamic determination before the echocardiographic examination were considered for statistical analysis.

## Results

**Hemodynamic findings:** By definition, only Group A patients had a right atrial-pulmonary capillary pressure relation indicative of ischemic RV dysfunction. In all patients from Group AI, ischemic RV dysfunction was spontaneous, whereas in 5 patients from Group B it was observed only after volume loading.

**Two-D echocardiographic findings: Right ventricular segmental wall motion:** The number of patients with asynergy and the number of segments with abnormal wall motion found in each group in the different echocardiographic views are shown in Table I.

*Transverse plane:* Regional abnormalities in segmental wall motion were observed in 29 patients: 19 in Group AI, 7 in Group AII, and 3 in Group B. (Fig. 3 and 4).

When subcostal and parasternal views were compared, no difference was found in either the number of patients with wall motion abnormalities, the number of segments with asynergy, or the type of asynergy, between both short-axis views obtained. However, 2 patients had akinesia of the inferior RV wall in the subcostal short-axis view although the movement of these segments was considered normal in the parasternal short-axis view. Good quality images of the subcostal transversal plane were obtained in 62 patients; adequate imaging of the parasternal transversal plane could only be obtained in 42 patients.

In the longitudinal parasternal view, dyskinesia of the RV outflow tract was observed in 1 patient (Group AI). In the remaining 50 patients in whom good quality echocardiographic images were obtained, contraction of the RV outflow tract was normal.

In the *apical 4-chamber view*, asynergy of the lateral RV wall occurred in 9 patients (Fig. 5), 8 of whom were in Group AI. In the other patient, included in Group AII, akinesia of the RV apex was the only abnormality.

**Ventricular septal motion:** In Group A, septal motion was normal in 18 patients (56%), akinetic in 5 (16%), and dyskinetic in 9 (28%). Paradoxical motion of the ventricular septum was always accompanied by some alteration in the movement of the RV posterior wall ($p < 0.001$) (Fig. 4). In group B, septal motion was normal in 24 patients (77%), and akinetic in the remaining 7 (23%).

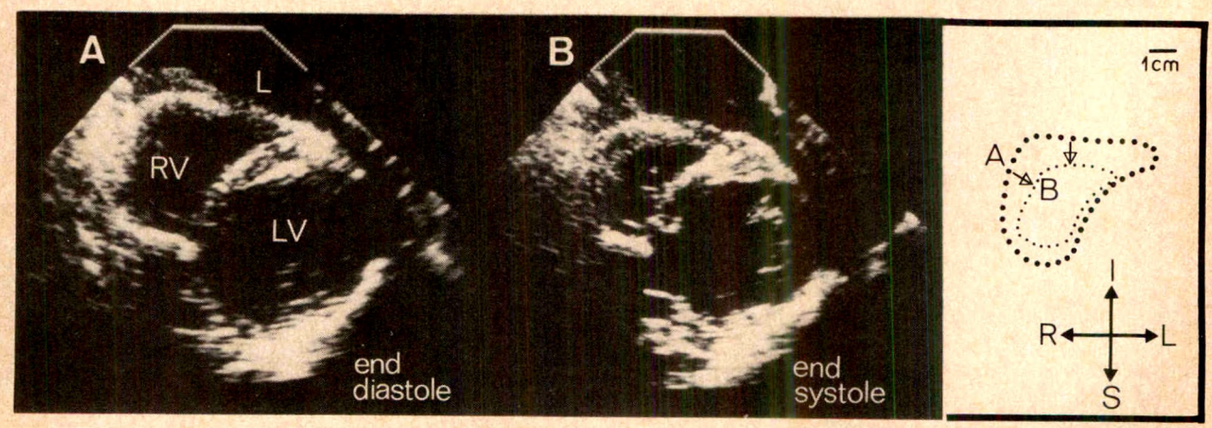



**FIGURE 2.** Subcostal short-axis view of both ventricles. Normal motion of the RV wall and interventricular septum. L = liver or lateral; other abbreviations as in Figure 1.

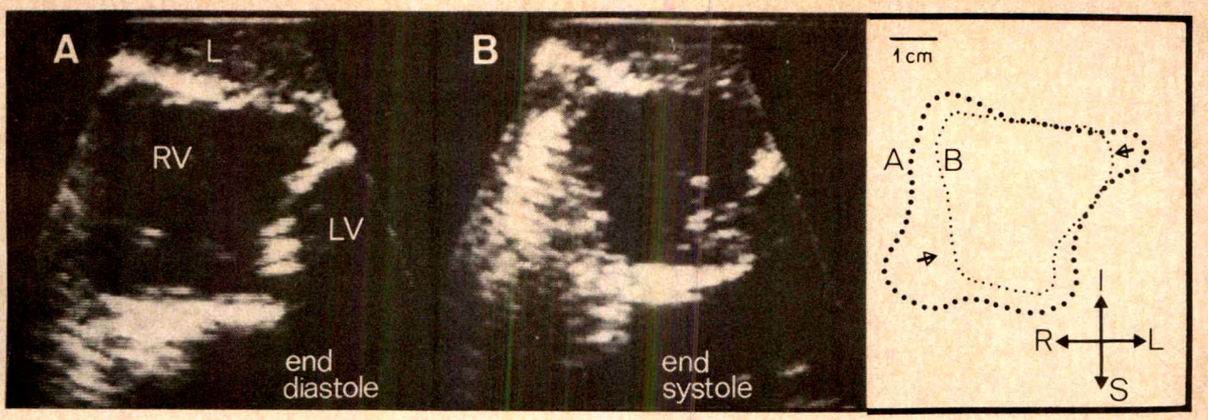



**FIGURE 3.** Subcostal short-axis view: akinesia of the inferior RV wall. Abbreviations as before.

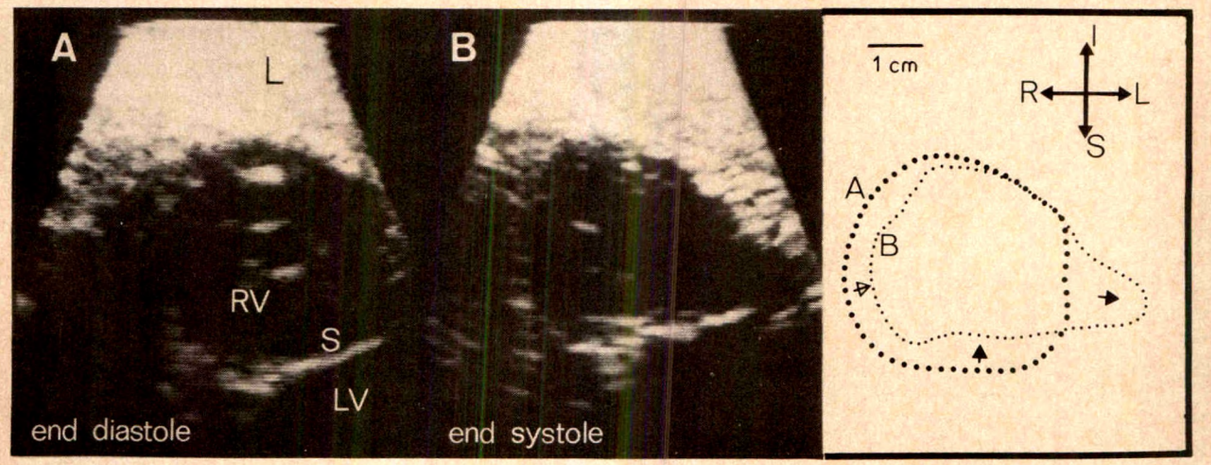



**FIGURE 4.** Subcostal short-axis view: dyskinesia of the inferior RV wall adjacent to the interventricular septum. Paradoxical septal motion. **Open arrows,** normal contraction. **Solid arrows,** dyskinesia. S = interventricular septum or superior; other abbreviations as before.

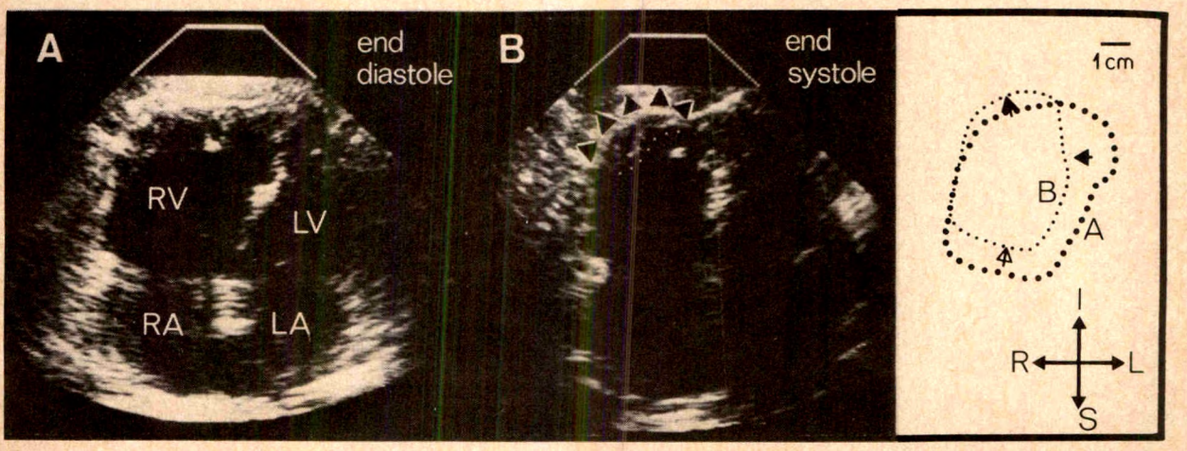



**FIGURE 5.** Apical 4-chamber view: dyskinesia of the RV apex. Paradoxical septal motion. A thrombus can be identified in the RV apex. Abbreviations as before.

**TABLE I Frequency of Asynergy in the Different Groups: RV Wall Motion**

| | All 2-D Echocardiographic Views | | Number of Segments With Asynergy | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Transverse View | | | | Four-Chamber View | | | | Long-Axis View | |
| Patients | Normal | Asynergy | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 | 0 | 1 |
| | | | | | | Group AI | | | | | | |
| N | 0 | 19 | 0 | 7 | 8 | 4 | 7 | 5 | 3 | 0 | 15 | 1 |
| % | ... | 100 | ... | 37 | 42 | 21 | 47 | 33 | 20 | ... | 94 | 6 |
| | | | | | | Group AII | | | | | | |
| N | 5 | 8 | 6 | 7 | 0 | 0 | 11 | 1 | 0 | 0 | 13 | 0 |
| % | 38.5 | 61.5 | 46 | 54 | ... | ... | 91.7 | 8.3 | ... | ... | 100 | ... |
| | | | | | | Group B | | | | | | |
| N | 28 | 3 | 28 | 2 | 1 | 0 | 28 | 0 | 0 | 0 | 22 | 0 |
| % | 90 | 10 | 90 | 6 | 3 | ... | 100 | ... | ... | ... | 100 | ... |
| | $p < 0.001$ | | | $p < 0.001$ | | | | $p < 0.001$ | | | | |

**Correlation between hemodynamics and 2-D echocardiographic findings:** *Right ventricular wall:* A significant relation was found between hemodynamic data of ischemic RV dysfunction and alterations in segmental RV wall motion. A highly significant difference was found either in the frequency of wall motion abnormalities or the number of segments with asynergy among the 3 groups of patients ($p < 0.001$) (Table I). Furthermore, a highly significant difference was also found between the incidence and number of segments with abnormal wall motion and the presence of a right atrial pressure equal to or greater than the pulmonary capillary pressure ($p < 0.001$) (Table II), indicating that the severity of asynergy is related to the severity of ischemic RV dysfunction.

*Ventricular septum:* A significant relation was found between the presence of dyskinetic or paradoxical septal motion and the hemodynamic data indicative of ischemic RV dysfunction ($p < 0.001$). All 9 patients with paradoxical septal motion were included in Group AI and all had a right atrial pressure equal to or higher than pulmonary capillary pressure. However, 2 patients without paradoxical septal motion also had a right atrial pressure equal to or greater than pulmonary capillary pressure when the echocardiographic examination was performed.

**TABLE II Frequency of Asynergy in Relation to Hemodynamic Data**

| | Number of Segments With Asynergy | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| RAP <PCP | | | |
| Number of patients | 0 | 2 | 9 |
| Percent | ... | 3 | 14 |
| RAP ≥PCP | | | |
| Number of patients | 33 | 14 | 5 |
| Percent | 52 | 22 | 8 |
| | | $p < 0.001$ | |

PCP = pulmonary capillary pressure; RAP = right atrial pressure.

## Discussion

**Segmental RV contraction in acute MI:** Asynergy of the RV wall has been reported in patients with RV MI.[2,5–9] Our results demonstrate that abnormalities in segmental RV wall motion are common in patients with acute MI and can easily be appreciated by 2-D echocardiography. The actual frequency of such abnormalities cannot be accurately defined from this study because not all patients with acute MI admitted to the coronary care unit were included.

Although acute RV infarction is generally associated with posterior left ventricular infarction,[11,13] a small number of patients with anterior MI also had RV asynergy, correlating well with hemodynamic alterations consistent with ischemic RV dysfunction.

Asynergy may be identified in all segments of the RV wall, including the outflow tract, ventricular apex, and the anterior wall, but is, in general, specifically located in the posterior RV wall. Asynergy of other regions without posterior wall involvement is rare, and in this study was found in only 1 patient. Moreover, anatomicopathologic studies indicate that in most cases, RV infarctions are confined to the posterior RV wall[11,13] which can be identified only in the transversal plane. The transversal plane is the most useful echocardiographic view for the identification of such abnormalities.

The greater frequency of wall motion abnormalities in the long-axis and 4-chamber planes reported in previous studies[8,9] can be attributed to a more rigid criteria of patient selection, inclusion being restricted to patients with strong clinical evidence of RV infarction.

**Segmental RV contraction and RV infarction:** Recent echocardiographic and anatomic studies[3,4] demonstrated that necrotic segments of the left ventricle almost always present motion abnormalities, but the latter far less frequently imply MI, and a number of nonnecrotic myocardial segments show segmental wall motion abnormalities. In the absence of transmural

pool scanning. Clinical application. Am J Cardiol 1976;38:739–746.
6. **Marmor A, Geltman EM, Biello DR, Sobel BE, Siegel BA, Roberts R.** Functional response of the right ventricle to myocardial infarction: dependence on the site of left ventricular infarction. Circulation 1981;64: 1005–1011.
7. **Lorell B, Leinbach RC, Pohost GM, Gold HK, Dinsmore RE, Hutter AM Jr, Pastore JO, DeSanctis RW.** Right ventricular infarction. Clinical diagnosis and differentiation from pericardial tamponade and pericardial constriction. Am J Cardiol 1979;43:465–471.
8. **Yung-Dae P, Shintaro B, Seiki N, Hiroshi S, Yasuharu N, Kazuo H, Tsunehiko N, Katsuhiko H.** Assessment of asynergy in right ventricular infarction with real time two-dimensional echocardiography (abstr). Circulation 1980;62:Suppl III:III-329.
9. **D'Arcy B, Nanda NC.** Two-dimensional echocardiographic features of right ventricular infarction. Circulation 1982;65:167–173.
10. **Forrester JS, Diamond GA, Swan HJC.** Correlative classification of clinical and hemodynamic function after acute myocardial infarction. Am J Cardiol 1977;39:137–145.
11. **Lopez-Sendon J, Coma-Canella I, Gamallo C.** Sensitivity and specificity of hemodynamic criteria in the diagnosis of acute right ventricular infarction. Circulation 1981;64:515–525.
12. **Lopez-Sendon J, Coma-Canella I, Viñuelas Adanez J.** Volume loading in patients with ischemic right ventricular dysfunction. Eur Heart J 1981;2: 329–338.
13. **Isner JM, Roberts WC.** Right ventricular infarction complicating left ventricular infarction secondary to coronary heart disease. Am J Cardiol 1978;42:885–894.
14. **Wyatt HL, Forrester JS, DaLuz PL, Diamond GA, Chagrasolis R, Swan HJC.** Functional abnormalities in nonoccluded regions of myocardium after experimental coronary occlusion. Am J Cardiol 1976;37:366–372.
15. **Maurer G, Nanda NC.** Two-dimensional echocardiographic evaluation of exercise-induced left and right ventricular asynergy: correlation with thallium scanning. Am J Cardiol 1981;48:720–727.
16. **Ramanathan K, Bodenheimer MM, Banka VS, Helfant RH.** Natural history of contractile abnormalities after acute myocardial infarction in man: severity and response to nitroglycerin as a function of time. Circulation 1981;63: 731–738.
17. **Holman BL, Wynne J, Idoine T, Neill RT.** Disruption in the temporal sequence of regional ventricular contraction. Circulation 1980;61:1075–1083.
18. **Erhardt LR, Sjogren A, Wahlberg I.** Single right-sided precordial lead in the diagnosis of right ventricular involvement in inferior myocardial infarction. Am Heart J 1976;91:571–576.
19. **Coma-Canella I, Lopez-Sendon J, Oliver J.** Premature pulmonic valve opening and inverted septal convexity in acute ischemic right ventricular dysfunction. Am Heart J 1981;101:684–685.
20. **Candell Riera J, Gutierrez Palau L, Valle Tudela V, Rius-Garriga J.** Estudio ecocardiográfico del infarto agudo de miocardio inferiór propagado a ventriculo derecho. Rev Esp Cardiol 1980;33:403–408.
21. **Lopez-Sendon J, Coma-Canella I, Lombera F, Benito F.** Diagnosis of ischemic right ventricular dysfunction by M-mode echocardiography. Eur Heart J 1982;3:230–237.

Truth flourishes where the students' lamp has shone, and there above. . .

W. B. Yeats

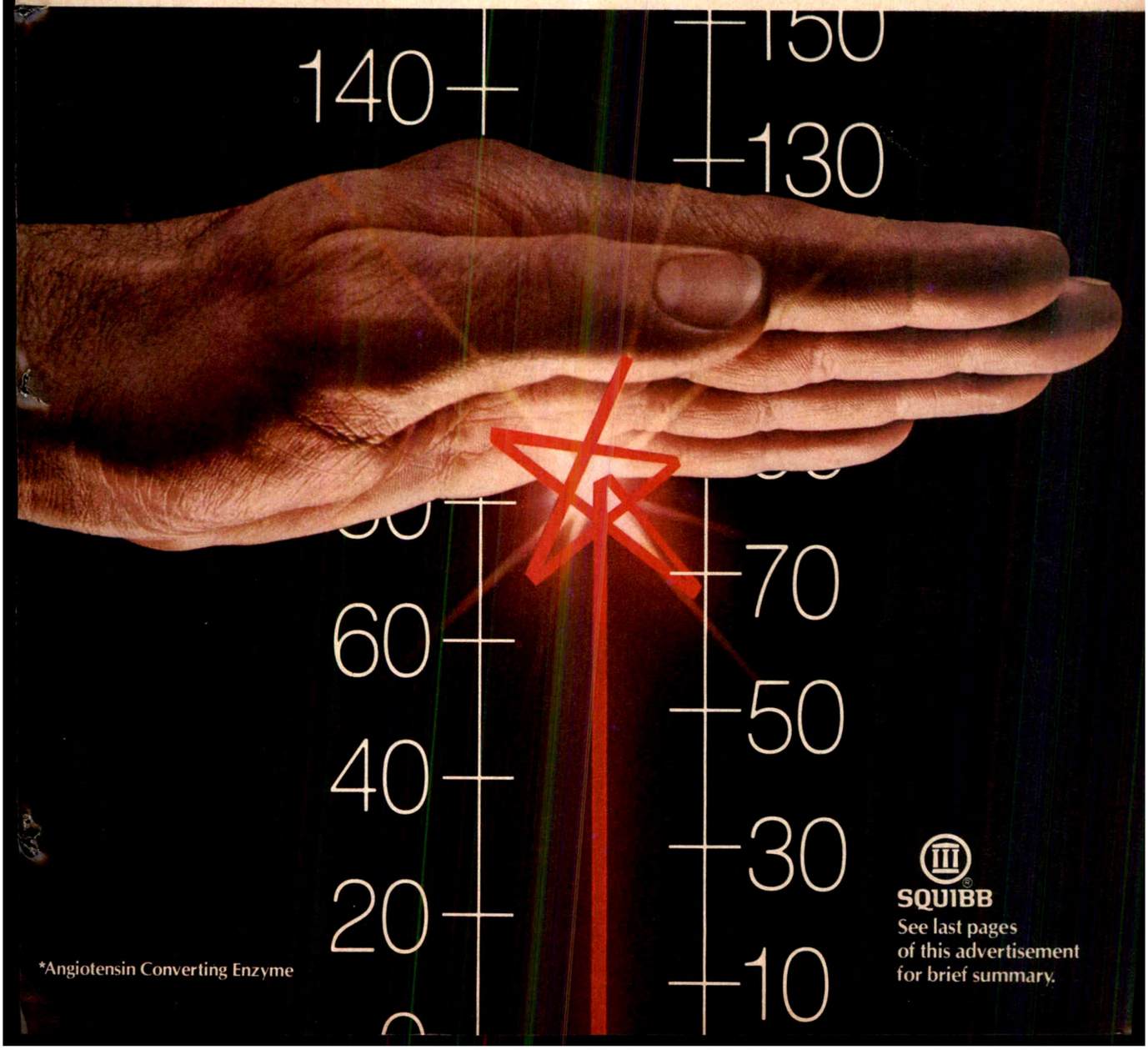
# Designed to achieve your therapeutic goals in hypertension

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For hypertensive patients

- **Who experience unacceptable side effects with beta blockers, antiadrenergic agents, or vasodilators**
- **In whom standard multidrug regimens are ineffective in controlling blood pressure**
- **Who have concomitant conditions contraindicating use of other antihypertensive agents**



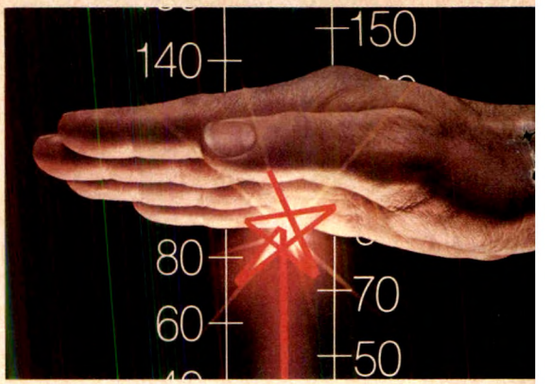

*Angiotensin Converting Enzyme

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See last pages of this advertisement for brief summary.

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## (captopril tablets)




**CAPOTEN controls blood pressure without the following usual antihypertensive side effects†:**

- No cardiac depression
- No glucose intolerance
- No bradycardia
- No mental depression
- No sleep disturbances
- No nasal congestion
- No hypokalemia
- Rare impotence/loss of libido
- Rare bronchospasm
- Rare tachycardia
- Rare fatigue



## CAPOTEN is appropriate therapy when coexisting disorders complicate hypertension management

Unlike some other antihypertensive agents, CAPOTEN is appropriate for use in the presence of a wide range of cardiovascular and metabolic disorders that often coexist with hypertension.

- Bronchospastic disease
- Cardiac arrhythmias
- Congestive heart failure
- Diabetes mellitus
- Hepatic disease

## CAPOTEN is effective in controlling many kinds of hypertension when conventional multidrug regimens have proven inadequate

- Essential hypertension
- Hypertension resistant to standard triple therapy (STT)
- Hypertension associated with low, normal, and high plasma renin levels
- Renovascular hypertension

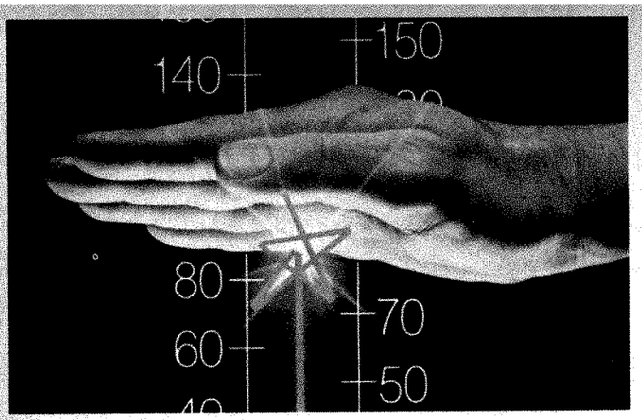
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# CAPOTEN®
## (captopril tablets)

*Angiotensin Converting Enzyme

† Please see brief summary of prescribing information on the last pages of this advertisement for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.






ACE* INHIBITOR

# CAPOTEN®
# (captopril tablets)

**CAPOTEN has been associated with the development of neutropenia, agranulocytosis, or proteinuria.† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.**

**The following precautionary guidelines are recommended for all patients receiving CAPOTEN:**

- **Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.**
- **Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.**
- **Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.**
- **The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.**

SQUIBB®

*Angiotensin Converting Enzyme

† Please see brief summary of prescribing information, for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

**CAPOTEN® TABLETS**
**Captopril Tablets**

**INDICATIONS: Hypertension —** Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.
**Heart Failure:** CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.
**WARNINGS: Proteinuria —** Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.
Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine — the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.
**Neutropenia/Agranulocytosis —** Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).
**Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.**
The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever), if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.
**Hypotension —** Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).
In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.
**BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.**
**PRECAUTION: General:** *Impaired Renal Function.* Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.
*Surgery/Anesthesia* — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.
**Drug Interactions:** *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.
*Agents Having Vasodilator Activity:* In heart failure patients vasodilators should be administered with caution.
*Agents Causing Renin Release* — Captopril's effect will be augmented by

(Continued on next page.)

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antihypertensive agents that cause renin release.

*Agents Affecting Sympathetic Activity* — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

*Agents Increasing Serum Potassium* — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

**Drug/Laboratory Test Interaction:** Captopril may cause a false-positive urine test for acetone.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

**Usage in Pregnancy:** There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

**Nursing Mothers:** Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

**Pediatric Use:** Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

**ADVERSE REACTIONS:** Reported incidences are based on clinical trials involving about 4000 patients.

*Renal* — One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

*Hematologic* — Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

*Dermatologic* — Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients — reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

*Cardiovascular* — Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

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'Oh yes, you are', she said. 'You're my Inglés', and reached and took hold of both his ears and kissed him on the forehead.

'There', she said. 'How is that? Do I kiss thee better?'

Then they were walking along the stream together and he said, 'Maria, I love thee and thou art so lovely and so wonderful and so beautiful and it does such things to me to be with thee that I feel as though I wanted to die when I am loving thee'.

'Oh', she said. 'I die each time. Do you not die?'

'No. Almost. But did thee feel the earth move?'

'Yes. As I died. Put thy arm around me, please'.

'No. I have thy hand. Thy hand is enough".

The Dialogue of Robert Jordan and Maria from "For Whom the Bell Tolls".

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# Variable Threshold Exertional Angina in Patients With Transient Vasospastic Myocardial Ischemia

## Repeat Exercise Test Results and Therapeutic Implications

STEFANO DE SERVI, MD, GIUSEPPE SPECCHIA, MD, COLOMBA FALCONE, MD, ANTONELLO GAVAZZI, MD, ANTONIO MUSSINI, MD, LUIGI ANGOLI, MD, EZIO BRAMUCCI, MD, DIEGO ARDISSINO, MD, LAURA VACCARI, MD, JORGE SALERNO, MD, and PIERO BOBBA, MD

**Thirty-five of 70 patients with vasospastic angina at rest complained of chest pain during exercise or during usual daily activity. In 22, the angina threshold was described as variable during exercise: that is, the amount of exertion that induced angina was not always the same. In 12 patients with variable threshold exertional angina, 3 exercise tests performed in the morning on different days yielded different results, because chest pain and ischemic electrocardiographic changes occurred at different work loads with a wide range in heart rate-systolic pressure product. Two patients, in whom great cardiac vein flow was measured during exercise before and after taking nifedipine, tolerated heavier work loads after receiving the drug, with a more marked increase in flow during exercise. It is concluded that variable threshold exertional angina can be objectively demonstrated by repeat exercise tests in patients with vasospastic angina. Variability of the angina threshold may be due to a functional mechanism that causes myocardial ischemia in addition to the increased myocardial metabolic requirements provoked by exercise. Because in such patients fluctuations in coronary arterial tone play an important role in determining the response to exercise, calcium antagonistic drugs, which lower coronary tone and prevent the occurrence of coronary spasm, are effective in increasing exercise capacity.**

Patients with vasospastic angina at rest may also have chest pain during exercise or during usual daily activity.[1,2] In these patients the angina threshold may vary from time to time; a few patients have recently been described[3–5] in whom repeated exercise tests induced myocardial ischemia at different values of heart rate-systolic blood pressure product, an index of myocardial oxygen consumption.[6] However, the incidence of this phenomenon is not yet appreciated, and it is not clear whether the clinical suspicion of variable threshold exertional angina can always be confirmed by repeated exercise tests.

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This study describes the results of repeated exercise tests in patients with vasospastic angina presenting with this clinical manifestation. We believe that the recognition of variable threshold exertional angina may have important therapeutic implications.

### Methods

**Patients: Criteria of selection:** Between October 1979 and October 1981 we observed 70 patients with vasospastic angina at rest without evidence of previous transmural myocardial infarction. Coronary vasospasm was considerd responsible for the occurrence of chest pain at rest on the basis of the following criteria: Sixty patients showed transient S-T segment elevation during at least 1 episode of chest pain at rest,[7] whereas the remaining 10 patients showed S-T segment depression repeatedly during chest pain as well as after the administration of intravenous ergonovine maleate in the coronary care unit.[14,15] Thirty-five patients also complained of chest pain during exercise or usual daily activity. In 22 of these patients the angina threshold was described as variable dur

**TABLE I Results of Repeated Exercise Tests in 12 Patients With Variable Threshold Exertional Angina**

| | First Exercise Test | | | | Second Exercise Test | | | |
|---|---|---|---|---|---|---|---|---|
| Case | Work Load | End-point | RPP | ECG Changes | Work Load | End-point | RPP | ECG Changes |
| 1 | 50 W × 1 min | Ang | 128 | ↓S-T 3 mm $V_2$-$V_6$ | 125 W × 3 min | Ang | 260 | ↓S-T 1 mm $V_4$-$V_6$ |
| 2 | 50 W × 3 min | Ang | 176 | ↓S-T 1 mm II, III, aVF | 125 W × 3 min | Exh | 259 | — |
| 3 | 50 W × 1 min | ↑S-T | 143 | ↑S-T II, III, aVF | 125 W × 1 min | Exh | 300 | — |
| 4 | 125 W × 1 min | Ang | 364 | ↑S-T $V_1$-$V_2$ | 175 W × 1 min | Exh | 285 | ↓S-T 1 mm $V_5$-$V_6$ |
| 5 | 75 W × 3 min | Ang | 304 | ↑S-T $V_1$-$V_2$ | 125 W × 1 min | Ang | 286 | ↑S-T $V_1$-$V_3$ |
| 6 | 100 W × 1 min | Exh | 246 | ↓S-T 1,5 mm $V_3$-$V_6$ | 50 W × 1 min | Ang | 189 | ↓S-T 2,5 mm $V_3$-$V_6$ |
| 7 | 100 W × 1 min | Ang | 158 | ↓S-T 2 mm $V_4$-$V_6$ | 100 W × 1 min | Exh | 145 | — |
| 8 | 75 W × 2 min | Ang | 240 | ↓S-T 2,5 mm $V_3$-$V_6$ | 75 W × 1 min | Ang | 271 | ↓S-T 1 mm $V_3$-$V_6$ |
| 9 | 50 W × 3 min | Ang | 163 | ↓S-T 1,5 mm II, III, aVF, $V_5$-$V_6$ | 75 W × 3 min | Ang | 213 | ↓S-T 1,5 mm II, III, aVF, $V_5$-$V_6$ |
| 10 | 125 W × 3 min | Exh | 176 | ↓S-T 1 mm $V_3$-$V_6$ | 125 W × 1 min | Exh | 209 | — |
| 11 | 50 W × 1 min | Ang | 140 | ↓S-T 4 mm $V_3$-$V_6$ | 50 W × 3 min | Ang | 163 | ↓S-T 3 mm $V_3$-$V_6$ |
| 12 | 100 W × 1 min | Ang | 162 | ↓S-T 1,5 mm $V_3$-$V_6$ | 50 W × 1 min | Ang | 143 | ↓S-T 4 mm $V_3$-$V_6$ |

Ang = angina; ECG = electrocardiographic; Exh = exhaustion; RPP = heart rate-systolic pressure product, mm Hg × beats/min × $10^{-2}$; ↑S-T = S-T segment elevation; ↓ST = S-T segment depression; — = no electrocardiographic changes.

exercise; these patients could not recognize a critical amount of exertion they could perform before experiencing angina but the level of activity that determined the symptoms varied from time to time. Twelve of these 22 patients were selected for this study. The selection was not done in a random fashion but depended on the clinical characteristics of the patients. We excluded patients with more than 3 episodes of chest pain at rest per day or with severe ventricular arrhythmias or left ventricular failure during anginal attacks.[16] In the 12 patients studied, drug therapy consisting of nitrates and nifedipine could be suspended 12 hours before exercise tests without any manifestation of withdrawal phenomena, such as accelerated angina or other coronary events. No patient was receiving beta-adrenergic blocking agents or digitalis.

**Exercise testing:** The 12 patients selected performed 3 bicycle exercise tests in the morning (8:30 to 11:00 A.M.) on different days during hospitalization. The mean interval between the first and the third exercise test was 7.8 ± 6 days. Two of these patients were described recently.[3] The exercise tests were performed in the supine position with an initial work load of 50 W and subsequent increments of 25 W every 3 minutes. Exercise was stopped when angina, dyspnea, exhaustion, S-T segment elevation ≥2 mm, or S-T segment depression >3 mm occurred. A 12-lead electrocardiogram was taken before and at the end of exercise, and every minute during recovery; leads $V_4$, $V_5$, and $V_6$ were monitored during exercise. Cuff blood pressure was measured at 3-minute intervals. The criteria for a positive exercise test were a horizontal or downsloping S-T segment depression ≥1 mm for 0.08 second compared with the resting tracing and S-T segment elevation ≥1 mm at 0.04 second after the J point compared with *the baseline* electrocardiogram. An estimate of myocardial oxygen consumption was made from the double product, obtained by multiplying systolic arterial pressure and heart [illegible].[6]

**Coronary arteriography:** The 12 patients studied underwent coronary arteriography using the Sones technique after premedication with 10 mg of diazepam. Left ventriculography was performed in the right anterior oblique projection before arteriography. Narrowing >50% of 1 or more coronary arteries was considered evidence of significant coronary artery disease. When a significant lesion was noted, the vessel was filmed again after sublingual administration of nitroglycerin.

**Coronary flow study:** In 2 patients with isolated left anterior descending artery disease, exercise tests were performed before and 20 minutes after sublingual administration of 20

**TABLE II Electrocardiographic (ECG) Changes During Chest Pain at Rest and Coronary Arteriographic Findings**

| Case | Age (yr) & Sex | ECG Changes (Spontaneous Angina) | Coronary Arteriographic Findings |
|---|---|---|---|
| 1 | 54M | ↓↑S-T ant | LAD 75% |
| 2 | 48M | ↑S-T inf | Normal |
| 3 | 38M | ↑S-T inf | RCA 90% |
| 4 | 54M | ↑S-T ant | LAD 90%, cfx 75% |
| 5 | 55M | ↑S-T ant | LAD 75%, cfx 75% |
| 6 | 44M | ↑S-T inf | Cfx 90% |
| 7 | 61M | ↓S-T ant | Normal |
| 8 | 44F | ↓S-T ant | LAD 75% |
| 9 | 62M | ↑S-T inf | RCA 90%, cfx 75% |
| 10 | 53M | ↑S-T ant | LAD 75% |
| 11 | 55M | ↑S-T ant | LAD 90% |
| 12 | 59M | ↓S-T ant | LAD 90% |

ant = anterior leads; cfx = circumflex branch; inf = inferior leads; LAD = left anterior descending artery; RCA = right coronary artery; ↑S-T = ST-T segment elevation; ↓S-T = ST-T segment depression.

**TABLE I (Continued)**

| Case | Third Exercise Test: Work Load | End-point | RPP | ECG Changes |
|---|---|---|---|---|
| 1 | 75 W × 3 min | Ang | 225 | ↓S-T 2 mm $V_3$-$V_6$ |
| 2 | 125 W × 3 min | Ang | 260 | ↓S-T 2 mm II, III, aVF |
| 3 | 150 W × 3 min | Exh | 391 | — |
| 4 | 150 W × 2 min | Exh | 250 | — |
| 5 | 125 W × 2 min | ↓S-T | 300 | ↓S-T 4 mm $V_4$-$V_6$ |
| 6 | 150 W × 3 min | Exh | 278 | ↓S-T 2,5 mm $V_3$-$V_6$ |
| 7 | 125 W × 1 min | Exh | 184 | ↓S-T 1 mm $V_4$-$V_6$ |
| 8 | 75 W × 1 min | Ang | 232 | ↓S-T 1 mm $V_3$-$V_6$ |
| 9 | 75 W × 3 min | Exh | 209 | ↓S-T 1,5 mm II, III, aVF, $V_5$-$V_6$ |
| 10 | 125 W × 3 min | Ang | 176 | ↓S-T 1 mm $V_3$-$V_6$ |
| 11 | 75 W × 3 min | Exh | 221 | ↓S-T 1 mm $V_4$-$V_6$ |
| 12 | 75 W × 2 min | Ang | 213 | ↓S-T 3 mm $V_3$-$V_6$ |

mg of nifedipine; the tests were done with the patient in the supine position with an initial work load of subsequent increments of 25 W every 3 minutes. A triple thermistor thermodilution catheter (Wilton Webster Laboratories, Altadena, California) was inserted into the coronary sinus with the tip advanced to the great cardiac vein, so that the flow recorded was entirely from the great cardiac vein.[17] Its position was confirmed with fluoroscopy and frequently checked throughout the procedure. Flow measurements were obtained in basal conditions and at peak exercise[15,18] by injecting physiologic saline solution at 24° per 30 seconds using a pump at a rate of 56 ml/min. The left brachial artery was punctured to measure intraarterial pressure.

An interval of 30 minutes was allowed to elapse between the end of the first exercise test and the administration of nifedipine. Great cardiac vein flow (GCVF) was calculated using the following formula: $GCVF = V_i \times [(T_b - T_i)/(T_b - T_m) - 1] \times 1.08$, where $V_i$ represents the volume of injectate (ml/min) and $T_b$, $T_i$, and $T_m$ the temperatures of blood, injectate, and mixture of blood and injectate; 1.08 is a constant of the saline solution.

Informed consent was obtained from all patients before each test. No complications were observed during the procedures.

## Results

**Clinical features:** Eleven patients were men and 1 a woman, with an average age of 52.7 years (range 38 to 62). In 8 patients, anginal attacks at rest were associated with S-T segment elevation, occurring in the anterior leads in 4 patients and in the inferior leads in 4, whereas 1 patient had episodes associated with either S-T segment elevation or depression in the anterior leads. Three patients showed S-T segment depression in the anterior leads during chest pain at rest. In 6 patients, angina was of recent onset (<3 months).

**Exercise tests (Table I):** Four patients (Cases 2, 4, 7, and 10) had 1 negative test and 2 positive tests; 1 patient (Case 3) had 2 negative tests and 1 positive test. Seven patients had all 3 positive tests. Chest pain occurred during all 3 exercise tests in 3 patients, while 8 patients had at least 1 exercise test ended because of exhaustion. In 1 patient the end point was angina in 2 tests and S-T segment depression >3 mm without angina in the third test.

S-T segment elevation was observed in 2 patients (Cases 3 and 4) during 1 exercise test and in 1 patient (Case 5) during 2 tests. In 6 patients (Cases 1, 6, 8, 9, 11, and 12) all 3 exercise tests induced S-T segment depression. In 5 of these patients, S-T segment depression occurred at different work loads with a wide range of values of double product. One illustrative case is shown in Figure 1. In 1 patient (Case 8) exercise tolerance did not change substantially during the 3 tests; however S-T depression was more marked during the first than during the second exercise test although a higher value of double product was attained during the latter.

**Angiographic features:** No patient had akinetic or dyskinetic areas of the left ventricle. The average ejection fraction was 59 ± 7 and the average left ventricular end-diastolic pressure was 12.5 ± 5 mm Hg. Coronary

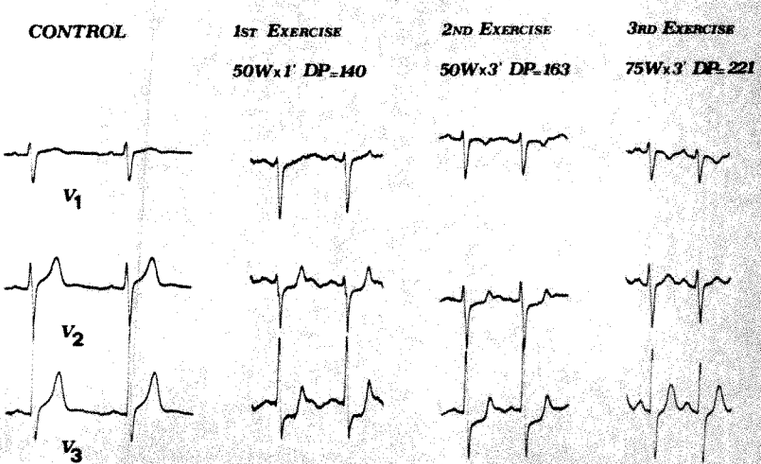



**FIGURE 1.** Case 11. Three exercise tests performed in the morning on different days yielded different results. The first and second tests induced chest pain and S-T segment depression, whereas the third test was negative despite a higher double product. DP = double product (mm Hg × beats/min × $10^{-2}$).

**TABLE III Great Cardiac Vein Flow During Exercise Tests Before and After Administration of Nifedipine**

| | Work Load | End-point | ECG Changes | Double Product (mm Hg beats/min $10^{-2}$) | GCVF (ml/min) |
|---|---|---|---|---|---|
| Case 11 | | | | | |
| Control | ... | ... | ... | ... | 72 |
| Peak exercise | 75 W × 3 min | Ang | ↓S-T 1 mm $V_4$-$V_6$ | 208 | 152 |
| After nifedipine | ... | ... | ... | ... | 64 |
| Peak exercise | 100 W × 2 min | Exh | — | 269 | 194 |
| Case 12 | | | | | |
| Control | ... | ... | ... | ... | 103 |
| Peak exercise | 25 W × 2 min | Ang | ↓S-T 4 mm $V_3$-$V_6$ | 131 | 105 |
| After nifedipine | ... | ... | ... | ... | 116 |
| Peak exercise | 75 W × 2 min | Ang | ↓S-T 4 mm $V_3$-$V_6$ | 183 | 164 |
| | | | ... | ... | ... |

Ang = angina; ECG = electrocardiographic; Exh = exhaustion; GCVF = great cardiac vein flow; ↓S-T = S-T segment depression; — = no electrocardiographic changes.

arteriography (Table II) showed normal coronary arteries in 2 patients. Seven patients had single-vessel disease with involvement of the left anterior descending artery in 5, of the right coronary artery in 1 and of the circumflex branch in 1.

Three patients had 2-vessel disease. During the procedure, 2 patients exhibited a spontaneous spasm of the right coronary artery and 1 of the left anterior descending artery. One patient had an ergonovine-induced spasm of the left anterior descending artery.

**Great cardiac vein flow measurements (Table III):** Both patients showed an increase in flow at peak exercise. After administration of nifedipine they tolerated heavier work loads than before and attained higher values of double product. Despite that, electrocardiographic signs of ischemia did not appear in 1 patient and occurred at far greater values of double product in the other. The increase in flow in the great cardiac vein at peak exercise was more marked after than before administration of nifedipine (Fig. 2).

## Discussion

**Variability of angina threshold during exercise:** Stable exertional angina is caused by increased myocardial oxygen consumption in the presence of fixed stenoses of the large coronary arteries. The concept that coronary lesions are fixed implies that myocardial ischemia occurs reproducibly at a given level of myocardial oxygen consumption. Epstein and Talbot[19] recently challenged this concept, because it does not explain several clinical characteristics often observed in patients with angina pectoris. For instance, "... it does not explain why angina threshold should vary markedly during different times of the day, different times of the week, or different seasons of the year."[19] This lack of reproducibility and predictability has been reported in classic descriptions of angina of effort.[20,21] Friedberg,[20] observing that some patients have only occasional seizures at intervals of days, weeks, or months, comments that "these intervals depend to some extent on avoidance of the factors which elicit the anginal attacks."

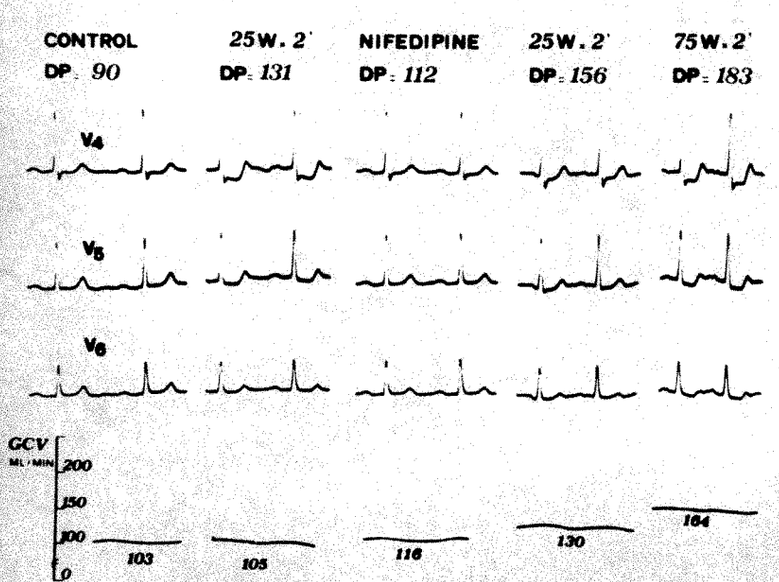



**FIGURE 2.** Case 12. In this patient with disease of an isolated left anterior descending artery, measurements of great cardiac vein flow were performed during exercise, before and after administration of nifedipine. After the drug, the patient tolerated a greater work load and attained a higher value of double product. This beneficial effect was achieved by an increase in great cardiac vein flow. DP = double product (mm Hg × beats/min × $10^{-2}$); GCVF = great cardiac vein flow measurements (ml/min).

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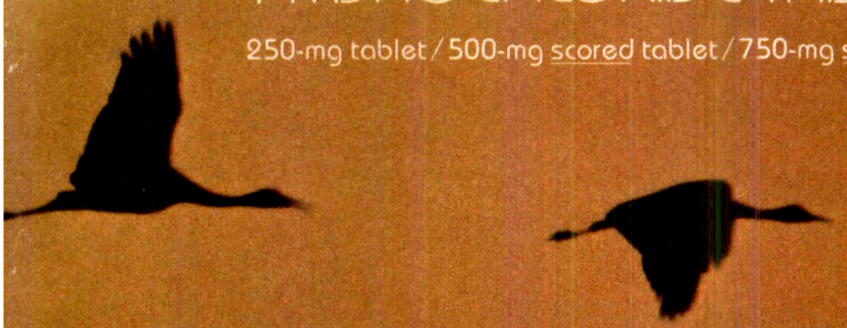
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The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

**INDICATIONS AND USAGE:** Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

**CONTRAINDICATIONS:** It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

**PRECAUTIONS: General** —During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia have been reported which may be related to this syndrome.

**Laboratory Tests**—Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

Routine blood counts are advisable during maintenance procainamide therapy.

**ADVERSE REACTIONS:** Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS).

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

**DOSAGE AND ADMINISTRATION:** Procan SR (procainamide hydrochloride) tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every-three-hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

**Ventricular tachycardia**—Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dose of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three-hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six-hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

**Atrial fibrillation and paroxysmal atrial tachycardia**—Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dose of 0.5 to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

**HOW SUPPLIED:** Procan SR 250 mg (green, film-coated tablet, P-D 202) is available in bottles of 100 (N 0071-0202-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0202-40). Each sustained-release tablet contains 250 mg procainamide hydrochloride.

Procan SR 500 mg (yellow, scored, film-coated tablet, P-D 204) is available in bottles of 100 (N 0071-0204-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0204-40). Each sustained-release tablet contains 500 mg procainamide hydrochloride.

Procan SR 750 mg (orange, scored, film-coated tablet, P-D 205) is available in bottles of 100 (N 0071-0205-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0205-40). Each sustained-release tablet contains 750 mg procainamide hydrochloride.

**Storage—Protect from moisture. Store bottles below 86° F (30° C). Store unit-dose packages at controlled room temperature, 59°-86° F (15°-30° C).**

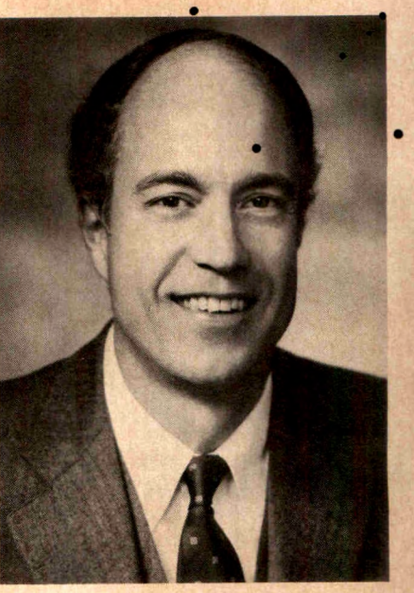
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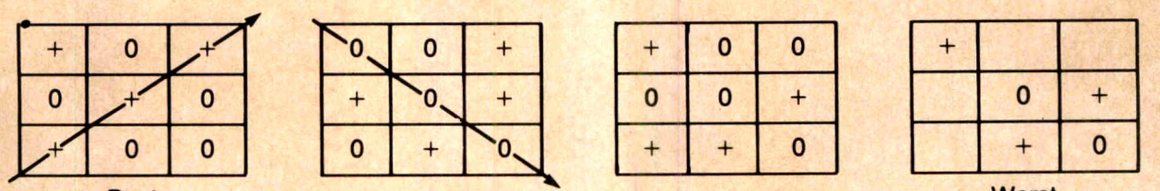
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# Getting the Manuscript Accepted: Think Like a Lawyer and Cover the Flanks

A manuscript might be viewed as a legal brief in which an author presents logical arguments supporting the contention that he has created and proven a new concept. Reviewers, in a way, are like defense lawyers who attempt to find a flaw in the author's contention. Finding such flaws often casts doubt on other claims of the author or claimant. Indeed, the finding by reviewers or the Editor of *omissions of mention* can be a major stumbling block preventing the acceptance of a manuscript.

A manuscript's quality may be compared to the game of tic-tac-toe, in which 2 players, in turn, fill in 9 compartments, 1 at a time, with X's and O's. The *best paper* fills in all the blocks—covers all the bases—and in addition lines up 3 X's in a row (see the figure below), signifying focus and clarity. A row of zeros indicates that the manuscript provides an essentially negative observation. A manuscript also can have all the blocks filled in but no symbols lined up in a row, indicating a lack of clarity and focus. The *worst paper* fails to fill in 1 or more compartments with either symbol (omissions of mention) and none line up in a row, an indication that the author has failed to mention all the points necessary to prove his case and to focus the points properly.




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# In Hypertension*...When You Need to Conserve $K^+$

# Every Step of the Way




Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a $K^+$ supplement or $K^+$-sparing agent), and a maintenance phase (a diuretic alone or in combination with a $K^+$ supplement or $K^+$-sparing agent).

Serum $K^+$ and BUN should be checked periodically (see Warnings).

**Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.**

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

**Contraindications:** Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

**Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum $K^+$ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict $K^+$ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

**Precautions:** Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

**Adverse Reactions:** Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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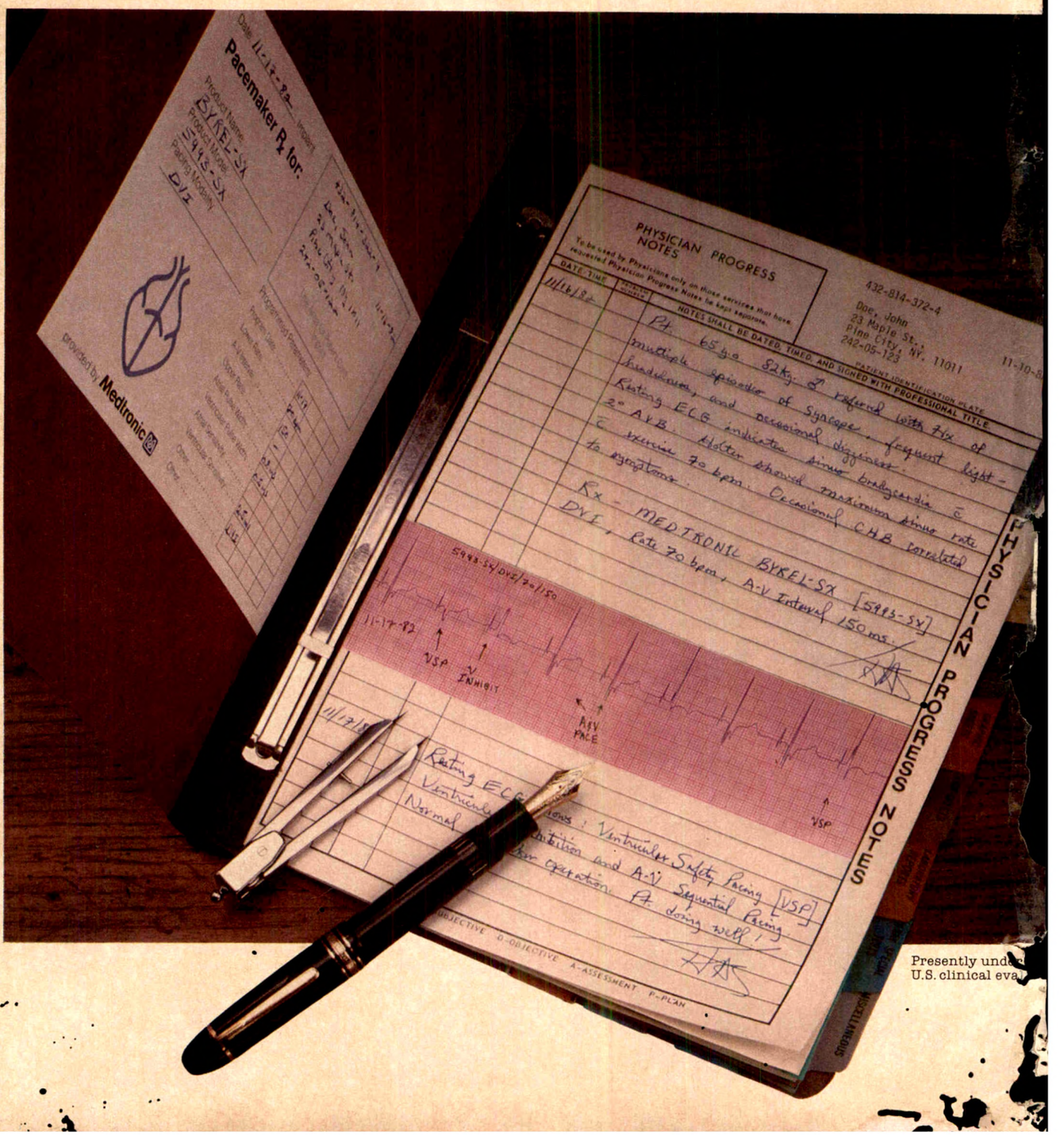
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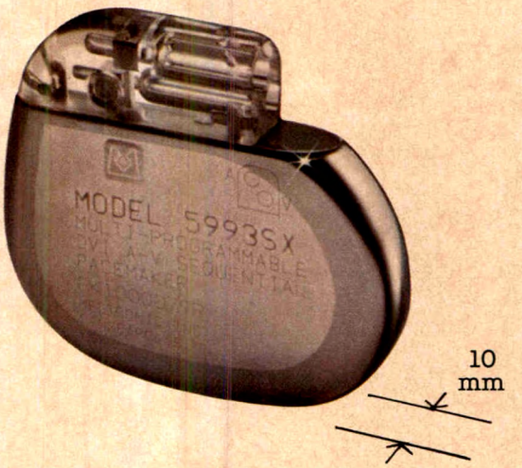
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## Byrel-SX Model 5993-SX Programmable Parameters

| | DVI | VVI |
|---|---|---|
| Rate | 40-120 bpm | 40-130 bpm |
| A-V Internal | 25-250 ms | NA |
| Atrial Pulse Width | 0.05, 0.1, 0.2...1.5 ms | NA |
| Ventricular Pulse Width | 0.05, 0.1, 0.2...1.5 ms | 0.05, 0.1, 0.2...1.5 ms |
| Ventricular Sensitivity | 2.5, 5.0 mv Asynchronous | 2.5, 5.0 mv Asynchronous |

**Power Source Depletion Characteristics**

**Initial Stage**

| | |
|---|---|
| Mode | as programmed |
| Voltage | 2.2 V |
| Magnet rate | 75 bpm |

**Secondary Stage**

| | |
|---|---|
| Mode | VVI at 65 bpm |
| Voltage | 2.0 V |

**INTENDED USE**

The Model 5993-SX universal A-V pulse generator has a wide range of application in patients requiring permanent cardiac pacing or to protect against arrhythmias related to the sequence of cardiac impulse propagation.

In the A-V sequential (DVI) mode, the Model 5993-SX has application in the following:

Sick Sinus Syndrome (sinus brady-cardia, sinus arrest, S-A block, and the brady-tachy syndrome).
A-V nodal reentrant tachycardias. (Short A-V interval settings may be useful in controlling reentrant tachy-cardias.)
Atrial and ventricular ectopic arrhythmias.

At any time, the Model 5993-SX can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry (e.g., atrial lead malfunction).

NOTE: The Medtronic® Model 5993-SX A-V pulse generator is under clinical investigation. The procedures for using this pulse generator, as well as its safety and efficacy, will be evaluated during this investigational study according to the Clinical Investigation Protocol. Therefore, the "Intended Use" section is based on Medtronic's experience with other physiologic pulse generators. No claims for safety and efficacy can be made for the Model 5993-SX pulse generator during its clinical investigation. Patients should be advised that the Model 5993-SX generator is under clinical investigation.

**CONTRAINDICATIONS**

There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician. In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation of flutter.

**WARNINGS**

Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site. Electrosurgical units should never be used in the vicinity of unipolar pulse generators because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

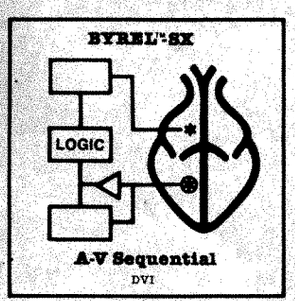
Positioning a magnet or the programmer over the pulse generator makes it subject to programming. Do not use electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programmer has been positioned over the pulse generator.

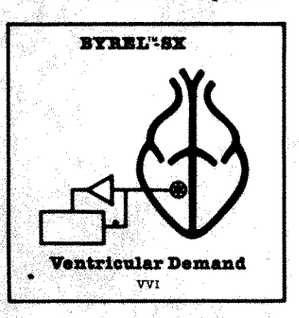
**PRECAUTIONS**

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

**SIDE EFFECTS**

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.




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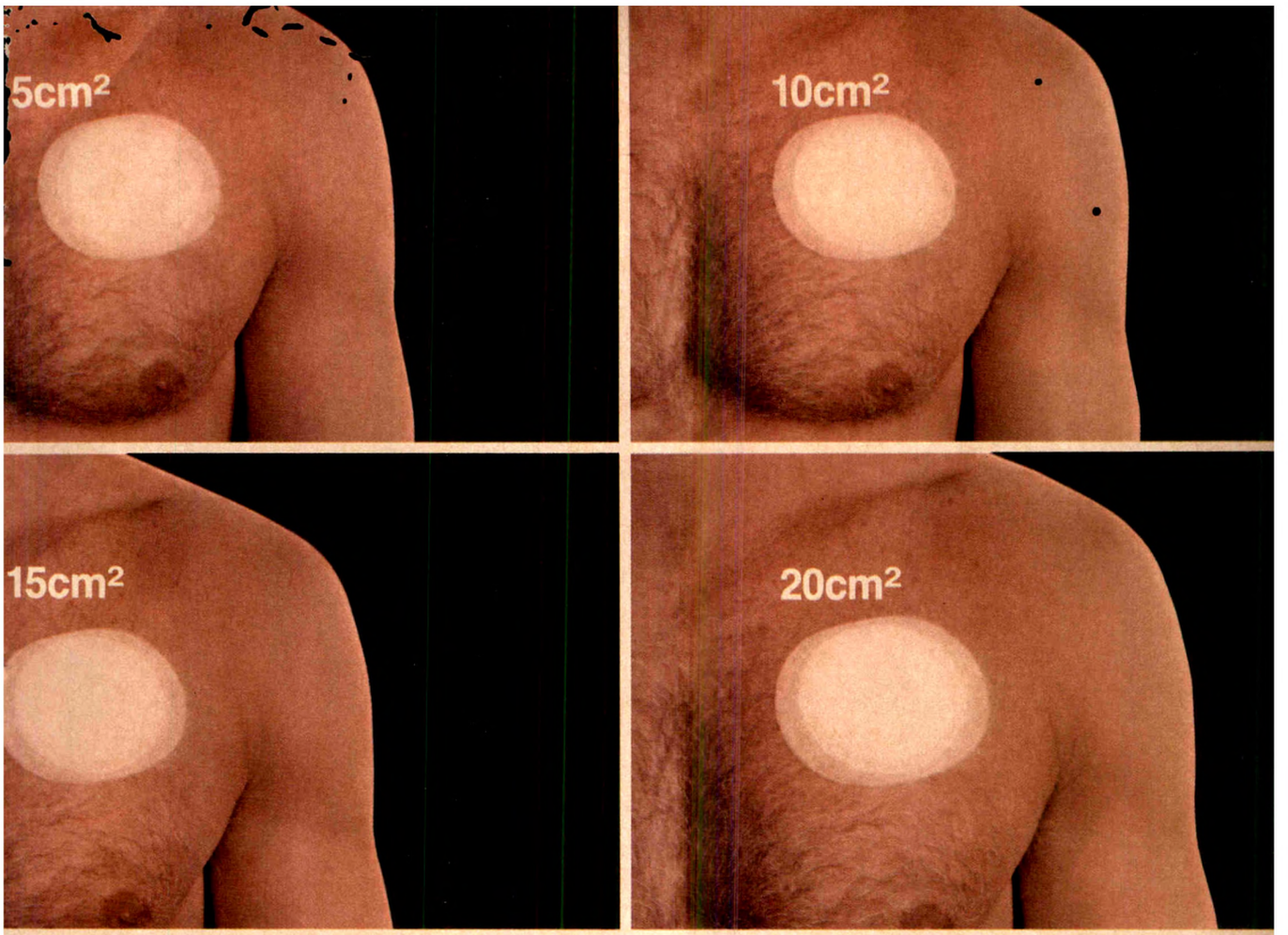
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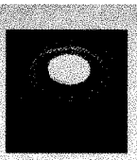
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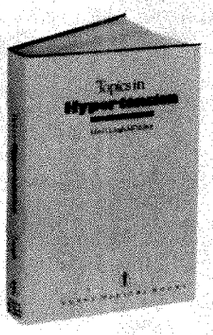
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# The American Journal of CARDIOLOGY®

VOLUME 51

NUMBER 1

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1 **Exercise 2-Dimensional Echocardiography. Quantitation of Left Ventricular Performance in Patients With Severe Angina Pectoris**

MICHAEL H. CRAWFORD, K. WRAY AMON, and WILLIAM S. VANCE

The feasibility and reproducibility of exercise biapical 2-dimensional echocardiography for quantitating left ventricular performance was assessed in 25 patients with severe coronary artery disease and in 10 normal subjects. In 18 of the 25 patients (72%) adequate echoes were recorded during upright bicycle exercise. Ejection fraction increased in the normal subjects during exercise but not in the patients. After nitroglycerin administration 7 patients (39%) showed marked increases in ejection fraction during exercise. Wall motion score worsened during exercise in the patients before nitroglycerin, but was significantly improved after nitroglycerin administration. Therefore, quantitation of left ventricular performance during exercise by biapical 2-dimensional echocardiography can be accomplished in a high proportion of patients with coronary artery disease.

7 **Importance of Complete Revascularization in Performance of the Coronary Bypass Operation**

ELLIS L. JONES, JOE M. CARVER, ROBERT P. GUYTON, DAVID K. BONE, CHARLES R. HATCHER, Jr., and NORMAN RIECHWALD

Data bank records of 1,238 patients with triple vessel disease and coronary bypass surgery were retrospectively divided into 2 groups depending on whether complete or incomplete revascularization had been accomplished. Patients with complete revascularization had a higher incidence of normal preoperative electrocardiograms than did patients with incomplete revascularization (23% versus 14%, respectively). There was no significant difference between the completely and incompletely revascularized patients with regard to postoperative inotropic requirements (8% and 7%), ventricular arrhythmias (1.8% and 1%), necessity for intraaortic balloon pumping (1.6% and 1.5%), hospital mortality (1.2% and 2.8%), or myocardial infarction (4.3% and 4.8%). Survival at 5 years was significantly greater in patients with complete (88.5%) than in those with incomplete revascularization (83.5%). Reemployment was more common in patients with complete (52%) than in those with incomplete revascularization (40%) and more patients were angina-free. Long-term survival appeared to be mediated primarily through improved revascularization rather than differences in left ventricular function.

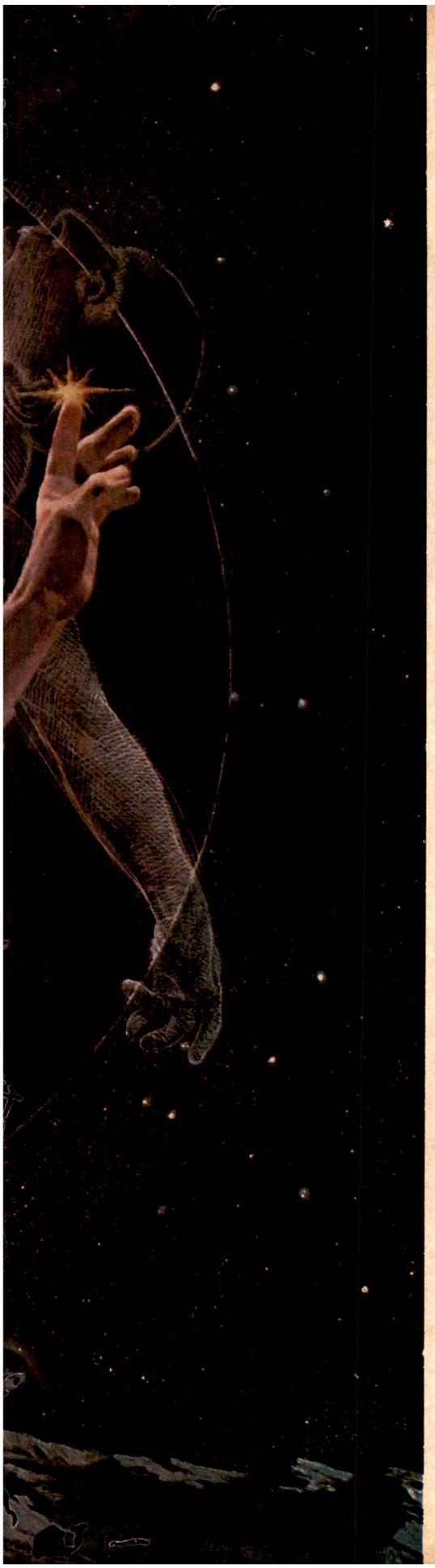
13 **Antianginal Efficacy and Improved Exercise Performance With Timolol. Twice-Daily Beta Blockade in Ischemic Heart Disease**

FRED J. HARRIS, REGINALD I. LOW, LINDA PALMER, EZRA A. AMSTERDAM, and DEAN T. MASON

Antianginal efficacy and improved exercise performance of timolol, a new beta blocker, was assessed in 23 patients with chronic stable angina pectoris in an 11-week, double-blind, placebo-controlled study. Twenty-two of 23 subjects completed the open-label phase (weeks 0 to 6) while receiving 10 to 30 mg of timolol twice daily to optimize exercise capacity. Weekly anginal episodes and nitroglycerin consumption decreased on timolol compared with placebo. Resting heart rate (HR), systolic blood pressure (SBP), peak exercise HR, peak exercise SPB, and peak exercise double product were significantly ($p < 0.05$) reduced 12 to 13 hours after timolol compared with placebo. Exercise duration was prolonged and the time of onset of 1 mm S-T segment depression was delayed in 15 patients. During the double-blind phase (weeks 7 to 10), resting HR, peak exercise HR, and peak exercise double product were significantly attenuated in 8 timolol patients although unchanged in 11 placebo subjects. Exercise duration was again prolonged at week 8 in timolol subjects compared with initial placebo, but not at week 10. Placebo patients demonstrated no difference at week 8 or 10 in exercise performance compared with initial placebo treatment. Timolol twice daily, therefore, is potentially useful in some patients with angina pectoris. Others may, however, require a more frequent dosing interval for optimal angina control and maximal improvement in exercise capacity.

Continued on Page A17


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*Usage in Children:* No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

**Precautions:** When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

**Adverse Reactions:** The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

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43 **Radionuclide Analysis of Peak Filling Rate, Filling Fraction, and Time to Peak Filling Rate. Response to Supine Bicycle Exercise in Normal Subjects and Patients With Coronary Disease**

G. B. JOHN MANCINI, ROBERT A. SLUTSKY, SHARON L. NORRIS, VALMIK BHARGAVA, WILLIAM L. ASHBURN, and CHARLES B. HIGGINS

Using gated equilibrium radionuclide angiography, parameters of diastolic filling were analyzed at rest and during exercise in normal subjects and patients with coronary disease with both normal and reduced resting ejection fractions. Indexes analyzed were peak filling rate and the filling fraction during the first third of diastole. At rest the peak filling rate and filling fraction were significantly lower in coronary patients than in normal subjects, and these differences persisted at peak exercise. The time from end-systole to peak filling was also analyzed and found to be longer at rest in patients with a normal resting ejection fraction than in normal subjects. This also remained true when the time to peak filling was normalized by the R-R interval. Although the exercise time to peak filling was longer in coronary patients than in normal subjects, these differences were not apparent when the interval was normalized by the R-R interval. It is concluded that abnormalities in peak filling rate and filling fraction exist in patients with coronary disease both at rest and during exercise; however, large overlaps exist between normal subjects and such patients. Furthermore, caution is advised in the comparison of timing of events during diastole because apparent group differences may be partly related to rest or exercise heart rate.

52 **Determinants of Variable Exercise Performance Among Patients With Severe Left Ventricular Dysfunction**

MICHAEL B. HIGGINBOTHAM, KENNETH G. MORRIS, ERIC H. CONN, R. EDWARD COLEMAN, and FREDERICK R. COBB

Cardiovascular responses were assessed in 17 patients with reduced left ventricular function and widely varying exercise tolerance. Maximal aerobic capacity was expressed as multiples of the resting oxygen consumption ($\dot{V}O_2$), or Mets. Radionuclide ejection fraction (EF), end-diastolic counts (EDC), stroke counts, and count output (CO) were measured at rest and during exercise; arteriovenous oxygen difference was derived from $\dot{V}O_2$ and CO. Exercise performance was reduced in patients compared with normal controls, and was limited by a poor CO response, since arteriovenous oxygen difference increased normally. The reduced CO response in patients resulted from failure of EF to increase or a diminished chronotropic reserve, or both. The resting EF in patients ranged from 0.09 to 0.36, but was unrelated to the variable Mets achieved in the group. Analysis of exercise responses identified changes in heart rate, CO, and arteriovenous oxygen difference, but not EF or stroke counts, as important determinants of Mets. The variable exercise performance among patients with severe left ventricular dysfunction was determined predominantly by variable heart rate and arteriovenous oxygen difference response rather than by rest or exercise indexes of left ventricular function.

61 **Determinants of Ventricular Tachycardia in Patients With Coronary Artery Disease and Ventricular Aneurysm. Clinical, Hemodynamic, and Angiographic Factors**

MARC COHEN, ISAAC WEINER, AUGUSTO PICHARD, JAMES HOLT, HARRY SMITH, Jr., and RICHARD GORLIN

In order to determine which factors are associated with the development of ventricular tachycardia in patients with ventricular aneurysms, the records of 154 patients with coronary artery disease and ventricular aneurysms were reviewed. Eighty-five of these patients had Holter monitoring or continuous electrocardiographic monitoring within 6 months of catheterization. Nineteen patients had ventricular tachycardia and 66 did not. There were no significant differences in the 2 groups with respect to age, time from first myocardial infarction to catheterization, congestive heart failure, or ejection fraction. Patients with ventricular tachycardia had significantly larger aneurysms and a much higher prevalence of septal akinesia.

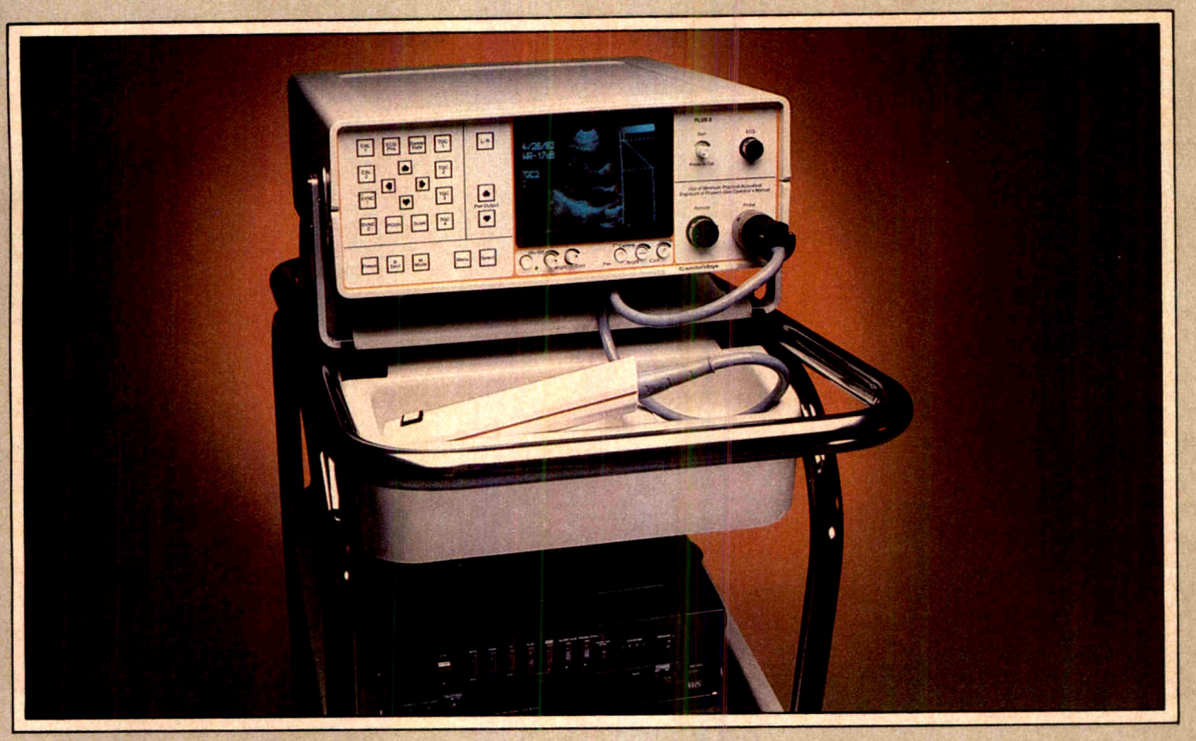
65 **Relation of Exercise to the Recurrence Rate of Myocardial Infarction in Man. Ontario Exercise-Heart Collaborative Study**

PETER A. RECHNITZER, DAVID A. CUNNINGHAM, GEORGE M. ANDREW, CAROL W. BUCK, NORMAN L. JONES, TERENCE KAVANAGH, NEIL B. OLDRIDGE, JOHN O. PARKER, ROY J. SHEPHARD, JOHN R. SUTTON, and ALLAN P. DONNER

The Ontario Exercise-Heart Collaborative Study was a randomized clinical trial for the prevention of recurrent infarction in men under 56 years of age. Three hundred seventy-nine men were assigned to a high intensity exercise program designed to produce a significant training effect, and 354 men were allocated to a low intensity exercise program structured to produce a minimal training effect. The trial was stratified for blue collar occupation,

Continued on Page A27

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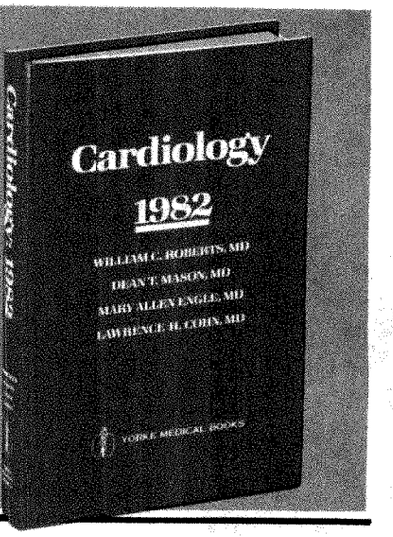
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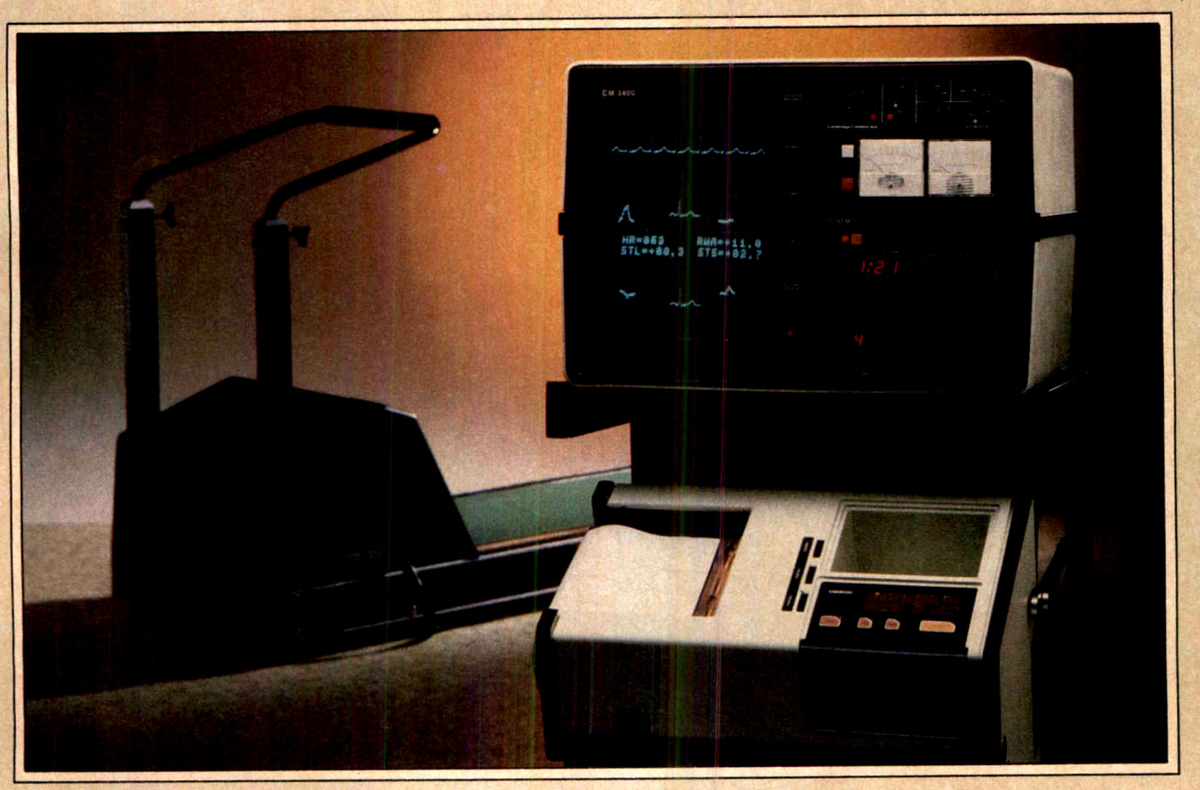
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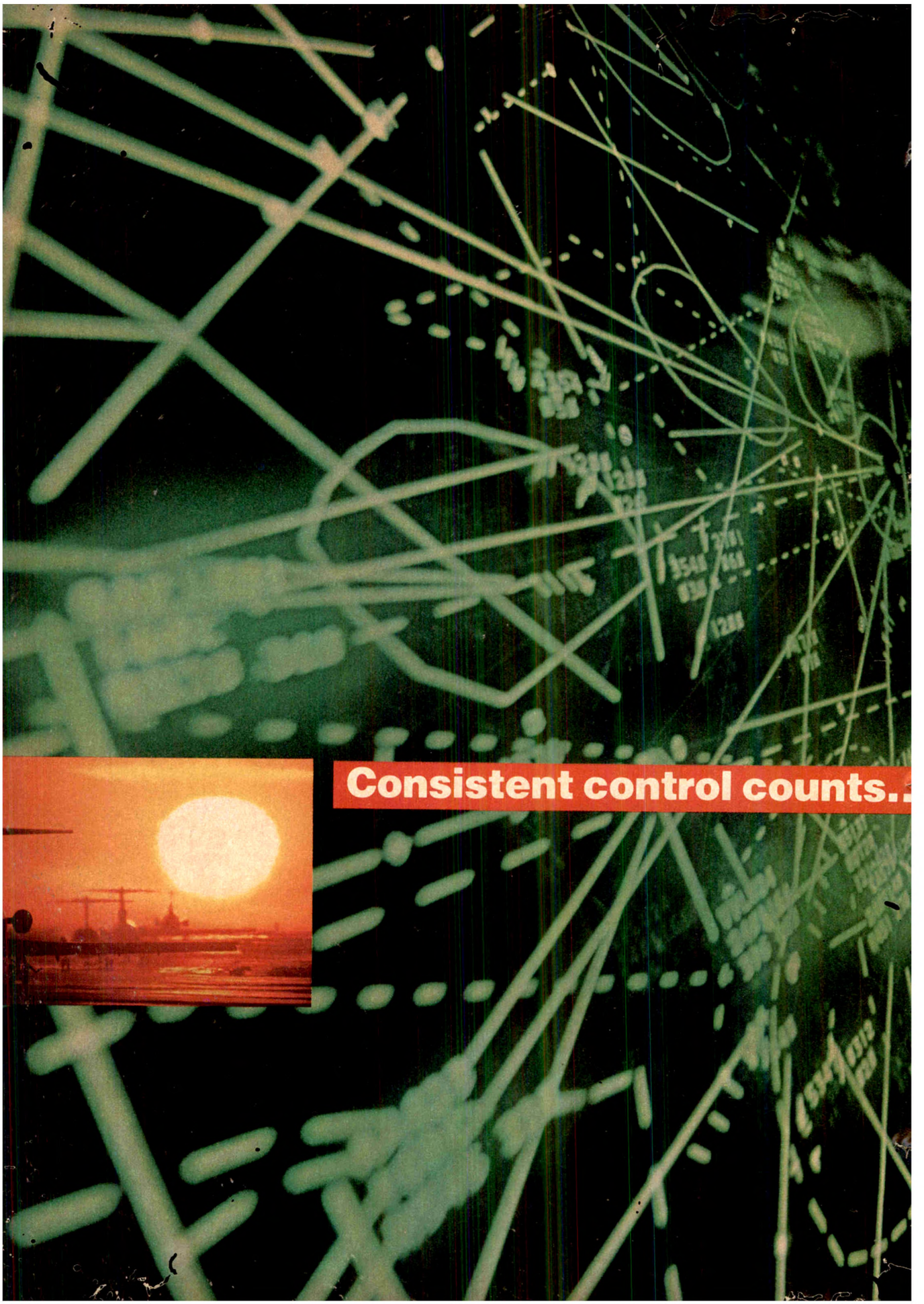
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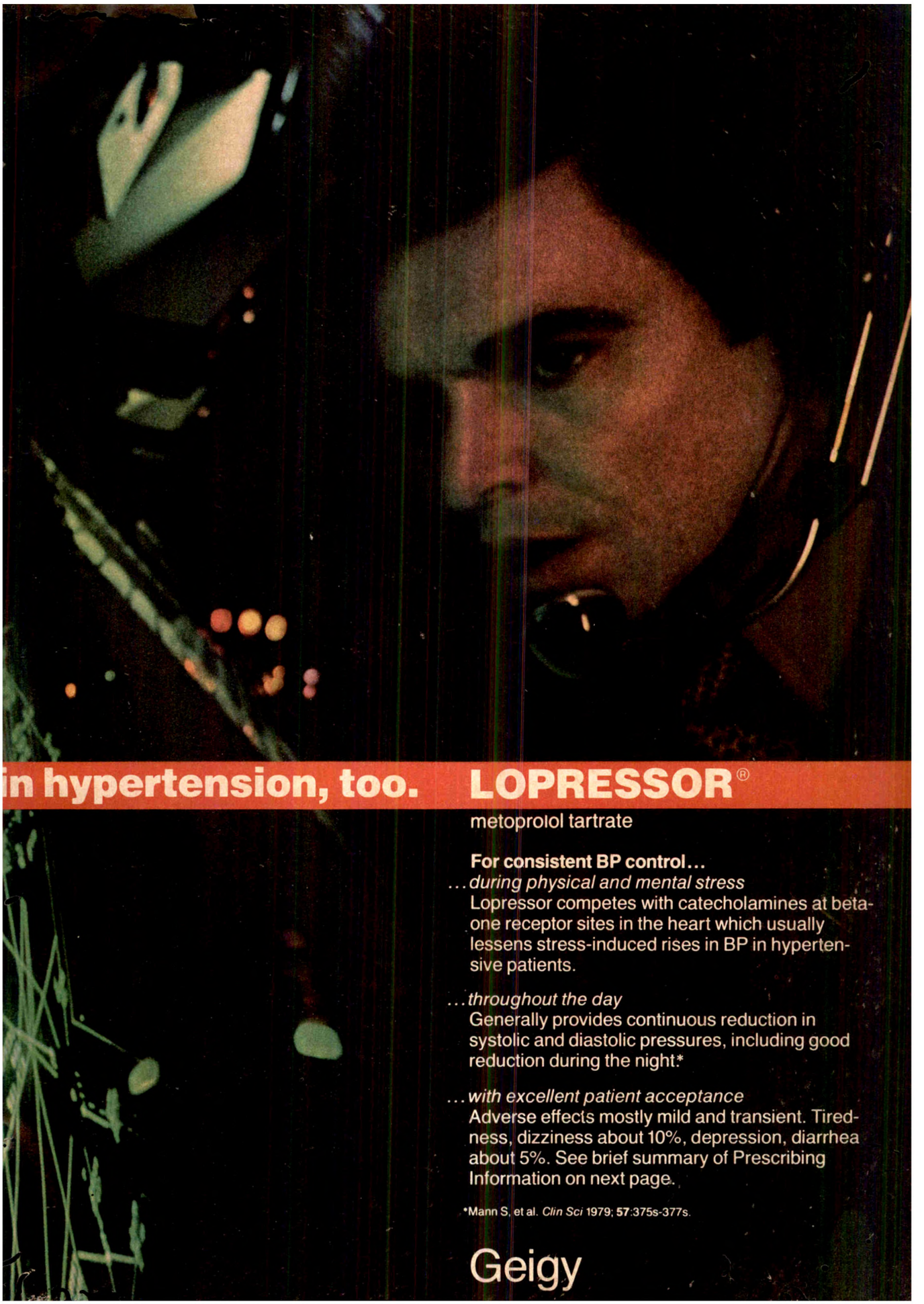
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*Brief Summary of Prescribing Information*

**Indications** Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

**Contraindications** Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

**Warnings** ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

***In Patients Without a History of Cardiac Failure:*** Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

***Ischemic Heart Disease:*** Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

***Bronchospastic Diseases:*** **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

***Major Surgery:*** The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

***Diabetes Mellitus:*** Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

***Thyrotoxicosis:*** Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

**Precautions** ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

***Drug Interactions:*** Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

***Long-Term Animal Studies:*** Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

***Usage in Pregnancy:*** Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

***Nursing Mothers:*** It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

***Usage in Children:*** Safety and effectiveness in children have not been established.

**Adverse Reactions** Most adverse effects have been mild and transient.

***Central Nervous System:*** Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

***Cardiovascular:*** Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

***Respiratory:*** Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

***Gastrointestinal:*** Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

***Allergic:*** Pruritus has occurred in less than 1 of 100 patients.

***Miscellaneous:*** Peyronie's disease has been reported in less than 1 of 100,000 patients. The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

***Potential Adverse Effects:*** In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

*Central Nervous System:* Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

*Cardiovascular:* Intensification of AV block (see **Contraindications**).

*Hematologic:* Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

*Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

*Miscellaneous:* Reversible alopecia.

*Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

**Dosage and Administration** Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

**How Supplied** Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

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hypertension, angina, and type A behavior personality. The mean follow-up period was 3.3 years and the dropout rate was 45% in each group. The relative risk of recurrence over 4 years in the high intensity group was 1.09 with 95% confidence limits of 0.61 and 1.96. These results indicate that a program of endurance training is no more effective than a program of low intensity activity in reducing the 4 year reinfarction rate in this study population.

**70 Predictors of Dropout From Cardiac Exercise Rehabilitation. Ontario Exercise-Heart Collaborative Study**

NEIL B. OLDRIDGE, ALLAN P. DONNER, CAROL W. BUCK, NORMAN L. JONES, GEORGE M. ANDREW, JOHN O. PARKER, DAVID A. CUNNINGHAM, TERENCE KAVANAGH, PETER A. RECHNITZER, and JOHN R. SUTTON

The dropout phenomenon in a multicenter clinical trial investigating the relation between exercise rehabilitation and recurrent myocardial infarction in men is described. The dropout rate was 46.5% over 3 years. Smoking and blue collar occupation were significant predictors of dropout; angina was a predictor only when reinfarctions were excluded. Identification of subgroups with an increased likelihood of dropout may optimize the potential of compliance-improving strategies in exercise rehabilitation trials and programs.

**75 Ventricular Electrical Instability: A Predictor of Death After Myocardial Infarction**

DAVID A. RICHARDS, DAVID V. CODY, ALAN R. DENNISS, PAUL A. RUSSELL, ALAN A. YOUNG, and JOHN B. UTHER

A standardized protocol of right ventricular programmed stimulation was used to assess ventricular electrical stability in 165 patients 6 to 28 days after acute myocardial infarction. Patients in whom ventricular fibrillation or sustained (>10 seconds) ventricular tachycardia (VT) was induced (38) were classified as unstable (23%). The remainder (127) were classified as stable (77%). The clinical profiles of the unstable and stable patients were initially similar. During the subsequent year, 8 unstable patients died instantaneously and 4 were resuscitated from spontaneous VT. No stable patient died instantaneously, and 2 developed spontaneous VT. Thus the risk of instantaneous death or spontaneous VT among unstable patients was 1:3, whereas the risk among stable patients was only 1:50 ($p < 0.001$). Prospective studies of antiarrhythmic therapy are required to determination whether sudden death can be prevented in unstable patients.

**81 Status of the Major Epicardial Coronary Arteries 80 to 150 Days After Percutaneous Transluminal Coronary Angioplasty. Analysis of 3 Necropsy Patients**

BRUCE F. WALLER, BRUCE M. McMANUS, H. JOEL GORFINKEL, JOAN C. KISHEL, EDWARD C. H. SCHMIDT, KENNETH M. KENT, and WILLIAM C. ROBERTS

Clinical and necropsy cardiac findings are described in 3 men who had percutaneous transluminal coronary angioplasty (PTCA) of the left anterior descending (LAD) coronary artery 80, 90, and 150 days before sudden death. Each patient had a decrease in the mean transstenotic coronary gradient (17, 38, and 43 mm Hg) and an angiographic increase in the LAD luminal diameter (55, 60, and 65%). At necropsy, the LAD coronary artery in the area of the PTCA in each patient was narrowed 76 to 95% in cross-sectional area by atherosclerotic plaques. No cracks in plaques or other lesions which may have resulted from the PTCA procedure were identified histologically in the LAD coronary artery of any patient.

## ARRHYTHMIAS AND CONDUCTION DISTURBANCES

**85 Electrophysiologic Testing in the Management of Survivors of Out-of-Hospital Cardiac Arrest**

FRED MORADY, MELVIN M. SCHEINMAN, DAVID S. HESS, RUEY J. SUNG, EDWARD SHEN, and WILLIAM SHAPIRO

In 45 patients who survived a cardiac arrest due to ventricular tachycardia (VT) or ventricular fibrillation, programmed ventricular stimulation induced sustained VT in 58% and nonsustained VT in 18%. Patients without inducible VT had no recurrent sudden death with treatment directed at the underlying heart disease. Serial electropharmacologic testing with conventional antiarrhythmic drugs was disappointing, with a low incidence (26%) of arrhythmia suppression. Among patients treated with amiodarone, 21 of 23 (91%) had no recurrence of VT or sudden death over a follow-up period of 18 ± 14 months (mean ± standard deviation). Chronic oral amiodarone therapy may supplant the need for serial drug testing in patients with inducible VT.

Continued on Page A28

90 **Quinidine for Ventricular Arrhythmias: Value of Electrophysiologic Testing**

JOHN P. DiMARCO, HASAN GARAN, and JEREMY N. RUSKIN

Eighty-nine patients with a history of ventricular tachycardia (VT) or ventricular fibrillation in response to programmed cardiac stimulation received quinidine in an attempt to suppress their arrhythmias. Quinidine at a mean serum concentration of 2.9 ± 0.8 μg/ml suppressed the initiation of VT during repeated ventricular stimulation in 30 of these patients. In an additional 8 patients, quinidine plus a second antiarrhythmic drug prevented the initiation of VT by ventricular stimulation. During chronic therapy, 32 of these 38 patients remained free of recurrent arrhythmia, while 3 had a clinical recurrence and 3 were forced to discontinue quinidine because of adverse effects. These data demonstrate that when patients are selected for chronic therapy on the basis of electrophysiologic studies, quinidine can provide long-term protection against recurrent arrhythmias.

96 **Enhanced Parasympathetic Tone Shortens Atrial Refractoriness in Man**

ERIC N. PRYSTOWSKY, GERALD V. NACCARELLI, WARREN M. JACKMAN, ROBERT L. RINKENBERGER, JAMES J. HEGER, and DOUGLAS P. ZIPES

Twelve patients were studied to determine the effects of enhanced vagal tone on human right atrial refractoriness. A lead neck collar connected to a vacuum source was placed around the patient's neck, and neck suction produced enhanced vagal tone. Atrial refractory periods were determined during high right atrial pacing. Induced neck suction increased spontaneous sinus cycle length from 837 ± 96 to 1,136 ± 273 ms ($p < 0.001$) and shortened the atrial effective refractory period from 241 ± 24 to 230 ± 20 ms ($p < 0.01$) and the atrial functional refractory period from 272 ± 32 to 262 ± 29 ms ($p < 0.01$). In 2 patients collar-induced decreases in atrial refractoriness and increases in spontaneous cycle length were prevented after atropine (0.03 mg/kg intravenously) was given. We conclude that enhanced vagal tone mediated through muscarinic receptors shortens atrial refractory periods in man.

101 **Effect of Local Lidocaine Anesthesia on Ventricular Escape Intervals During Permanent Pacemaker Implantation in Patients With Complete Heart Block**

BERNARD D. KOSOWSKY, SHAHID I. MUFTI, GURINDER S. GREWAL, RICHARD H. S. MOON, W. LINDA CASHIN, JOHN O. PASTORE, and K. RAMASWAMY

The role of subcutaneous lidocaine anesthesia in the occurrence of transient asystole during permanent pacemaker implantation was studied in 9 patients with complete heart block. Ventricular escape intervals were measured before and 10, 30, and 45 minutes after subcutaneous lidocaine administration for permanent pacemaker implantation. The total lidocaine dose ranged from 170 to 400 mg. Therapeutic blood levels were achieved in 7 patients. The mean ventricular escape interval before lidocaine was 2.06 ± 0.30 seconds, which increased to 3.80 ± 1.44 seconds ($p < 0.01$). The percent increase in maximal escape interval was directly related to the peak lidocaine level achieved. After lidocaine administration, 5 patients had asystole >4 seconds. Thus, subcutaneous lidocaine contributes to the occurrence of asystole seen during permanent pacemaker implantation even in the absence of previous asystole.

105 **Relation Between Late Potentials on the Body Surface and Directly Recorded Fragmented Electrograms in Patients With Ventricular Tachycardia**

MICHAEL B. SIMSON, WILLIAM J. UNTEREKER, SCOTT R. SPIELMAN, LEONARD N. HOROWITZ, NORMAN H. MARCUS, RITA A. FALCONE, ALDEN H. HARKEN, and MARK E. JOSEPHSON

The relation between directly recorded electrograms and late potentials recorded on the body surface with a signal-averaged electrocardiogram was studied in 8 patients with and 11 patients without ventricular tachycardia (VT). Four patients without VT, each with a previous myocardial infarction, had fragmented endocardial electrograms; the latest electrogram for each patient ended 87 ± 8 ms after QRS onset within the high amplitude portion of the filtered QRS complex. All VT patients had fragmented electrograms recorded, predominantly from endocardial sites; the latest fragmented electrogram for each patient ended 161 ± 40 ms after QRS onset. Late potentials recorded in 6 patients with VT and were shown to correlate in time with fragmented electrographic activity. Two VT patients did not have late potentials; 1 had left bundle branch block, and the other had brief fragmented electrograms. The late potential recorded on the body surface corresponds to delayed and fragmented electrographic activity.

Continued on Page A33

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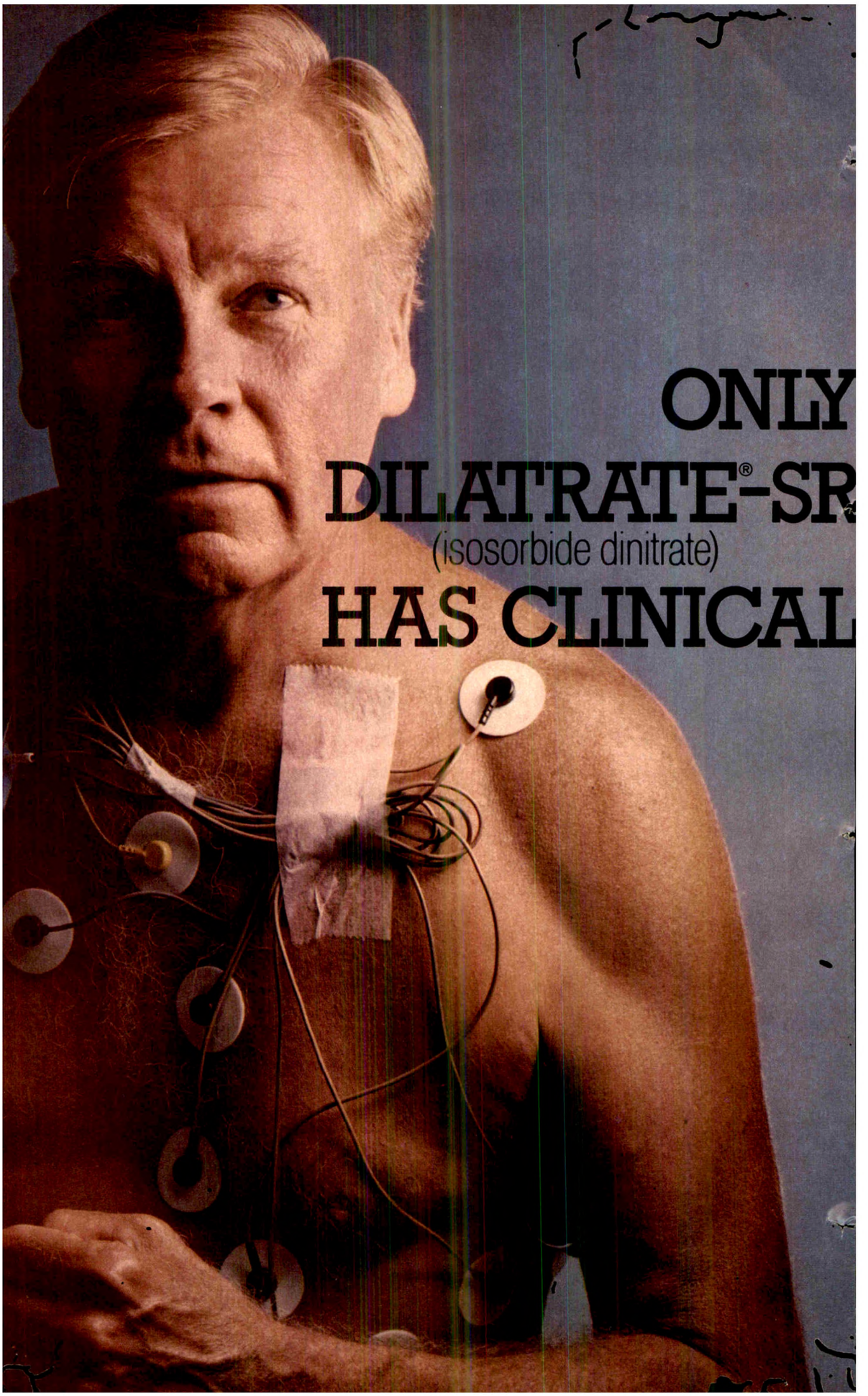
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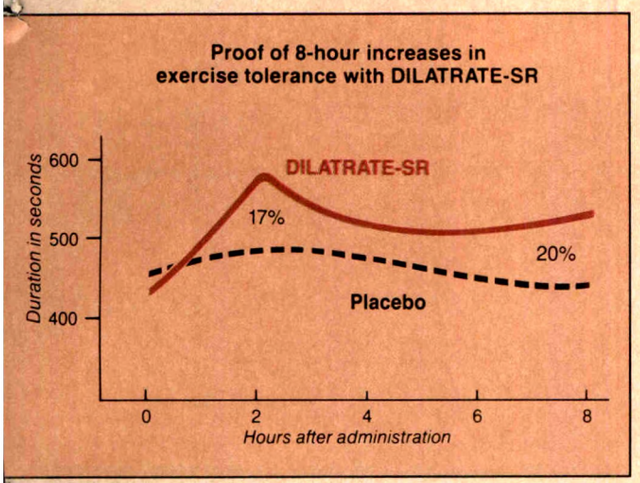
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In a double-blind, placebo-controlled study involving patients with chronic stable angina, significant improvement in exercise capacity was sustained for eight hours following administration of one 40 mg DILATRATE-SR capsule.[1]

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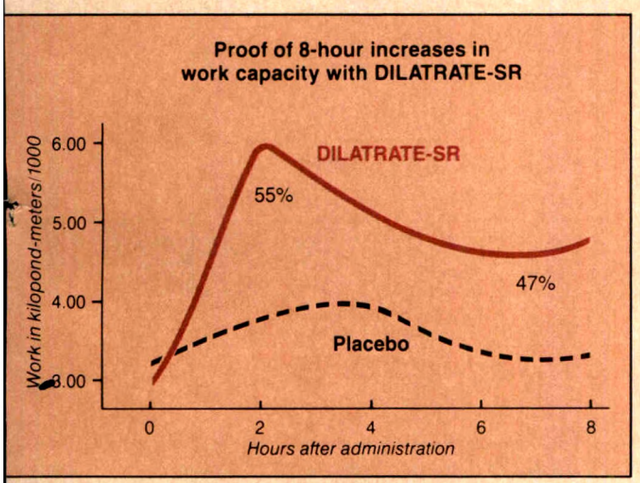
### *Increases in exercise tolerance translate into true patient benefits*

Exercise tolerance tests provide objective measurements of improvement in work capacity that can be correlated with the anginal patient's daily activities. These results demonstrate that DILATRATE-SR can provide a positive impact on your patient's lifestyle.

### *Clinical support of plasma level studies*

This clinical study supports previous blood assays which demonstrated that DILATRATE-SR provides significant plasma levels of ISDN for up to 12 hours.[2]

# PROOF: 8-hour antianginal activity*




A 20% increase in duration of treadmill exercise means another minute or two at higher speed on a steeper incline. When mean work performance was calculated, DILATRATE-SR provided a 47% increase at 8 hours.

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DILATRATE-SR employs a unique delivery system — an advanced microdialyzing membrane that releases ISDN at a steady rate independent of gastric pH and enzymes. The water-activated membrane continually adjusts permeability to maintain constant nitrate release.

### *DILATRATE-SR simplifies antianginal therapy*

The proven sustained activity of DILATRATE-SR offers anginal patients convenient b.i.d. dosage and can reduce the need for sublingual nitroglycerin.

*Please see brief summary of full prescribing information on following page. For full prescribing information, consult package insert.

**References:**

1. DiBianco R et al: Effects of a new oral slow release form of isosorbide dinitrate on the hemodynamics and exercise capacity of patients with angina — a placebo controlled and double blind study. *Circulation* (Supp II) 66:381, Oct 1982.
2. Dinsdale J, Allen J: Data on file, Medical Department, Reed & Carnrick.

**Dilatrate®-SR**
(isosorbide dinitrate) 40 mg

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# Dilatrate®-SR
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**BRIEF SUMMARY**

Indications: Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: When taken by the oral route, is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indication requires further investigation.

**CONTRAINDICATION:** Idiosyncrasy to this drug.

**WARNINGS:** Data supporting the use of nitrates and nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

**PRECAUTIONS:** Tolerance to this drug, and cross-tolerance to other nitrates or nitrites may occur.

In patients with functional or organic gastrointestinal hypermotility or malabsorption syndrome it is suggested that either the 5 mg. or 10 mg. oral tablets or 2.5 mg. or 5 mg. sublingual tablets be the preferred therapy.

**ADVERSE REACTIONS:** Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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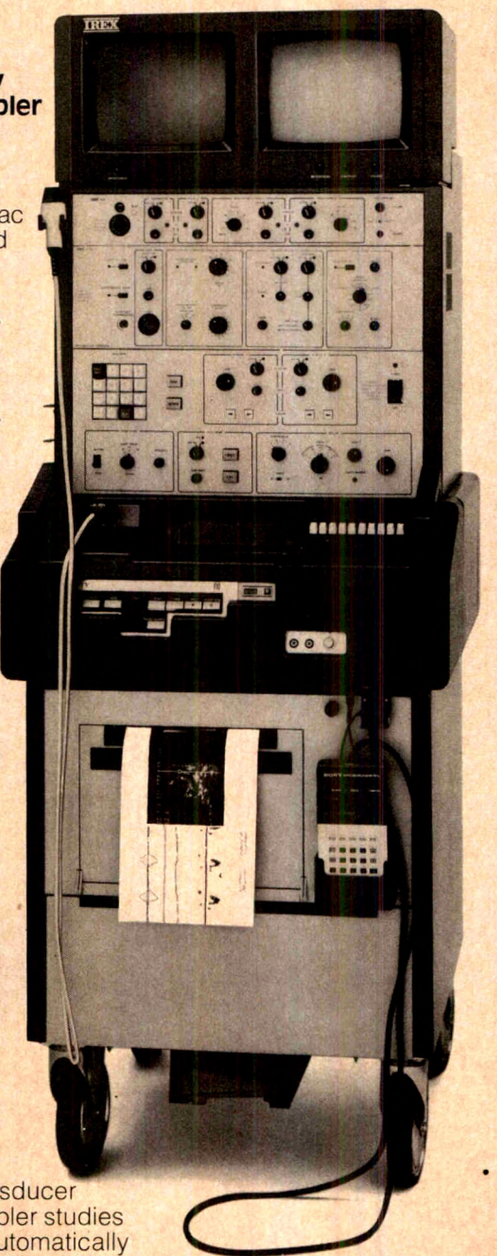
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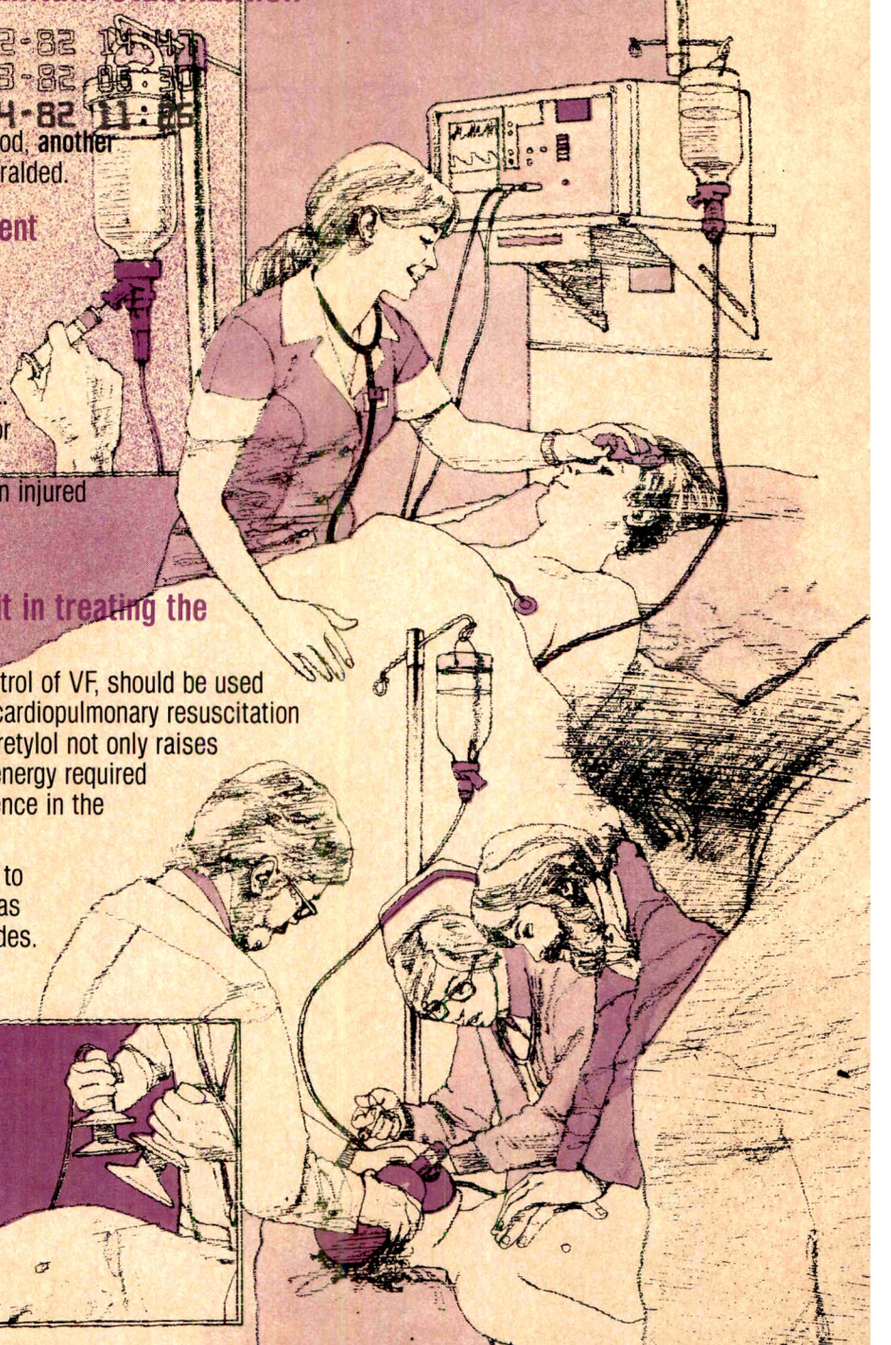
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In the CCU, after conversion of VF...

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## Follow-up therapy helps maintain stabilization

During the two or three days **after** conversion of ventricular fibrillation, the patient may still be electrically unstable. During this critical high risk period, **another** episode of VF may occur, completely unheralded.




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1. Bretylol raises the VF threshold almost three times control, protecting the heart from fibrillation.[1]*
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2. Bretylol also suppresses reentry, a major cause of VF by helping to equalize the electrophysiological differences between injured and normal ventricular tissue.[2]*
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Bretylol, a first-line agent in the acute control of VF, should be used in the very first stages of VF, as soon as cardiopulmonary resuscitation and countershock have been attempted. Bretylol not only raises the fibrillation threshold...it reduces the energy required for defibrillation.[3,4]* Another critical difference in the Bretylol mechanism of action.

That's why it makes sense to use Bretylol to maintain stabilization in the CCU, as well as in the first few minutes of acute VF episodes.

There are no contraindications to the use of Bretylol in VF. Hypotension and postural hypotension have been the most frequently reported adverse reactions. Consult brief summary of prescribing information on the following page.



For further information, please contact the Medical Services Department, American Critical Care, a division of American Hospital Supply Corporation, 1600 Waukegan Road, McGaw Park, IL 60085, Phone 312/473-3000.

*based on laboratory animal studies

1. Bacaner, M.B., *Am. J. Cardiol.*, *21*(4):504-512, April, 1968. 2. Cardinal, R. and Sasyniuk, B.I., *J. Pharmacol. Exp. Ther.*, *204*(1):159-174, 1978. 3. Tacker, W.A., Niebauer, M.J., Babbs, C.F., Combs, W.J., Hahn, B.M., Barker, M.A., Seipel, J.F., Bourland, J.D. and Geddes, L.A., *Am. Heart J.*, *98*(3):345-350, September, 1979. 4. Babbs, C.F., Yim, G.K.W., Whistler, S.J., Tacker, W.A. and Geddes, L.A., *Am. Heart J.*, *98*(3):345-350, September, 1979.

**Bretylol...adds a different and unique dimension in control of ventricular fibrillation**

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# Bretylol®
## (bretylium tosylate)

**Brief summary of prescribing information**

**INDICATIONS**—BRETYLOL is indicated in the prophylaxis and therapy of ventricular fibrillation.

BRETYLOL is also indicated in the treatment of life-threatening ventricular arrhythmias, such as ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

**CONTRAINDICATIONS**—There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

**WARNINGS**—**1. Hypotension:** Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, lightheadedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

**2. Transient Hypertension and Increased Frequency of Arrhythmias:** Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

**3. Caution During Use with Digitalis Glycosides:** The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL (bretylium tosylate) should be avoided.

**4. Patients with Fixed Cardiac Output:** In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

**USE IN PREGNANCY**—The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

**USE IN CHILDREN**—The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

**PRECAUTIONS**—**1. Dilution for Intravenous Use:** BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

**2. Use of Various Sites for Intramuscular Injection:** When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

**3. Reduce Dosage in Impaired Renal Function:** Since BRETYLOL is excreted principally via the kidney, the dosage interval should be increased in patients with impaired renal function.

**ADVERSE REACTIONS**—Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

**HOW SUPPLIED**—NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP, pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, non-pyrogenic.

Oct. 1980

Please refer to complete prescribing information prior to use.

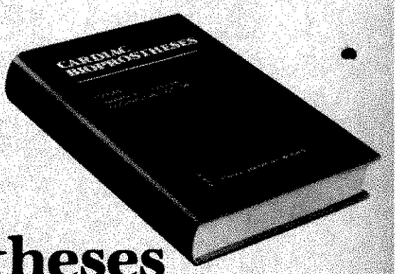
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# Cardiac Bioprostheses

**Proceedings of the Second International Symposium**
**Rome, Italy, May 17-19, 1982**

**edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD**
**ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $65.00**

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## Who are the editors?

**Lawrence H. Cohn, MD,** is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

**Vincenzo Gallucci, MD,** is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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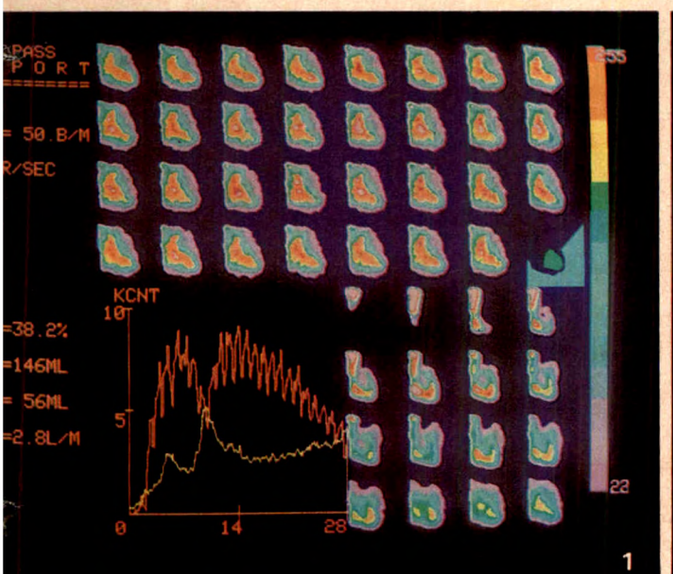
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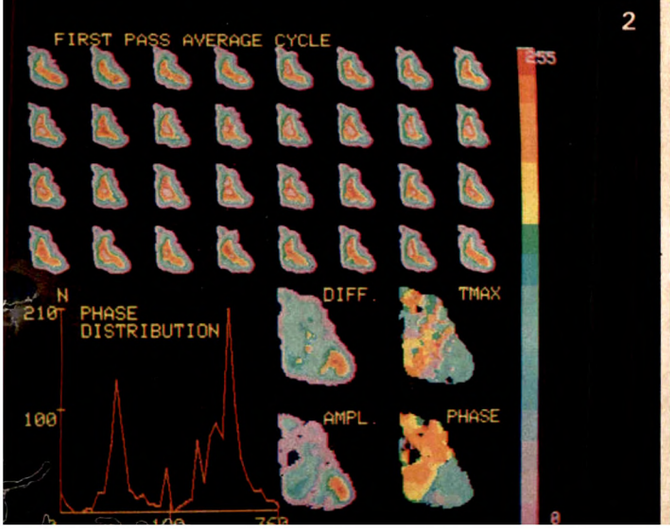
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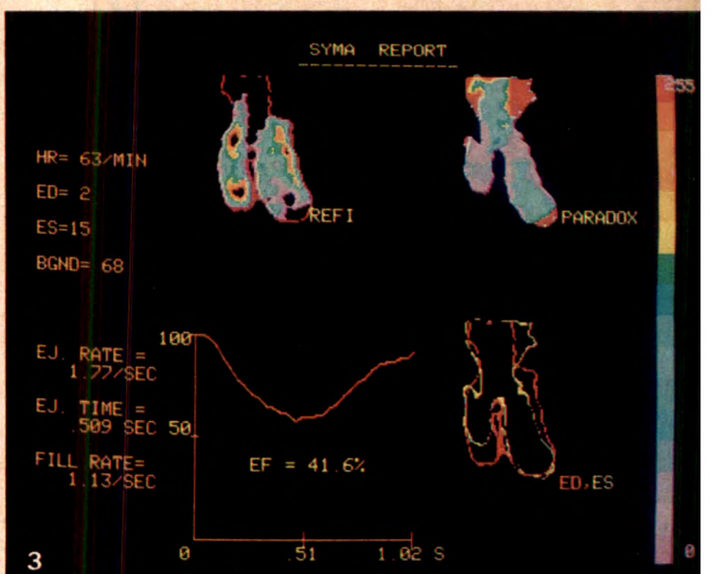



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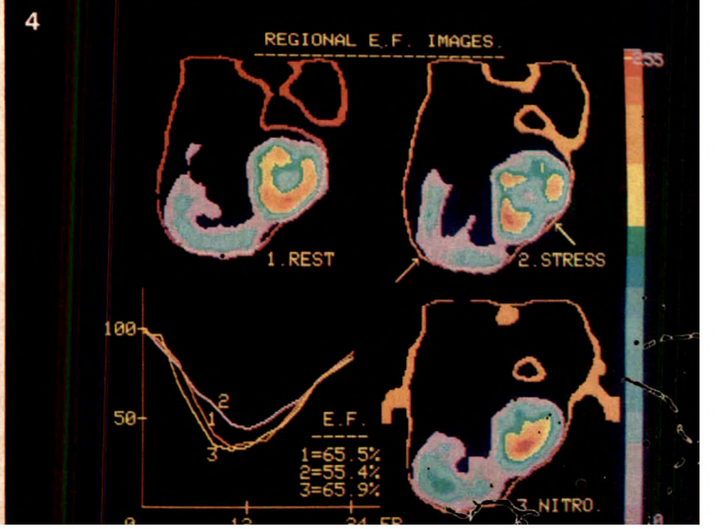



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*Photos 1 & 2:* Apex 215M's high count rates enable superior definitive first-pass studies. Typical of its capabilities are global and regional ventricular function analysis and direct quantification through volume.




3




4

*Photos 3 & 4:* Apex 215M can clearly display various global and regional functions on a single image monitor. In these examples, ventricular functions in a resting heart appear above; the lower image compares the resting heart with two different intervention situations.

# CONTENTS


149 **Cryosurgery for Cardiac Arrhythmias: Acute and Chronic Effects on Coronary Arteries**

WILLIAM L. HOLMAN, MASATOSHI IKESHITA, ROSS M. UNGERLEIDER, PETER K. SMITH, RAYMOND E. IDEKER, and JAMES L. COX

In this study, the acute and chronic effects of cryothermia on coronary arterial patency and integrity were examined. In the acute study, coronary arterial and regional myocardial blood flow were determined during and immediately after cryothermic exposure. Arterial occlusion occurred 20 ± 4 seconds after institution of cryothermia, and patency returned 29 ± 8 seconds after termination of cryothermia. Analysis of postthaw regional myocardial blood flow showed no evidence of embolization of debris after thawing. In the chronic study, coronary arteries subjected to cryothermia were examined histologically 48 hours, 2 weeks, or 6 months postoperatively. Intimal hyperplasia was often present at the site of the cryolesion. This intimal hyperplasia was most marked in lesions created during hyperthermic cardioplegic arrest. Thus, cryothermia-induced coronary arterial damage may produce hemodynamically significant coronary arterial stenosis, and caution should be exercised when it is necessary to create cryolesions in the vicinity of major coronary arteries.

156 **Intravenous Amiodarone in the Acute Treatment of Recurrent Symptomatic Ventricular Tachycardia**

FRED MORADY, MELVIN M. SCHEINMAN, EDWARD SHEN, WILLIAM SHAPIRO, RUEY J. SUNG, and LORENZO DiCARLO

Fifteen patients had frequent episodes of ventricular tachycardia refractory to at least 2 conventional antiarrhythmic drugs. All patients received an initial bolus of 5 mg/kg of amiodarone. Seven patients also received a continuous infusion of 600 to 1,000 mg of amiodarone over 12 to 24 hours. Additional doses depended on the clinical response. Previously ineffective antiarrhythmic drugs were continued in 11 of 15 patients. In 12 of 15 patients there was acute control of ventricular tachycardia by intravenous amiodarone either alone or in combination with previously ineffective drugs. The use of intravenous amiodarone represents a significant advance in the acute treatment of frequent life-threatening ventricular tachycardia refractory to other drugs.

160 **Books Received**

## SYSTEMIC HYPERTENSION

161 **Alterations in Left Ventricular Filling With Beta-Adrenergic Blockade**

FETNAT M. FOUAD, MAREK J. SLOMINSKI, ROBERT C. TARAZI, and JOE GALLAGHER

The cardiac and hemodynamic effects of 1 month of treatment with beta blockage (metoprolol in 8 patients and nadolol in 13 patients) in hypertension revealed differences in the ventricular volume curves between responders and nonresponders. Responders maintained the same ejection velocity and had a more rapid early filling rate. In contrast, nonresponders showed a reduced velocity of ejection and a slower rate of ventricular filling. Thus, alteration of ventricular function with beta blockade can be overshadowed by blood pressure reduction.

165 **Intravascular Volume, Extracellular Fluid Volume, and Total Body Water in Obese and Nonobese Hypertensive Patients**

JOCELYNE H. RAISON, APOSTOLOS D. ACHIMASTOS, JEAN E. BOUTHIER, GERARD M. LONDON, and MICHEL E. SAFAR

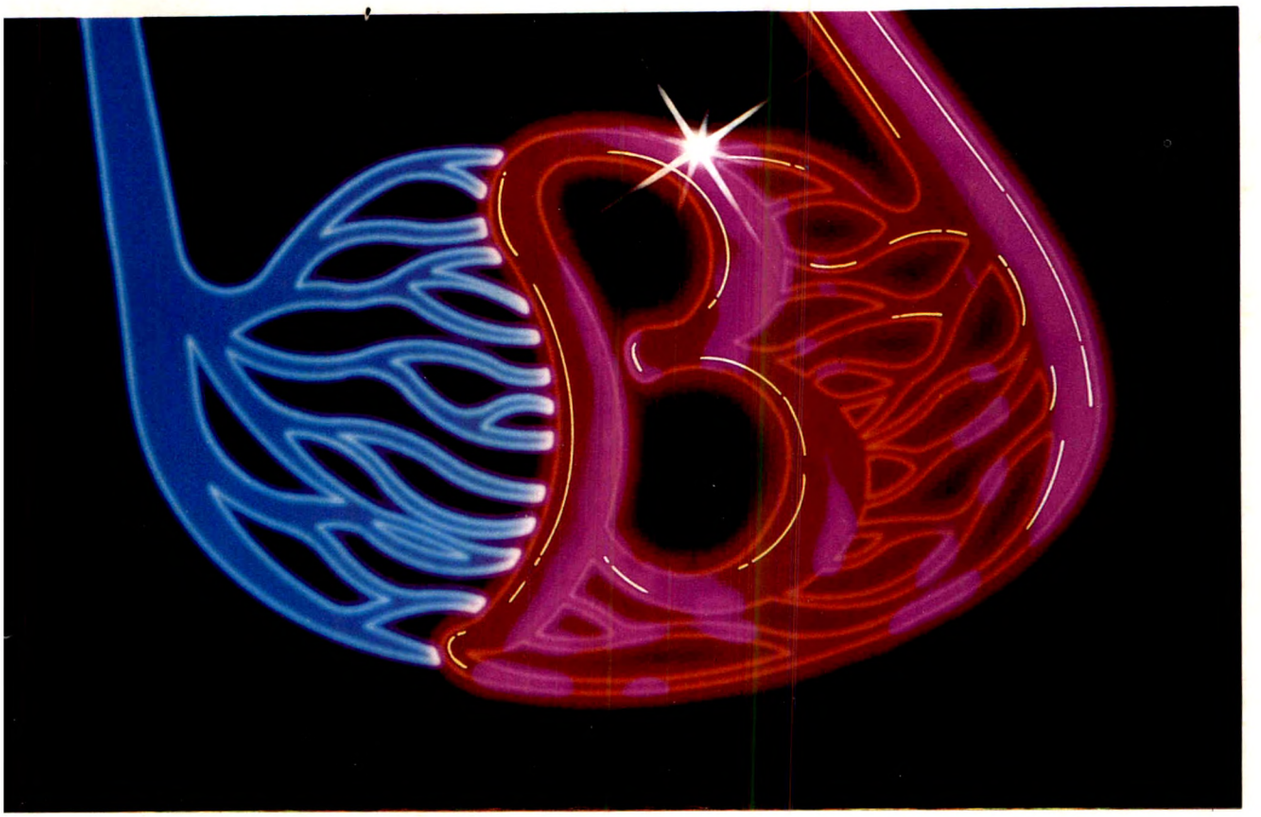
Intraarterial blood pressure, plasma volume, extracellular and interstitial (IFV) fluid volumes, and total and intracellular (IBW) body water were evaluated in 47 men: 16 obese hypertensive patients, 16 nonobese hypertensive patients and 15 normal subjects of similar age. In obese hypertensive subjects, the IBW/IFV ratio was significantly increased ($p < 0.01$) in comparison with both control subjects and nonobese hypertensive patients. After body weight reduction, blood pressure ($p < 0.01$), heart rate ($p < 0.05$), and the IBW/IFV ratio ($p < 0.01$) significantly decreased. The decrease in the ratio was due to an absolute increase in interstitial fluid volume, related to a shift of fluid volume from the intracellular to the interstitial space. Thus, obese hypertensive patients have an increased water cell content, causing an altered partition between the intracellular and the interstitial spaces.

171 **Relation of Hemodynamic Load to Left Ventricular Hypertrophy and Performance in Hypertension**

RICHARD B. DEVEREUX, DANIEL D. SAVAGE, IRENE SACHS, and JOHN H. LARAGH

One hundred untreated patients with essential hypertension were studied by echocardiography and cuff blood pressure to assess the relation between hemodynamic load and left ventricular hypertrophy and performance. Indexes of left ventricular hypertrophy were poorly related to resting blood pressure ($r = 0.16$ to 0.32). However,


Continued on Page A49



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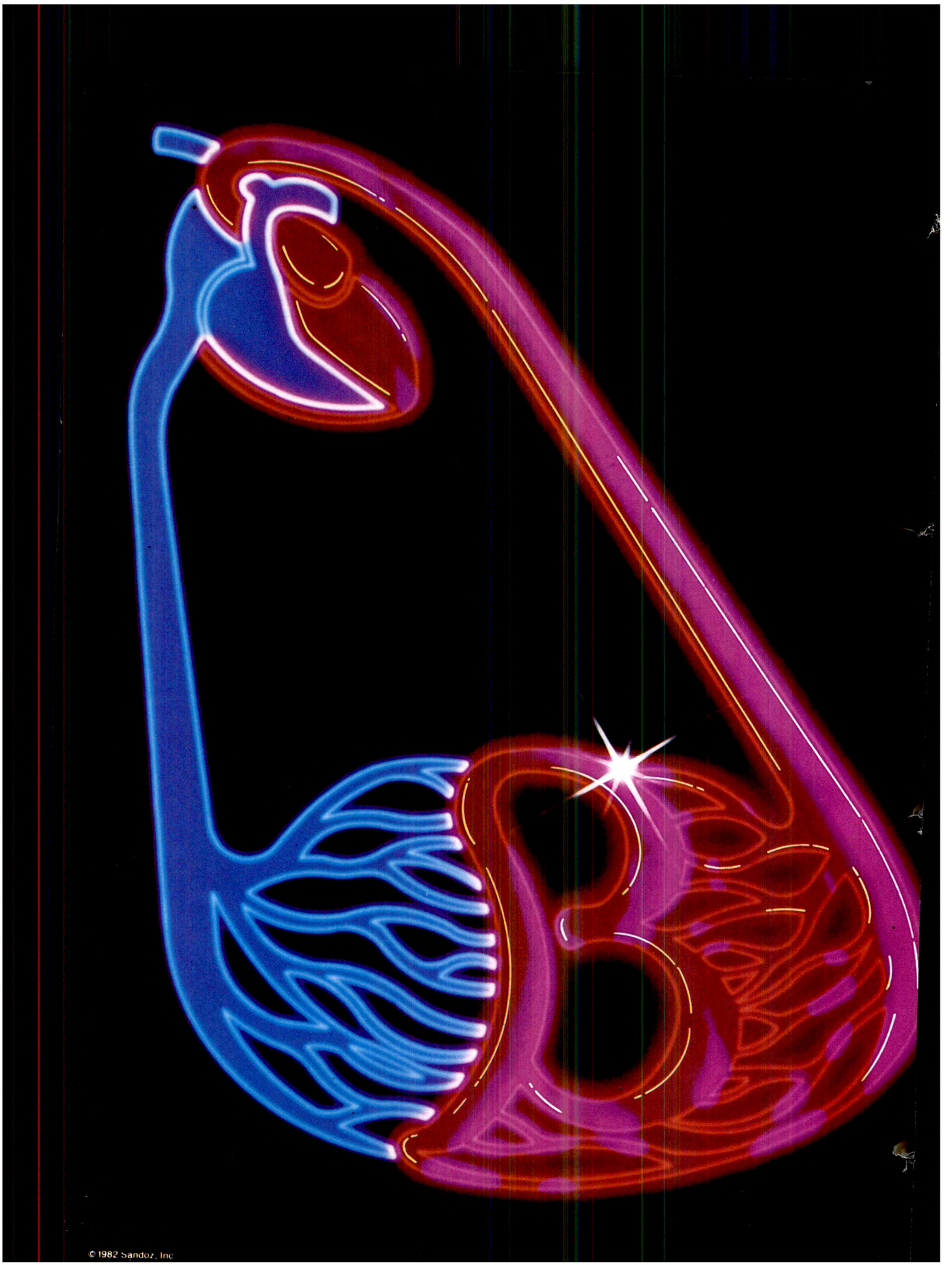
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## Here's the difference:

### Blood pressure

Blood pressure equals cardiac output times total peripheral resistance.

$$bp = co \times tpr$$

### Visken (pindolol)

Visken (pindolol) is the only beta blocker that reduces blood pressure while maintaining resting cardiac output and reducing total peripheral resistance during long-term therapy.

$$\underline{bp} = \underline{\overline{co}} \times \underline{tpr}$$

### All other beta blockers

All other beta blockers reduce blood pressure, and reduce cardiac output with an initial reflex rise in total peripheral resistance and a subsequent return to baseline in many cases.

$$\underline{bp} = \underline{co} \times \underline{\overline{tpr}}$$

Please see last page of this advertisement for brief summary of prescribing information.




# Here's the result:

## Reduced blood pressure

U.S. studies at 29 major medical centers[1] have shown that Visken (pindolol) is an effective antihypertensive. It is as effective as propranolol in normalizing blood pressure (dbp≤90 mmHg) when used alone. It is also effective when used in combination with a diuretic.

This antihypertensive effectiveness is supported by 13 years of clinical use throughout the world. In fact, Visken (pindolol) is the #2 beta blocker in the rest of the world.

## Reduced peripheral resistance

Studies of 178 patients treated with Visken (pindolol) for at least two weeks have shown that Visken therapy reduces total peripheral resistance.[1]

## Reduction of exercise-induced tachycardia

Like other beta blockers, Visken (pindolol) blocks stimulation by catecholamines to reduce exercise-induced increases in systolic blood pressure and heart rate.

# Prescribing information:

## Available in 5 mg and 10 mg tablets

## Convenient bid dosage

Dosage should be titrated on an individual basis. Many patients respond to 10-30 mg a day in divided doses.

**References:**

1. Data on file, Sandoz Pharmaceuticals.
2. Wilcox CS, Lewis PS, Peart WS, et al: Renal function, body fluid volumes, renin, aldosterone, and noradrenaline during treatment of hypertension with pindolol. *J Cardiovasc Pharmacol* 3:598–611, 1981.

Please see last page of this advertisement for brief summary of prescribing information.

# New Visken® (pindolol)

*Before prescribing or administering, see package circular for full product information. The following is a brief summary.*

**INDICATIONS AND USAGE**
Visken (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

**CONTRAINDICATIONS**
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

**WARNINGS**
**Cardiac Failure:** Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

**In Patients Without A History of Cardiac Failure:** In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal:** Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers:** Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

**Major Surgery:** Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken* (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

**Diabetes and Hypoglycemia:** Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

**Thyrotoxicosis:** Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

**PRECAUTIONS**
**Impaired Renal or Hepatic Function:** Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

**Information for Patients:** Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

**Drug Interactions:** Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

**Pregnancy—Category B:** Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**CLINICAL LABORATORY**
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

**ADVERSE REACTIONS**
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

| Body System/ Adverse Reaction | Total (Volunteered and Elicited) Visken (pindolol) (N = 322) % | Active Controls* (N = 188) % | Placebo (N = 78) % |
|---|---|---|---|
| Central Nervous System | | | |
| Anxiety | 4 | <1 | 1 |
| Bizarre or Many Dreams | 8 | 3 | 8 |
| Dizziness | 17 | 23 | 8 |
| Fatigue | 15 | 19 | 12 |
| Hallucinations | 1 | 0 | 0 |
| Insomnia | 19 | 8 | 12 |
| Lethargy | 3 | 6 | 4 |
| Nervousness | 11 | 5 | 9 |
| Weakness | 7 | 5 | 4 |
| Autonomic Nervous System | | | |
| Paresthesia | 5 | 2 | 8 |
| Visual Disturbances | 4 | 3 | 4 |
| Cardiovascular | | | |
| Dyspnea | 9 | 8 | 9 |
| Edema | 11 | 9 | 3 |
| Heart Failure | 2 | <1 | 0 |
| Palpitations | 2 | 2 | 0 |
| Weight Gain | 3 | 5 | 0 |
| Musculo-Skeletal | | | |
| Chest Pain | 5 | 3 | 5 |
| Joint Pain | 11 | 6 | 8 |
| Muscle Cramps | 8 | 2 | 0 |
| Muscle Pain | 12 | 12 | 9 |
| Gastrointestinal | | | |
| Abdominal Discomfort | 7 | 7 | 5 |
| Nausea | 7 | 4 | 1 |
| Skin | | | |
| Pruritus | 2 | <1 | 0 |
| Rash | 2 | 3 | 3 |

*Active Controls: Patients received either propranolol, ∝-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

**POTENTIAL ADVERSE EFFECTS**
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agen and should be considered potential adverse effects of Visken (pindolol).

**Central Nervous System:** Reversible mental depressi progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, shor term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

**Cardiovascular:** Intensification of AV block. See CONTRAINDICATIONS.

**Allergic:** Erythematous rash; fever combined with achi and sore throat; laryngospasm; respiratory distress.

**Hematologic:** Agranulocytosis; thrombocytopenic and nonthrombocytopenic purpura.

**Gastrointestinal:** Mesenteric arterial thrombosis; ischemic colitis.

**Miscellaneous:** Reversible alopecia; Peyronie's diseas

The oculomucocutaneous syndrome associated with th beta-blocker practolol has not been reported with Viske (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

**OVERDOSAGE**
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the followin general measures should be employed as appropriate i addition to gastric lavage:

**Excessive Bradycardia:** administer atropine; if there i no response to vagal blockade, administer isoproterenc cautiously.

**Cardiac Failure:** digitalize the patient and/or administe diuretic. It has been reported that glucagon may be use ful in this situation.

**Hypotension:** administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pres sure. (There is evidence that epinephrine may be the drug of choice.)

**Bronchospasm:** administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ⩾80 beat/min. Recovery was uneventful. In anothe case 250 mg of Visken (pindolol) was taken with 150 m diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

**DOSAGE AND ADMINISTRATION**
The dosage of Visken (pindolol) should be individualize The recommended initial dose of Visken (pindolol) is 10 mg b.i.d. alone or in combination with other antihyperter sive agents. Many patients will respond to 15 mg per da (5 mg t.i.d.). The antihypertensive response usually occurs within the first week of treatment. If a satisfactor reduction in blood pressure does not occur within 2-3 weeks, the dose may be adjusted in increments of 10 m per day at 2-3 week intervals up to a maximum of 60 m per day.

**HOW SUPPLIED**
White, round, scored tablets: 5 mg and 10 mg, packaged of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" or one side, and "78-73" and scored on other side (NDC 0078-0073-05). [VIS-Z2 9/1-82]

**Pharmaceutical Division**
**SANDOZ, INC.**
East Hanover, NJ 07936

VIS-1182-

end-diastolic relative wall thickness, an index of concentric hypertrophy, was directly related to peripheral resistance ($r = 0.52$, $p < 0.001$) and inversely to cardiac output ($r = -0.47$, $p < 0.001$). Left ventricular fractional systolic shortening was unrelated to blood pressure or left ventricular mass, but showed a close inverse relation with end-systolic wall stress ($r = -0.71$, $p < 0.001$). It is concluded that resting blood pressure correlates poorly with left ventricular hypertrophy or function in patients with hypertension. However, the "typical" hypertensive abnormalities of concentric left ventricular hypertrophy and elevated peripheral resistance appear pathophysiologically interdependent, and left ventricular performance is dependent on compensatory hypertrophy, which keeps wall stress normal.

## CONGESTIVE HEART FAILURE

**177 Failure of Dobutamine to Increase Exercise Capacity Despite Hemodynamic Improvement in Severe Chronic Heart Failure**

CAROL S. MASKIN, ROBERT FORMAN, EDMUND H. SONNENBLICK, WILLIAM H. FRISHMAN, and THIERRY H. LeJEMTEL

The acute hemodynamic and metabolic effects of dobutamine administered during upright, graded bicycle exercise were studied in 8 patients with severe chronic heart failure. During exercise performed with administration of dobutamine, the cardiac index was significantly greater than during control period exercise, $3.23 \pm 0.78$ versus $2.67 \pm 0.59$ liters/min/m$^2$ ($p < 0.001$), while the arteriovenous oxygen difference was lower, $11.2 \pm 2.1$ versus $12.5 \pm 2.4$ ml/100 ml ($p < 0.01$). Although dobutamine tended to increase maximal oxygen uptake compared with control period exercise, it did not significantly increase exercise capacity. Thus, administration of dobutamine to patients with severe chronic heart failure increased the cardiac index during maximal exercise but failed to increase exercise capacity. Since the arteriovenous oxygen difference is reduced, dobutamine probably augments blood flow to the nonexercising tissues and not to the actively metabolizing muscles.

**183 Quantitative Differences in the Hemodynamic Effects of Captopril and Nitroprusside in Severe Chronic Heart Failure**

MILTON PACKER, JOSE MELLER, NORMA MEDINA, and MADELINE YUSHAK

The hemodynamic effects of oral captopril and intravenous nitroprusside were compared in 15 patients with severe chronic heart failure. At doses of both drugs titrated to produce similar decreases in systemic vascular resistance, nitroprusside produced greater increases in cardiac index but smaller decreases in mean arterial pressure than did captopril. This finding was due to a significant decrease in heart rate with captopril (not seen with nitroprusside), since changes in stroke volume index with both drugs were similar. Nitroprusside decreased pulmonary arteriolar resistance significantly, whereas captopril did not. This finding helped explain the smaller decreases in right ventricular filling pressure with captopril; yet, the decreases in left ventricular filling pressure with captopril were greater than with nitroprusside. These data indicate that angiotensin, in addition to its direct systemic arterial vasoconstrictor actions, exerts positive chronotropic effects and alters ventricular compliance but has minimal direct effects on the limb venous circulation and on the pulmonary circulation.

## CARDIOMYOPATHY

**189 Relation of Electrocardiographic Abnormalities and Patterns of Left Ventricular Hypertrophy Identified by 2-Dimensional Echocardiography in Patients With Hypertrophic Cardiomyopathy**

BARRY J. MARON, JAMES K. WOLFSON, ELISABETTA CIRÓ, and PAOLO SPIRITO

Distribution of left ventricular hypertrophy was assessed by wide-angle, 2-dimensional echocardiography in 153 patients with hypertrophic cardiomyopathy and compared with the scalar electrocardiogram in the same patients. The most common electrocardiographic alterations were S-T segment changes and T-wave inversion (61%), left ventricular hypertrophy (47%), abnormal Q waves (25%), and left atrial enlargement (24%). Left ventricular hypertrophy on electrocardiography was most common in patients with the most extensive distribution of the left ventricular hypertrophy involving substantial portions of both the ventricular septum and the left ventricular free wall (sensitivity 74%). The majority of patients with hypertrophic cardiomyopathy and normal electrocardiograms had particularly localized hypertrophy. Abnormal Q waves were significantly more common in patients without hypertrophy of the anterior basal septum, and hence cannot be explained on the basis of ventricular septal hypertrophy alone. No single electrocardiographic abnormality is characteristic of a population of patients with hypertrophic cardiomyopathy, and 2-dimensional echocardiography clarifies the significance of certain electrocardiographic patterns.

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# CONTENTS

## EXPERIMENTAL STUDIES


**195 Comparative Effects of Nifedipine, Verapamil, and Diltiazem on Experimental Pulmonary Hypertension**

THOMAS E. YOUNG, LUCY J. LUNDQUIST, ELLIOT CHESLER, and E. KENNETH WEIR

This experimental study compared the hemodynamic effects of 3 calcium channel blocking agents (diltiazem, nifedipine, and verapamil) in 2 models of pulmonary hypertension in the anesthesized dog. The agents were given intravenously at 3 dose levels, either before acute hypoxic pulmonary vasoconstriction or before the stimulation of pulmonary hypertension by an infusion of prostaglandin $F_{2\alpha}$. During acute hypoxic pulmonary hypertension, verapamil decreased cardiac output by 30% ($p < 0.01$) without appreciably altering pulmonary arterial pressure. Nifedipine decreased hypoxic pulmonary vascular resistance to normoxic values ($p < 0.01$). Diltiazem administration produced no change in hypoxic pulmonary hemodynamics. During pulmonary hypertension stimulated by prostaglandin $F_{2\alpha}$, high dose verapamil tended to increase pulmonary vascular resistance. Nifedipine, however, completely blocked pulmonary vasoconstriction by decreasing pulmonary vascular resistance to pre-prostaglandin $F_{2\alpha}$ levels ($p < 0.01$). Again, diltiazem produced no change in pulmonary hemodynamics. Thus nifedipine appeared to be a more effective pulmonary vasodilator than verapamil or diltiazem.

**201 Compensatory Cardiac Mechanisms Evoked by Septal Ischemia in Dogs**

MALFRID MOLAUG, ODD GEIRAN, and FREDRIK KIIL

The cardiac responses to selective septal ischemia were studied in anesthesized open-chest dogs. Segment lengths were measured ultrasonically in the interventricular septum and the right and left ventricular free walls. At an average left ventricular end-diastolic pressure of 3 mm Hg, septal ischemia did not reduce stroke volume significantly, whereas left ventricular end-diastolic segment length increased 3%. This stimulation of the Frank-Starling mechanism counteracted the loss of septal function. After blood volume expansion to a left ventricular end-diastolic pressure of 7 mm Hg, end-diastolic dimensions in the left free wall did not increase and stroke volume decreased during septal ischemia. Ultrasonic recordings of the septum to right ventricular free wall distance showed increased systolic excursions and reduced end-systolic distance after occlusion of the septal artery, indicating paradoxical movement of the ischemic septum, which seems to act as a passive diaphragm pump on the right ventricle.

**207 Mechanisms of Spontaneous and Induced Ventricular Arrhythmias in the 24-Hour Infarcted Dog Heart**

BENJAMIN J. SCHERLAG, GLENN KABELL, JOHANNES BRACHMANN, LURA HARRISON, and RALPH LAZZARA

Two kinds of ventricular arrhythmias were consistently found in 14 dogs studied 1 day after left anterior descending coronary artery ligation. In the open-chest, anesthetized dog, electrocardiographic leads and electrograms from the infarct and normal zones were monitored. Spontaneous ventricular tachycardias were recorded which were irregular and multiform (average rate 154 ± 26 beats/min). In the same dogs, 3 ventricular paced beats at rates >300 beats/min induced rapid, uniform ventricular tachycardias (average rate 345 ± 17 beats/min). Only during the latter could continuous electrical activity within the interectopic intervals suggestive of a reentrant mechanism be consistently recorded. This experimental preparation is compared with ventricular arrhythmias described in clinical reports, and insights into the mechanism of entrainment of ventricular tachycardia are demonstrated.

**214 Instructions to Authors**


## METHODS


**215 Can Tracking of Contrast Echocardiographic Targets Be Used to Measure Intracardiac Flow Velocities?**

LILLIAM M. VALDES-CRUZ, DAVID J. SAHN, SUZANA HOROWITZ, DANIEL C. FISHER, STANLEY J. GOLDBERG, and HUGH D. ALLEN

Recent reports have suggested that the slopes of linearly moving echocardiographic contrast targets (microbubbles) can be used to predict flow velocities in the right heart. This study assessed the accuracy of velocities measured with contrast echocardiography by comparing them with those recorded with a previously calibrated quantitative range gated 2-dimensional echocardiographic Doppler flow meter. Venous saline echocardiographic contrast injections and Doppler studies were performed in 10 cardiac patients, aged 6 months to 16 years,


Continued on Page A53

# Baseline anginal therapy simplified

## Approximately 75% of angina patients were successfully controlled on the starting dosage—one Transderm-Nitro 5

*Once-daily application of Transderm-Nitro* was shown to provide effective 24-hour baseline therapy in the step-care approach to angina in a survey* of over 1,000 physicians with more than 10,000 patients under treatment.

Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

*For full details, please see the Prescribing Information on the next page.*

*Data on file, CIBA Pharmaceutical Company.

CIBA
the pioneer in
transdermal therapeutics

# Transderm®-Nitro
## nitroglycerin

one 10-second application
provides 24-hour anginal protection.



# Transderm®-Nitro
nitroglycerin

Simplifies baseline nitrate therapy

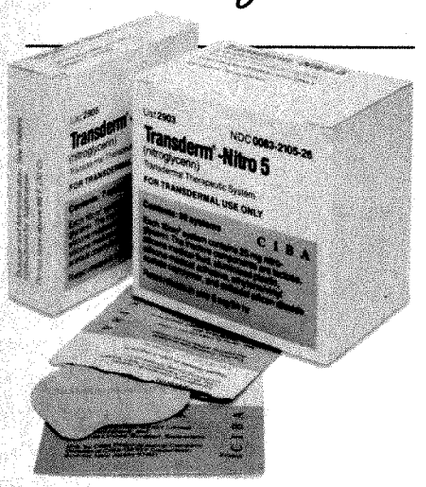
One application provides 24-hour anginal protection

Incorporates the unique, rate-controlling membrane from CIBA, for precise, predictable drug delivery

Simple to use, easy to live with

℞

Transderm-Nitro 5
#30
apply one system
daily




629-3688-A

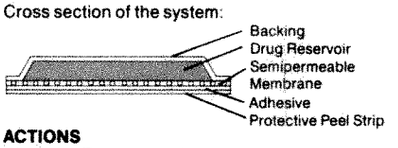
## Transderm®-Nitro (nitroglycerin)
**Transdermal Therapeutic System**

### DESCRIPTION
Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semipermeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 10 and 20 $cm^2$ respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system; 0.5 mg nitroglycerin is delivered *in vivo* for every $cm^2$ of system size.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface towards the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene/vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:




### ACTIONS
When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

### INDICATIONS AND USAGE
Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

### CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

### WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring. In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

### PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

### ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, the dose should be reduced or use of the product discontinued.

### DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

### PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

### HOW SUPPLIED

| Transderm-Nitro System Rated Release *in vivo* | Total Nitroglycerin in System | System Size | Carton Size |
|---|---|---|---|
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who had undergone operation for lesions in the left side of the heart. Instantaneous and peak velocities were determined at time-matched systolic points in cardiac cycles of identical R-R intervals. Significant but low-level correlations were found between contrast echocardiography and Doppler instantaneous ($r = +0.45$) or peak ($r = +0.18$) systolic velocities. The results suggest that while contrast echo microbubbles can be measured to yield a velocity, they do not behave like moving red blood cells which reflect ultrasound to produce a Doppler shift. Therefore, contrast echocardiography does not reliably measure flow velocities in the right heart.

**219 Cardiac Localization of Transvascular Bioptome Using 2-Dimensional Echocardiography**

JAMES W. FRENCH, RICHARD L. POPP, and PAUL T. PITLICK

Transvascular endomyocardial biopsy was performed in 7 children with heart muscle disease using both fluoroscopy and 2-D echocardiography to orient the bioptome. Twelve procedures (1 left ventricular and 11 right ventricular biopsies) were performed in these patients, aged 6 months to 18 years. There were no complications using the fluoroscopic-echocardiographic technique. By adding 2-D echocardiographic monitoring to the biopsy procedure, exposure to ionizing radiation was reduced, and localization of the bioptome with respect to intracardiac structures was more precise than with fluoroscopy alone.

**224 Validation of the Angiographic Accuracy of Digital Left Ventriculography**

ALLEN B. NICHOLS, ERIC C. MARTIN, THOMAS P. FLES, KAREN M. STUGENSKY, LAWRENCE A. BALANCIO, WILLIAM J. CASARELLA, and MELVIN B. WEISS

The angiographic accuracy of digital subtraction left ventriculograms, performed by intraventricular injection of 7 ml contrast medium diluted in saline solution, was validated in 28 patients undergoing conventional cineangiographic left ventriculography. Left ventricular volumes calculated from digital ventriculograms correlated highly with volumes calculated from conventional ventriculograms: end-diastolic volume ($r = 0.97$, end-systolic volume ($r = 0.97$), stroke volume ($r = 0.95$), ejection fraction ($r = 0.97$), and segmented left ventricular contraction ($r = 0.81$). After digital left ventriculography with diluted contrast medium, left ventricular pressures were unchanged and patients had no discomfort. Thus, the contrast enhancement afforded by digital subtraction angiography provides high resolution ventriculograms with markedly reduced doses of contrast medium, obviating the hemodynamic effects of conventional doses of contrast medium. This approach permits accurate measurement of left ventricular volumes, stroke volume, and ejection fraction and accurate assessment of left ventricular segmental contraction, without injection of large doses of contrast medium.

**MISCELLANEOUS TOPICS**

**231 In Vivo Ultrasonic Tissue Characterization of Human Intracardiac Masses**

STEPHEN E. GREEN, LINDA F. JOYNT, PETER J. FITZGERALD, DAVID S. RUBENSON, and RICHARD L. POPP

Noninvasive tissue characterization was attempted in vivo to separate both apical mural thrombi from the instrument-generated spurious signals seen on most 2-dimensional ultrasonoscopes, and atrial thrombi from atrial neoplasms. A stochastic analysis of the digitized echocardiographic signals from 15 patients was performed. In 10 subjects with 2-dimensional echocardiograms suggesting mural thrombi, surgery or necropsy confirmed thrombi in 6 and revealed no thrombi (designated artifact) in 4. The amplitude histograms suggested a totally random probability density function in 5 of 6 thrombi and suggested nonrandom probability density function in all 4 artifacts. All 5 neoplasms showed nonrandom probability density function. A method for in vivo ultrasonic tissue characterization to help differentiate thrombi from artifact or neoplasm is described.

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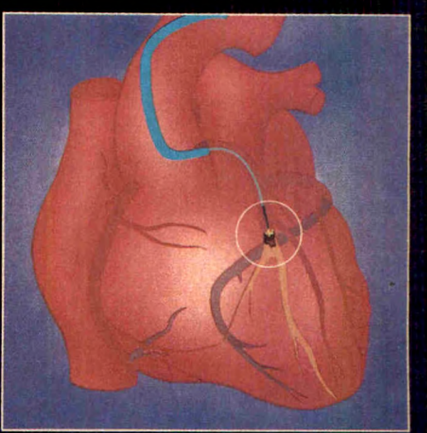
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3. Ganz, W., et al: "Intracoronary Thrombolysis in Evolving Myocardial Infarction." *American Heart Journal,* 101: 4-3, 1981.

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VOLUME 51
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CORONARY HEART DISEASE

# Exercise 2-Dimensional Echocardiography

## Quantitation of Left Ventricular Performance in Patients With Severe Angina Pectoris

MICHAEL H. CRAWFORD, MD, K. WRAY AMON, BS, and WILLIAM S. VANCE, MD

**To assess the feasibility and reproducibility of exercise 2-dimensional (2-D) echocardiography for quantitating left ventricular size and performance, 25 patients with angina pectoris due to severe coronary artery disease and 10 normal subjects were studied before and after the administration of nitroglycerin. In 18 (72%) of the 25 patients, suitable biapical 2-D echocardiograms for quantitative analysis were recorded during upright bicycle exercise. Left ventricular volume (Simpson's rule), ejection fraction (EF), and wall motion score (10 segments graded 0 to 3, normal to dyskinetic) were measured at rest, and at peak exercise (control), 30 minutes later at rest, after nitroglycerin at rest, and at peak exercise. EF increased during control exercise in the normal subjects from 57 ± 16 to 71 ± 22% ($p < 0.01$), but was unchanged in the patients during exercise before nitroglycerin. In 7 patients (39%), marked increases in EF (>0.05 units) during exercise occurred after nitroglycerin administration. The wall motion score increased significantly in the patients during control exercise, from 2.6 ± 3.4 to 5.6 ± 4.5, but was less at maximal exercise after nitroglycerin (3.4 ± 4.0, $p < 0.001$). Intra- and interobserver variability in these measurements was acceptable. Thus, quantitation of left ventricular performance during exercise by biapical 2-D echocardiography can be accomplished in a high proportion of patients with coronary artery disease (CAD) and can be used to assess the effects of therapeutic interventions.**

Recently, there has been considerable interest in echocardiography during exercise. We and others have demonstrated that the use of M-mode echocardiography during exercise to evaluate changes in left ventricular size and performance in response to various types of exercise[1] and cardiac drugs.[2,3] Mason et al[4] have detected new wall motion abnormalities on M-mode echocardiography during supine bicycle exercise in a select group of patients with CAD. Wann et al[5] applied an early 30° sector scanner in a similar group of patients to identify exercise-induced wall motion abnormalities, which corresponded in some of the patients to areas of decreased perfusion on exercise thallium scans. However, they noted a 25% incidence of falsely negative exercise echo studies, despite significant CAD. Morganroth et al[6] studied a larger group of patients with wide-angle 2-D echocardiography; this group often exhibited wall motion abnormalities during supine bicycle

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exercise, but the incidence of false-negative studies was 52%.

In studies employing exercise radionuclide angiography, the addition of quantitating global left ventricular performance has been additive to qualitative wall motion analysis and has improved sensitivity for detecting CAD.[7] We recently developed a technique for determining left ventricular volume and EF from biapical 2-D echocardiography and the EF measurements compared favorably to those by radionuclide angiography.[8] Accordingly, the purpose of this study was to evaluate the feasibility and reproducibility of determining left ventricular performance during upright bicycle exercise in patients with severe CAD and to document changes produced by the administration of nitroglycerin. Also, the observations in patients with CAD were compared to those in a group of normal subjects.

## Methods

**Subjects:** The patient population consisted of 25 men (mean age 59 years) who were evaluated because of severe angina pectoris. All were in functional class III and had a Bruce protocol treadmill exercise test positive for ≥0.1 mV of flat or downsloping electrocardiographic S-T segment depression and angina pectoris at <7 minutes of exercise. Eighteen (72%) were found to have 2-D echocardiograms suitable for analysis during upright bicycle exercise. Left heart catheterization with left ventriculography and selective coronary cineangiography were performed within 1 week of the exercise echocardiographic study. All patients had at least 1 vessel with ≥90% luminal diameter narrowing. Eleven patients had ≥50% narrowing of 3 vessels, 6 had double-vessel disease, and 1 had single-vessel disease. Thirteen of the 18 were taking propranolol and isosorbide dinitrate. Five were also taking digoxin. Due to the severity of these patients' angina, only the isosorbide dinitrate was discontinued 12 hours before the study. Ten normal men (mean age 26 years) without evidence of cardiac or other chronic disease by history, physical examination, electrocardiography, or echocardiography served as a control group.

**Study procedure:** A 2-D echocardiogram, 2-lead electrocardiogram, and blood pressure by cuff sphygmomanometer were obtained during the study as follows. First, measurements were made with the subjects at rest, sitting on the exercise bicycle. Then, the measures were repeated at each minute during symptom-limited graded upright bicycle exercise, performed on a braked bicycle ergometer with an initial work load of 150 kpm/min for 3 minutes, which was increased by 150 kpm/min at 3-minute intervals. Exercise was discontinued for 30 to 40 minutes and repeat resting measures were obtained. Then, 0.4 mg of nitroglycerin was administered sublingually and after ≥10 mm Hg decrease in systolic blood pressure, rest measurements were repeated, followed immediately by repeat exercise testing using the same exercise protocol.

**Echocardiographic technique:** Two-dimensional echocardiography was performed with a handheld transducer using our previously described upright exercise technique.[9] All subjects were studied with the apical 4-chamber and apical long-axis views using a phased array Varian V-3000 or V-3400 echocardiograph. Images were stored on 0.5-inch videotape for later playback and analysis using the Varian, microprocessor-controlled video light pen system. Measurements of end-diastolic and end-systolic volumes were made during expiration on stop-frame images of the biapical orthogonal views using Simpson's rule. This technique for estimating left ventricular size previously has been shown to consistently underestimate volume when compared with biplane cineangiography, but correlates well even in patients with marked wall motion abnormalities. Since each subject served as his own control, the volumes were not corrected by regression formulas. EF was calculated in the standard fashion and was shown in our previous study to accurately estimate biplane cineangiographic and radionuclide angiographic values.[8] An example of 1 apical view at rest and during exercise from 1 of the normal subjects is shown in Figure 1. Although endocardium can be appreciated in these stop-frame images, it must be realized that photographs of a video stop frame reproduced in a journal contain much less detail than is available on the original video recording.

Left ventricular wall motion was evaluated by 2 independent observers for 5 segments of equal arc length in each apical view (total 10 segments per subject) and scored as follows: 0 = normal, 1 = hypokinetic, 2 = akinetic, and 3 = dyskinetic as compared with the normal subject's wall motion for these same segments. The 2 observers never disagreed by more than 1 grade, and most disagreements involved the hypokinetic and normal grades. Therefore, the average score between the 2 observers was used in the final analysis.

**Statistical analysis:** Five measurement points were analyzed in each individual: initial resting measures, peak measures during the first exercise, second resting measures, resting measures after nitroglycerin administration, and peak measures during the postnitroglycerin exercise. A 2-way analysis of variance for repeated measures was employed to test for any significant differences between these 5 measurement times in all but 2 of the variables (wall motion and blood pressure). Individual mean differences were sought by the Student Newman-Keul's test based on the range. Wall motion score and blood pressure were found to have inhomogeneous variances, so a Friedman's test was used to assess significant changes in the 5 measurement points, and individual mean differences were sought by the Wilcoxon rank-sum method. The data for each measurement time are expressed as mean ± 1 standard deviation.

## Results

**Heart rate:** In the patients, the first and second resting measurements did not differ (65 ± 8 versus 60 ± 13 beats/min), but the resting value after nitroglycerin administration was significantly increased (78 ± 17 beats/min, $p < 0.01$). Heart rate increased during exercise, both before and after nitroglycerin, but there was no significant difference between the peak exercise values (103 ± 19 versus 105 ± 23 beats/min). Similar results were observed in the normal subjects, except that the exercise heart rates were faster.

**Systolic blood pressure:** There was no difference between the first and second resting measures in the patients (130 ± 13 versus 127 ± 10 mm Hg), but the resting value after nitroglycerin administration was significantly lower (114 ± 10 mm Hg, $p < 0.001$). At peak exercise systolic blood pressure had increased, but there was no significant difference in the values before and after nitroglycerin (149 ± 26 versus 157 ± 22 mm Hg). Similar results were observed in the normal subjects.

**End-diastolic volume:** In the patients, the first and second resting measurements of end-diastolic volume

did not differ (both 86 ± 32 ml), but the resting value after receiving nitroglycerin was significantly decreased (71 ± 30 ml, $p < 0.01$). The values at peak exercise were somewhat higher than the resting values, both before and after nitroglycerin, but did not differ significantly. By contrast, in the normal subjects, the values at peak exercise were significantly higher than the corresponding values at rest (106 ± 31 versus 88 ± 28 ml, $p < 0.05$) before and after nitroglycerin (97 ± 44 versus 65 ± 22 ml, $p < 0.05$). Also, peak exercise end-diastolic volume was significantly lower after nitroglycerin administration (97 ± 44 versus 106 ± 31 ml, $p < 0.05$).

**Ejection fraction:** There was no significant difference in EF in the patients at any point in the study. However, 7 patients exhibited a marked increase in EF (>0.05 units) during exercise after nitroglycerin as compared with the control exercise values (Fig. 2). EF increased markedly in the normal subjects with exercise from 57 ± 16% to 71 ± 22% ($p < 0.01$) before administration of nitroglycerin and from 58 ± 22% to 74 ± 16% ($p < 0.01$) after nitroglycerin (Fig. 3), but the postnitroglycerin values did not differ from the corresponding control values.

**Wall motion score:** The wall motion abnormality score in the patients did not differ in the 2 resting studies before nitroglycerin (2.6 ± 3.4 versus 2.6 ± 3.7). After nitroglycerin it was lower, but not significantly so (1.7 ± 2.6). The wall motion abnormality score increased at maximal exercise as compared with rest before nitroglycerin (5.6 ± 4.5 versus 2.6 ± 3.4, $p < 0.001$) and after nitroglycerin (3.4 ± 4.0 versus 1.7 ± 2.6, $p < 0.005$). However, the value at peak exercise after nitroglycerin was significantly lower than that before nitroglycerin (3.4 ± 4.0 versus 5.6 ± 4.5, $p < 0.001$) (Fig. 4). The normal subjects showed no wall motion abnormalities at rest or during exercise.

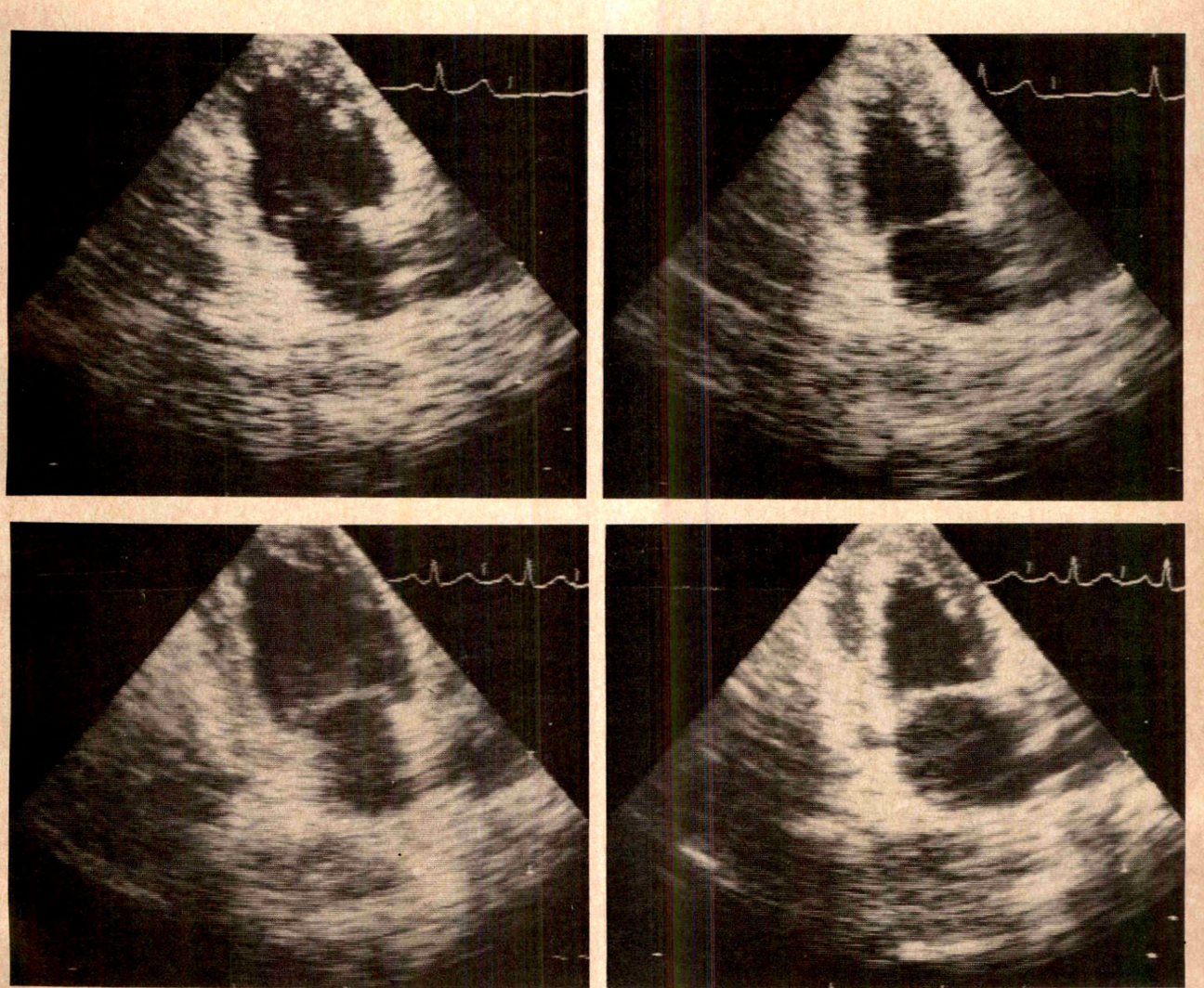


**FIGURE 1.** Apical long-axis view from a normal subject. **Top left,** end-diastole at rest; end-diastolic volume = 106 ml. **Top right,** end-systole at rest; EF = 51%. **Bottom left,** end-diastole during peak exercise; end-diastolic volume is larger than at rest at 140 ml. **Bottom right,** end-systole at peak exercise. Note the smaller end-systolic volume as compared with at rest, resulting in a higher EF of 78%.

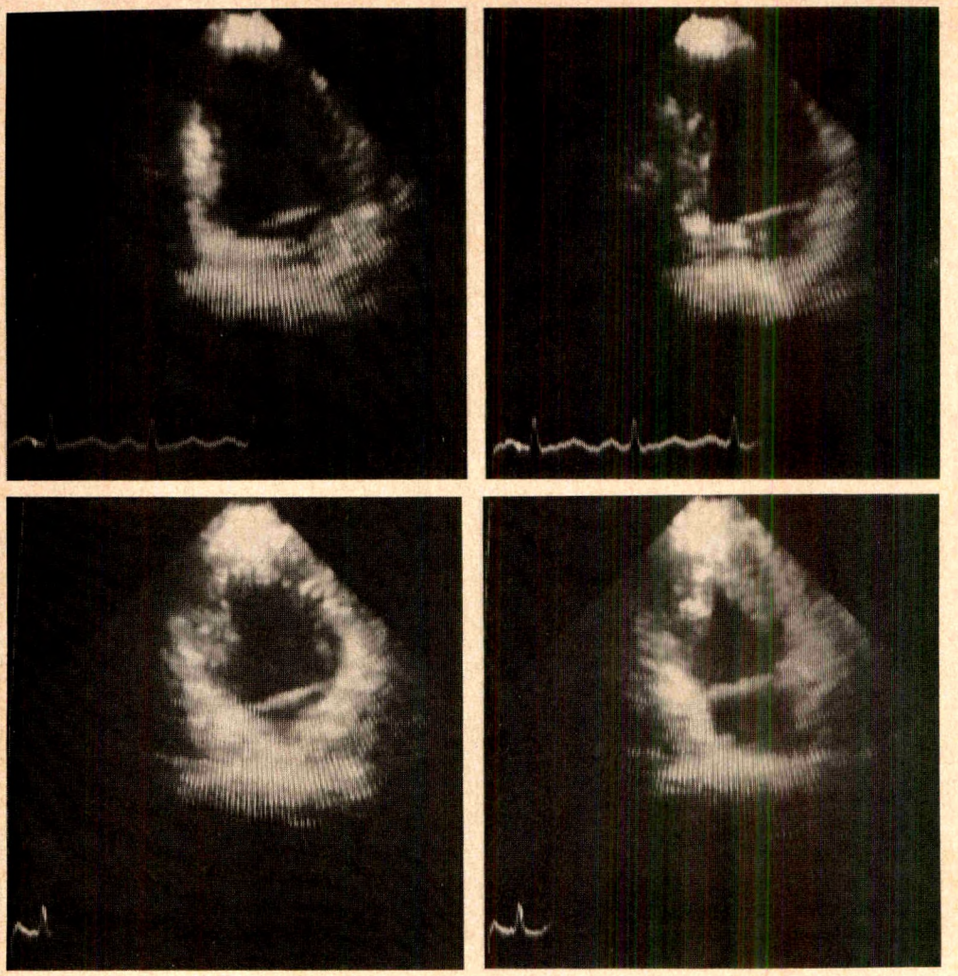


**FIGURE 2.** Apical long-axis echocardiograms during exercise from 1 patient in whom wall motion and EF improved after nitroglycerin. **Top left,** end-diastole at the peak of control exercise; end-diastolic volume = 121 ml. **Top right,** end-systole from the same cardiac cycle. Note the poor contractile effort, especially at the apex. EF = 13%, a decrease from 30% at rest. **Bottom left,** end-diastole at peak exercise after nitroglycerin administration. The end-diastolic volume has decreased to 108 ml. **Bottom right,** end-systole from the same cardiac cycle. Note the improvement in apical contraction. The EF has increased, as compared with control exercise, to 22%.

**Reproducibility:** The 2 resting control studies before and after the first exercise test made it possible to evaluate the individual reproducibility of the echo measurements from time to time by the same observer (intraobserver). The mean difference in end-diastolic volume was 8 ml, or 9% of the initial value. Wall motion classification was discordant at 9 (5%) of 170 sites, but never greater than 1 gradation and never concerning dyskinetic segments. Also, the maximal number of discordant sites in any patient was 2. In addition, because of the subjective nature of wall motion classification, 2 individuals reviewed all the studies indepen-

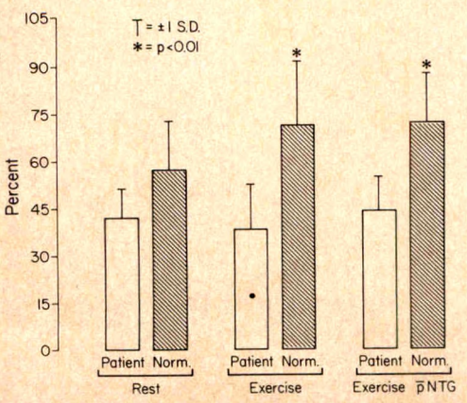



**FIGURE 3.** Mean EF at rest, during the peak of control exercise, and exercise after nitroglycerin (p̄NTG) in the patients and normal (Norm.) subjects. (See text for details.)

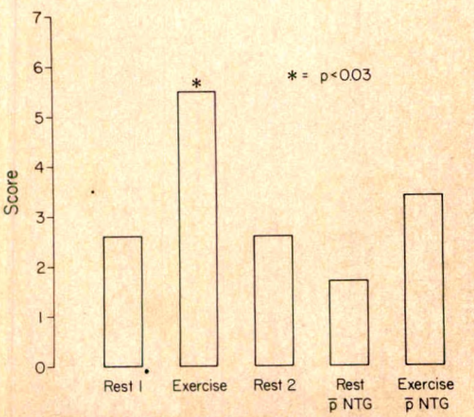



**FIGURE 4.** Mean wall motion score is depicted for each stage of the study. p̄NTG = postnitroglycerin.

dently (interobserver) and the mean number of discordant segment classification was 14% (23 of 170 segments). Again, the differences were never more than 1 grade and the exercise studies were as consistent as the resting ones. Furthermore, 4 patients consented to repeat the entire protocol in order to evaluate the intraobserver reproducibility of the echo measurements during exercise. The mean difference in end-diastolic volume on the first exercise test (control) was 8 ml and on the second (after nitroglycerin) was 4 ml. The mean difference in EF was 4% and 3%, respectively.

## Discussion

Our results demonstrate that biapical 2-D echocardiograms of sufficient quality for quantitating left ventricular global performance can be obtained during upright bicycle exercise in many patients with CAD. Our success rate of 72% for quantitative and qualitative analysis during upright exercise is similar to that of 71% by Wann et al[5] and 78% by Morganroth et al[6] for the qualitative assessment of wall motion abnormalities alone during supine exercise. Also, the 80% success rate reported by Maurer and Nanda[10] for the qualitative analysis of echoes recorded with the patient in the supine position immediately after treadmill exercise is not much better. In a previous study, we demonstrated that resting wall motion assessment by biapical 2-D echocardiography compared favorably with that by biplane cineangiography and radionuclide angiography.[11] Also, the interobserver agreement in qualitative wall motion analysis of 86% is similar to that of 95% reported by Morganroth et al[6] during supine exercise. In addition, the interobserver variability in the quantitative 2-D echocardiographic measurements of left ventricular performance at rest and on exercise are comparable to those reported for measuring left ventricular EF during exercise by radionuclide angiography.[12]

Our exercise EF results in the patients with CAD exhibit more variability than those reported in other studies using radionuclide angiographic techniques. Most studies using radionuclide angiography have shown a decrease in exercise EF, especially if the patient develops angina pectoris, as did all our patients.[13] Patients with CAD who do not have angina have been reported to show no change in EF.[14] We observed no significant difference in mean EF during exercise as compared with during rest, despite the fact that the value decreased markedly in 11 patients, because 3 showed no change and EF increased in 4. Although most radionuclide studies show an occasional patient whose EF increases with exercise, our group was unusual in that one fifth showed this response. Technical differences may explain this discrepancy. Since exercise radionuclide angiography uses only 1 view, the biplane capabilities of our 2-D echo approach may detect compensatory hyperactivity in normal segments during exercise not viewed in only 1 plane. Also, in some radionuclide studies in which first-transit techniques are used, resting studies were obtained soon after exercise—a time at which left ventricular function may be improved.[12]

EF was unchanged by nitroglycerin at rest and on exercise in both groups. The EF results in normal subjects are similar to those reported in others using radionuclide techniques,[15,16] but some studies in CAD patients have shown an improvement in exercise EF following nitrates.[16] However, these radionuclide studies used supine exercise, the results of which may differ from upright exercise, which we used. Also, these differences may represent patient population variations, since in our patients with severe CAD, only 7 showed a significant improvement in exercise EF after the administration of nitroglycerin.

The clinical utility of biapical 2-D exercise echocardiography remains in question. Although the apical approach allows for the visualization of the entire left ventricle in 2 orthogonal planes, a large area of endocardium is parallel to the sound beam. Poor endocardial images was the major limitation in the study, since our upright exercise echo technique minimizes problems with patient movement and all measurements were made during expiration when the heart is relatively stationary in the chest. By contrast, the almost 100% success rate of radionuclide angiography makes it an attractive procedure. However, echocardiographic equipment is less expensive and may be more readily available, and the lack of any potentially harmful radiation exposure makes serial studies before and after pharmacologic interventions feasible.

We believe that the addition of a quantitative assessment of left ventricular global performance, as we have described, will enhance the value of exercise echocardiography. The current study, however, was not designed specifically to assess this hypothesis, but rather to establish the feasibility and reproducibility of acquiring studies suitable for quantitative analysis. If the experience with radionuclide studies during exercise is shown to be applicable to echocardiography, then the sensitivity for detecting CAD will be increased by assessing global left ventricular performance. Also, an assessment of left ventricular function during exercise is valuable in studying symptoms in patients with known CAD, as is demonstrated in our study. All of our patients had angina and poor treadmill exercise tolerance, but in only 11 was the reduced exercise capacity due to a deterioration in left ventricular performance. In addition, nitrate administration improved exercise performance in 6 of these 11. Therefore, if further technological improvements increase the incidence of high quality studies, exercise biapical 2-D echocardiography could become an important addition to the evaluation of patients with suspected or overt CAD.

**Acknowledgment:** The advice and encouragement of Robert A. O'Rourke, MD is greatly appreciated.

## References

1. **Crawford MH, White DH, Amon KW.** Echocardiographic evaluation of left ventricular size and performance during handgrip and supine and upright bicycle exercise. Circulation 1979;59:1188–1196.
2. **Crawford MH, Lindenfeld J, O'Rourke RA, Amon KW.** Effects of oral propranolol on left ventricular size and performance during exercise and acute pressure loading. Circulation 1980;61:549–554.
3. **Crawford MH, Amon KW.** Effect of nitrate on determinants of myocardial oxygen consumption during exercise. Int J Cardiol 1982;1:229–237.

4. **Mason SJ, Weiss JL, Weisfeldt ML, Garrison JB, Fortuin NJ.** Exercise echocardiography: detection of wall motion abnormalities during ischemia. Circulation 1979;59:50–59.
5. **Wann LS, Faris JV, Childress RH, Dillon JC, Weyman AE, Feigenbaum H.** Exercise cross-sectional echocardiography in ischemic heart disease. Circulation 1979;60:1300–1308.
6. **Morganroth J, Chen CC, David D, Sawin HS, Naito M, Parrotto C, Meixell L.** Exercise cross-sectional echocardiographic diagnosis of coronary artery disease. Am J Cardiol 1981;47:20–26.
7. **Okada RD, Boucher CA, Strauss HW, Pohost GM.** Exercise radionuclide imaging approaches to coronary artery disease. Am J Cardiol 1980;46: 1188–1204.
8. **Starling MR, Crawford MH, Sorensen SG, Levi B, Richards KL, O'Rourke RA.** Comparative accuracy of apical biplane cross-sectional echocardiography and gated equilibrium radionuclide angiography for estimating left ventricular size and performance. Circulation 1981;63:1075–1084.
9. **Amon KW, Crawford MH.** Upright exercise echocardiography. J Clin Ultrasound 1979;7:373–376.
10. **Maurer G, Nanda NC.** Two-dimensional echocardiographic evaluation of exercise-induced left and right ventricular asynergy: correlation with thallium scanning. Am J Cardiol 1981;48:720–727.
11. **Sorensen S, Crawford M, Richards K, Chaudhuri T, O'Rourke R.** Noninvasive detection of ventricular aneurysm by combined two-dimensional echocardiography and radionuclide angiography. Am Heart J 1982;104: 145–152.
12. **Okada RD, Kirshenbaum HD, Kushner FG, Strauss HW, Dinsmore RE, Newell JB, Boucher CA, Block PC, Pohost GM.** Observer variance in the qualitative evaluation of left ventricular wall motion and quantitation of left ventricular ejection fraction using rest and exercise multigated blood pool imaging. Circulation 1980;61:128–136.
13. **Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS.** Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary artery disease. N Engl J Med 1977;296:839–844.
14. **Slutsky R, Karliner J, Ricci D, Schuler G, Pfisterer M, Peterson K, Ashburn W.** Response of left ventricular volume to exercise in man assessed by radionuclide equilibrium angiography. Circulation 1979;69:565–571.
15. **Sorensen SG, Ritchie JL, Caldwell JH, Hamilton GW, Kennedy JW.** Serial exercise radionuclide angiography: validation of count-derived changes in cardiac output and quantitation of maximal exercise ventricular volume change after nitroglycerin and propranolol in normal men. Circulation 1980;61:600–609.
16. **Slutsky R, Battler A, Gerber K, Gordon D, Froelicher V, Karliner J, Ashburn W.** Effect of nitrates on left ventricular size and function during exercise: comparison of sublingual nitroglycerin and nitroglycerin paste. Am J Cardiol 1980;45:831–840.

# Importance of Complete Revascularization in Performance Of the Coronary Bypass Operation

ELLIS L. JONES, MD, JOE M. CRAVER, MD, ROBERT A. GUYTON, MD, DAVID K. BONE, MD, CHARLES R. HATCHER, Jr., MD, and NORMAN RIECHWALD, PA

**Cardiac Data Bank records of 1,238 patients with triple-vessel disease (≥50% diameter reduction) who had undergone coronary bypass surgery were reviewed and divided into 2 groups depending on whether complete (n = 773) or incomplete (n = 465) revascularization had been accomplished. Patients with complete revascularization had a higher incidence of a normal preoperative electrocardiogram than did patients with incomplete revascularization (23 versus 14%, respectively, p <0.0001). The ejection fraction for both completely and incompletely revascularized patients was good (m = 0.60 and 0.57, respectively). The mean number of grafts per patient for the 2 groups was 3.8 and 2.6 (p <0.0001). There was no significant difference between the 2 groups with regard to postoperative inotropic requirements (8 and 7%), ventricular arrhythmias (1.8 and <1%), necessity for intraaortic balloon pumping (1.6 and 1.5%), hospital mortality (1.2 and 2.8%), or myocardial infarction (4.3 and 4.8%). Survival at 5 years was significantly greater (p <0.001) in patients with complete (88.5%) than in those with incomplete revascularization (83.5%). Reemployment occurred more often in patients with complete (52%) than in those with incomplete revascularization (40%) (p <0.001), and more patients were free of angina after complete (70%) than after incomplete revascularization (58%) (p <0.0005). Long-term survival appeared to be mediated primarily through improved revascularization rather than through differences in left ventricular function.**

A number of factors in the development of the coronary bypass operation have served to reduce hospital mortality, improve qualitative results, and increase long-term survival. One of these factors has been the technical ability to bypass smaller and often more diseased arteries and offer more "complete" revascularization to a progressively larger patient population. However, a comprehensive look at the effects of complete revascularization have only briefly been alluded to in the past.[1–5] Furthermore, clinical factors important in determining which patients will be candidates for complete revascularization have been infrequently discussed.

The purpose of this retrospective study is 2-fold: first, to define those clinical descriptors which influence satisfactory or unsatisfactory revascularization, and second, to define the differences in hospital mortality, perioperative complications, symptomatic improvement, and long-term survival effected by the completeness of the revascularization process.

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## Methods

Cardiac Data Bank records of 1,238 patients who underwent isolated coronary bypass surgery from January 1973 through March 1982 were retrospectively analyzed. All patients selected for this study had triple-vessel disease with ≥50% reduction in luminal diameter of the left anterior descending, the circumflex or its major branches, and the right coronary artery. Patients were classified into 1 of 2 groups on the basis of whether complete or incomplete revascularization had been performed. Complete revascularization was accomplished if any artery to those regions usually supplied by the left anterior descending, the circumflex, and the right coronary artery was bypassed. Inability to perform bypass grafting to arteries supplying 1 or more of these 3 areas was considered incomplete revascularization. For instance, when a lateral circumflex artery was bypassed (but not an obstructed posterolateral marginal branch) or when the left anterior descending artery

**TABLE I Clinical Profile and Risk Factors for Revascularization Series**

| | Revascularization | | | | |
|---|---|---|---|---|---|
| | Complete | | Incomplete | | p |
| Descriptor | n | % | n | % | Value |
| Interval (mo) most recent MI to surgery | 20 | ... | 23 | ... | NS |
| Congestive heart failure | 50/651 | 8 | 42/397 | 11 | NS |
| Systemic hypertension | 271/707 | 38 | 174/432 | 40 | NS |
| Diabetes mellitus | 106/697 | 15 | 61/429 | 14 | NS |
| Coronary event before age 55 in another family member | 198/501 | 40 | 98/274 | 36 | ... |

NS = not significant.

**TABLE II Infarction and Cardiomegaly Pattern of Revascularization Groups**

| | Revascularization | | | | |
|---|---|---|---|---|---|
| | Complete | | Incomplete | | p |
| Descriptor | n | % | n | % | Value |
| Normal ECG before surgery | 148/632 | 23 | 55/383 | 14 | <0.001 |
| ECG Q waves before surgery | | | | | |
| Anterior | 47/686 | 8 | 36/415 | 9 | <0.05 |
| Inferior | 219/686 | 32 | 157/415 | 38 | ... |
| Chest radiograph | | | | | |
| Normal | 407/526 | 77 | 274/342 | 80 | NS |
| Cardiomegaly | 98/526 | 19 | 56/342 | 16 | NS |

ECG = electrocardiogram; NS = not significant.

**TABLE III Characteristics of Left Ventricular (LV) Function**

| | Revascularization | | | | |
|---|---|---|---|---|---|
| | Complete | | Incomplete | | p |
| Descriptor | n | % | n | % | Value |
| LV wall motion* | | | | | |
| Normal | 409/768 | 53 | 193/459 | 42 | ... |
| Hypokinetic | 137/768 | 18 | 89/459 | 19 | <0.005† |
| Akinetic | 222/768 | 29 | 177/459 | 39 | ... |
| LV end-diastolic pressure >15 mm Hg at rest | 132/725 | 18 | 78/440 | 18 | NS |

* Angiographic, hypokinetic, and akinetic wall motion abnormalities present if 1 or more wall segments were so classified angiographically. † Represents the statistical difference between all 6 variables considered as a group. NS = not significant.

**TABLE IV Operative Profile**

| | Revascularization | | |
|---|---|---|---|
| Descriptor | Complete | Incomplete | p Value |
| Mean grafts/patient (n) | 3.8 | 2.6 | <0.0001 |
| Mean AoCCT/graft (min) | 11 | 13 | <0.0001 |
| Sequential or Y grafts | 218/773 (28%) | 76/465 (16%) | <0.05 |

AoCCT = aortic cross-clamp time.

**TABLE V Isolated Coronary Artery Bypass Hospital Mortality**

| | Mortality | |
|---|---|---|
| Year | n | % |
| 1973–1974 | 15/213 | 7.0 |
| 1975–1976 | 9/560 | 1.6 |
| 1977–1978 | 15/1,565 | 0.9 |
| 1979–1980 | 12/2,189 | 0.5 |
| 1981 | 14/1,216 | 1.1 |

was bypassed but a significantly obstructed diagonal branch remained ungrafted, then complete revascularization was said to have been accomplished since both the obtuse margin of the heart and anterior wall, respectively, received grafts to the area at risk.

Patients excluded from analysis were those with previous coronary bypass surgery, left ventricular aneurysm, left dominant circulation, combined operative procedures, and left main coronary artery disease, or patients who had had coronary bypass surgery within 30 days of myocardial infarction.

Systemic hypertension was defined as blood pressure elevation sufficiently severe to require antihypertensive medication at some time before cardiac catheterization. Congestive heart failure was said to be present if there was a history of dyspnea or orthopnea or if the patient had objective evidence of alveolar or interstitial pulmonary edema before catheterization. Unstable angina was defined according to the criteria of Logue et al[6] and did not require the presence of electrocardiographic ST-T changes. Pressure of cardiomegaly was determined by excessive enlargement of the cardiac silhouette on admission chest radiography.

Evaluation of left ventricular function was performed by angiographic analysis of left ventricular regional wall motion, ejection fraction (right anterior oblique), and resting end-diastolic pressure. Normal and mild impairment of segmental wall motion were treated as normal. Moderate and severe impairment were classified as abnormal.

**Operative technique:** A disposable bubble oxygenator and systemic hypothermia to 28°C nasopharangeal were used in all patients. Since 1975, patients have received propranolol therapy up to the time of surgery. Cold (4°C) potassium or potassium hyperosmolar cardioplegia has also been used since then for myocardial preservation (hyperkalemic solution: potassium chloride solution [20 mEq/liter] buffered to pH 7.40). Hyperkalemic-hyperosmolar solution (concentration in mEq/liter): potassium, 28; the bicarbonate radical, 9.3; sodium, 95.7; dextrose (50%), 3.2 ml; mannitol (15%), 200 ml with sterile water to 1,000 ml; pH 8.1; osmol = 415 mosmol at room temperature. Left ventricular filling pressure, cardiac output, and peripheral resistance are routinely monitored with a Swan-Ganz catheter. Since 1976, an uninterrupted cross-

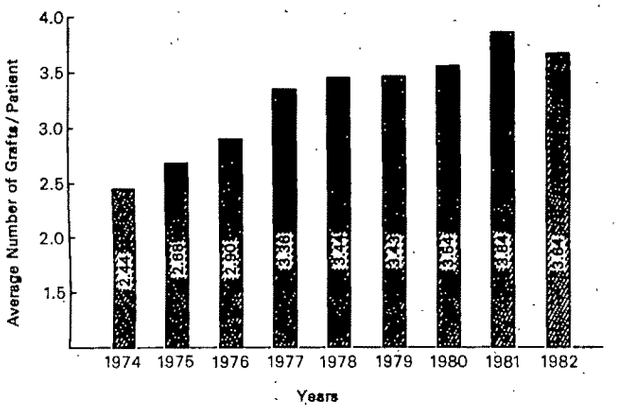



**FIGURE 1.** Relation between number of grafts per patient and year of surgery.

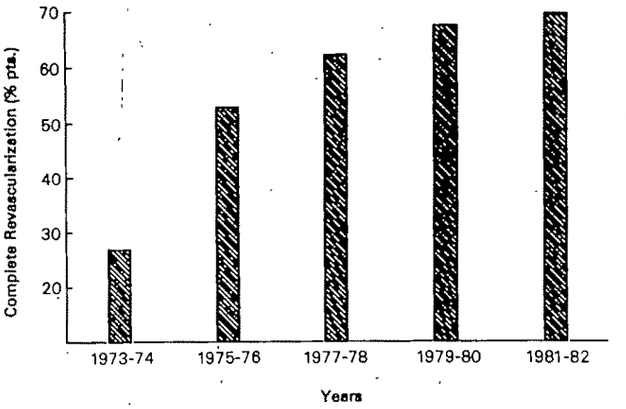



**FIGURE 2.** Frequency of complete revascularization as a function of year of surgery.

clamp technique has been used to perform all distal anastomoses. Coronary endarterectomy was not used in any patient.

**Perioperative data analysis:** Patients were classified as inotropic-dependent if they required an intravenous infusion of drugs to maintain blood pressure or adequate cardiac output after cardiopulmonary bypass. Perioperative infarction was said to have occurred if there was development of electrocardiographic new Q waves of ≥0.04-second duration. Hospital or operative mortality included any death occurring in the hospital from complications directly attributable to the operation. Survival curves were calculated by the actuarial method according to Cutter and Ederer[7] with time zero being the date of operation. Statistical differences between patient groups were determined by chi-square analysis. All survival curves depict gross and not cardiac survival.

Because of the voluminous amount of data relating to such a large patient population, the number of patients involved in any given comparison frequently varied as a function of missing data for the variables involved. Missing data were usually attributable to clinical evaluation and cardiac catheterization performed outside our medical facility.

## Results

The total series included 773 patients with complete and 465 with incomplete revascularization. The mean age of both groups of patients was 56 years, and 88% and 87% of the groups, respectively, were male.

There was no difference in the preoperative anginal pattern in the 2 groups of patients, with approximately 67% of the patients in each category having unstable angina pectoris. Approximately 50% of the patients in each category had pain at rest. The duration of angina for both groups of patients was 41 months. Risk factors such as hypertension and a history of family members aged <55 years with a past coronary event were a significant finding in both groups of patients. However, there was no statistically significant difference in the incidence of these risk factors between the 2 groups (Table I).

A higher percentage of patients with complete revascularization had a normal preoperative electrocardiogram than of those with incomplete revascularization, and the difference was statistically significant. The incidence of preoperative anterior transmural infarction in patients with incomplete revascularization was slightly higher than in those with complete revascularization. There was no significant difference in the incidence of cardiomegaly between the 2 groups (Table II).

**Catheterization profile: left ventricular function:** Angiographic analysis of left ventricular wall motion revealed that a significantly higher percentage of patients in the complete revascularization group had normal or minimally depressed contraction pattern, with a significantly higher incidence of 1 or more akinetic left ventricular wall segments in the incomplete revascularization group. There was no difference in the percentage of patients having increased resting left ventricular end-diastolic pressure (Table III). The mean ejection fraction was 0.60 for patients with complete revascularization and 0.57 for those with incomplete revascularization ($p < 0.001$). Although the difference achieved statistical significance, both values were well within normal range and the difference was not clinically significant. However, the percentage of patients with an ejection fraction <0.40 was significantly higher in the incomplete than in the complete revascularization group (10%, 44 of 436 patients; and 5.8%, 41 of 712 patients, respectively; $p < 0.005$). The incidence of mitral regurgitation (mild to moderate) was not significantly different in the 2 groups, averaging 4% (27 of 705) for the completely revascularized group and 4.7% (17 of 433) for the incompletely revascularized group.

**Operative profile:** The mean number of grafts performed per patient was significantly higher in patients with complete than in those with incomplete revascularization. In addition, the mean aortic cross-clamp time per graft was higher in those with incomplete revascularization. The greater number of grafts in the completely revascularized group was largely accomplished by using sequential grafting techniques or by taking advantage of natural Y-graft branches (Table IV). Figure 1 shows the average number of grafts per-

**TABLE VI Perioperative Complications**

| Descriptor | Revascularization: Complete n | Complete % | Incomplete n | Incomplete % | p Value |
|---|---|---|---|---|---|
| Inotropic requirements | 62/773 | 80 | 33/465 | 7.1 | NS |
| Ventricular arrhythmia requiring lidocaine treatment (in OR) | 14/773 | 1.8 | 4/465 | <1.0 | NS |
| IABP | 12/773 | 1.6 | 7/465 | 1.5 | NS |
| Hospital mortality | 9/773 | 1.2 | 13/465 | 2.8 | NS |
| New Q waves | 27/630 | 4.3 | 18/372 | 4.8 | NS |

IABP = intraaortic balloon pumping; NS = not significant; OR = operating room.

**TABLE VII Follow-Up Profile**

| Descriptor | Revascularization: Complete n | Complete % | Incomplete n | Incomplete % | p Value |
|---|---|---|---|---|---|
| Months followed after surgery | 22 | ... | 26 | | <0.005 |
| Employed before surgery | 494/626 | 78 | 294/364 | 81 | NS |
| Employed after surgery | 319/618 | 52 | 144/359 | 40 | <0.001 |
| Anginal status | | | | | |
| None | 426/610 | 70 | 206/358 | 58 | <0.0005 |
| Improved | 153/610 | 25 | 123/358 | 34 | NS |
| Same or worse | 31/610 | 5 | 29/358 | 8 | NS |

NS = not significant.

formed per patient in the years 1974 through 1982. Figure 2 shows the progressive increase in the percentage of patients receiving total revascularization throughout the years of the study. Hospital mortality by year of surgery is shown in Table V.

**Perioperative complications:** Surprisingly, there was no difference in the incidence of inotropic requirements, ventricular arrhythmias, or intraaortic balloon pumping after coronary bypass in patients with complete and incomplete revascularization. Although hospital mortality was higher in patients with incomplete than in patients with complete revascularization (2.8 versus 1.2%, respectively) this difference did not achieve statistical significance. The incidence of perioperative electrocardiographic new Q waves was slightly over 4% for the 2 groups of patients (Table VI).

**Follow-up:** Approximately 80% of patients in both groups were employed before coronary bypass surgery. However, 52% of the patients with complete revascularization were working at the time of follow-up, compared with only 40% of those with incomplete revascularization; this difference was highly statistically significant.

Of the patients with angina before surgery who had complete revascularization, a higher number were free of angina at follow-up compared with those with incomplete revascularization (70 and 58%, respectively) (Table VII). The average interval between surgery and follow-up evaluation was 22 months for those with complete and 26 months for those with incomplete revascularization.

The 5-year survival rates for patient with complete and incomplete revascularization were 88.5 and 83.5%, respectively (Fig. 3); this difference was significant ($p < 0.001$).

## Discussion

As noted by others,[1,2] the concept of complete revascularization is difficult to communicate, and therefore a regional myocardial definition has been substituted for the traditional one which required a bypass graft to every significantly obstructed coronary artery. It was felt that more importance should be given to the ability or inability to revascularize an entire region of myocardium (anterior wall, obtuse margin, or inferior surface). Clinical data obtained from patients in whom it is not possible to revascularize an entire cardiac segment should demonstrate a difference in early and late clinical results from those in whom all regions of the myocardium have been grafted. Patient with complete revascularization as defined by the traditional concept, in which every significantly obstructed artery must be bypassed, are not likely to demonstrate a significant clinical difference from those with incomplete revascularization when the only operative difference might be an unbypassed branch vessel such as the left anterior descending diagonal, a left ventricular branch of the right coronary system, or only 1 of several obtuse marginal arteries.

Classification of patients into revascularization groups at the time of surgery rather than at postoperative catheterization as reported in previous studies[3–5] was done in order to evaluate preoperative variables as predictors of future clinical performance and to obtain a sample size large enough for meaningful statistical analysis. In our patient population, only 8.7% of the

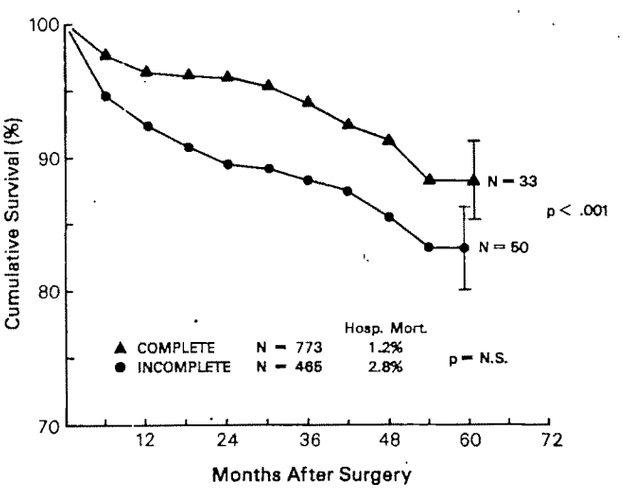



**FIGURE 3.** Actuarial survival curve (all deaths) for patients with complete and incomplete revascularization. Hosp. Mort. = hospital mortality; N.S. = not significant.

completely and 17.4% of the incompletely revascularized group had recatheterization data available for analysis. The fact that the major indication for recatheterization was recurrent ischemic symptoms precluded any meaningful conclusions based upon arteriographic studies; for this reason, such an analysis of postoperative catheterization information would have been biased and misleading.

Only patients with triple-vessel disease were included in this report. Previously reported series[1,4] included many patients with single- and double-vessel disease, and the heterogeneity of these patient populations explains many of the differences in results in the present series and others.

Incomplete revascularization has usually been attributed to myocardial fibrosis, minute vessel size, or diffuse atherosclerosis.[1] Even though the number of grafts per patients and the percentage of patients with complete revascularization has increased progressively over the years, reduction in hospital mortality is not necessarily a direct effect of these 2 factors as was previously suggested.[8] Decreases in hospital mortality and perioperative complications over the years are probably related more to improved anesthetic and surgical techniques, myocardial preservation, reduced intraoperative catastrophes (such as aortic dissection and massive intraoperative infarction), and better pharmacologic management in the postoperative period than to completeness of revascularization. This finding differs from those in previous studies.[2]

The lack of correlation between electrocardiographic evidence of postoperative myocardial damage and inability to revascularize an entire segment of myocardium suggests that perioperative infarction is related more to reperfusion injury in the area supplied by the grafted artery than to insufficient blood flow through the native circulation at the conclusion of the operative procedure.[9]

The relation between completeness of revascularization and long-term survival was found to differ from the effect of complete revascularization on hospital mortality. In the present study as well as previous reports,[1,2] 5-year survival is significantly improved in patients with complete revascularization. However, this finding differs from observations in patients assigned to revascularization status according to graft patency and freedom from new disease 1 year after surgery. When revascularization status was so defined, no difference in long-term survival could be demonstrated in patients with complete or incomplete revascularization.[3]

Several studies[2,10,11] have noted that late postoperative mortality was significantly elevated in patients with angiographic segmental wall motion abnormalities. This raises the question of whether improved long-term survival after complete revascularization in this group might be mediated primarily through better left ventricular function rather than through more extensive revascularization. As demonstrated in the present study, patients with incomplete revascularization had a high incidence of angiographic segmental wall motion abnormalities, which were probably a result of significant ventricular fibrosis and decreased segmental blood supply. However, other than depression of segmental wall motion, there was no clinical difference in left ventricular function (mean ejection fraction, left ventricular end-diastolic pressure) in patients with complete and incomplete revascularization, and therefore the mechanism of increased long-term survival was probably mediated through better revascularization. Loop et al[1] reported that patients with complete revascularization have a 5-year survival rate of approximately 94%, compared with 88% in those with incomplete revascularization. In some series in which complete revascularization was defined at the time of postoperative cardiac catheterization, the survival rate in totally revascularized patients was even higher.[3] In our own group, the lower 5-year survival rates of 88.5 and 83.5% for completely and incompletely revascularized patients can be explained by admission into the study of only patients with triple-vessel disease.

Considerable evidence supports the fact that patients who still have symptoms after coronary bypass surgery have either incomplete revascularization, graft closure, or progression of disease distal to the anastomosis.[12,13] The important relation of complete revascularization to alleviation of angina is demonstrated in the study of Cuckingnan et al.[5] Of patients with complete revascularization (all grafts patent and no new disease), 87% had no angina at the time of follow-up. In those with incomplete revascularization but all grafts patent, absence of angina was present in only 42%, further demonstrating the adverse effect of leaving a segment or region of myocardium unrevascularized. In our own series, 70 and 58% of patients with complete and incomplete revascularization (as defined) had no angina at the time of follow-up; these results agree with the findings of previous reports.[1,14]

In the present series, a retrospective analysis of employment status for patients with either complete or incomplete revascularization revealed that equal numbers of both groups were employed before surgery. However, after coronary bypass a significantly higher proportion of the patients with complete revascularization returned to work.

In summary, the definition of complete revascularization has been made according to region of myocardium perfused rather than anatomic vessel site. Ability to achieve complete revascularization was not adversely influenced by anginal pattern, duration of angina, heart failure, hypertension, diabetes, or cardiomegaly. Complete revascularization was more likely to be achieved in patients with a normal electrocardiogram preoperatively, angiographically normal left ventricular wall motion, and ejection fraction >0.40. Perioperative complications such as reduced cardiac output, ventricular ectopy, and myocardial infarction were not significantly affected by completeness of revascularization. Although hospital mortality was slightly greater in partly revascularized patients than in those with total revascularization, this difference did not achieve statistical significance. From the present study, complete revascularization was found to significantly enhance a patient's chances of returning to employment, being

angina-free, and having better long-term survival. Although the latter may be mediated through better left ventricular function in candidates for total revascularization, the observation that mean ejection fraction and resting left ventricular end-diastolic pressure did not differ significantly in the 2 groups suggests that improved long-term survival is truly accomplished by more complete myocardial revascularization. Consideration should be given to performing as many grafts as possible with the hope that regional revascularization will be preserved should there be progression of arterial disease or later graft failure.

## References


1. **Loop FD, Cosgrove DM, Lytle BW, Thurer RL, Simpfendorfer C, Taylor PC, Proudfit WL.** An 11 year evolution of coronary arterial surgery (1967–1978). Ann Surg 1979;190:444–455.
2. **Stiles QR, Lindesmith GG, Tucker BL, Hughes RK, Meyer BW.** Long-term follow-up of patients with coronary artery bypass grafts. Circulation 1976; 54: Suppl III:III-32–III-34.
3. **Vermeulen F, Alfieri O, Van Brussel B, Frey R, DeGeest R, Pieke R, Knaepen P, Schaepkens van Riempst A.** Late results of complete versus incomplete revascularization. In: Coronary Artery Disease Today. Proceedings of an International Symposium. Amsterdam: Excerpta Medica, 1982:285–295.
4. **Robert EW, Guthaner DF, Wexler L, Alderman EL.** Six-year clinical and angiographic follow-up of patients with previously documented complete revascularization. Circulation 1978;58:Suppl III:III-194–III-199.
5. **Cukingnan RA, Carey JS, Wittig JH, Brown BG.** Influence of complete coronary revascularization on relief of angina. J Thorac Cardiovasc Surg 1980;79:188–193.
6. **Logue RB, King SB, Douglas JS.** A practical approach to coronary artery disease with specific reference to coronary bypass surgery. Curr Probl Cardiol 1976;2:2–54.
7. **Cutler SJ, Ederer T.** Maximum utilization of the life-table method in analyzing survival. J Chronic Dis 1958;8:699–712.
8. **Kirklin JW, Kouchoukos NT, Blackstone EH, Oberman A.** Research related to surgical treatment of coronary artery disease. Circulation 1979;60: 1613–1618.
9. **Jones EL, Wallis TF, Craver JM, Bradford JM, Douglas JS, King SB, Bone DK, Dorney ER, Clements SD, Thompkins T, Hatcher CR.** Coronary bypass for relief of persistent pain following acute myocardial infarction. Ann Thorac Surg 1981;32:33–43.
10. **Jones EL, Craver JM, King SB, Douglas JS, Bradford JM, Brown CM, Bone DK, Hatcher CR.** Clinical, anatomic, and functional descriptors influencing morbidity, survival and adequacy of revascularization following coronary bypass. Ann Surg 1980;192:390–402.
11. **Bruschke AVG, Proudfit WL, Sones FM.** Progress study of 590 consecutive non-surgical cases of coronary disease followed 5 to 9 years. II. Ventriculographic and other correlations. Circulation 1973;47:1154–1163.
12. **Sheldon WC, Rincon G, Pichard AD, Razavi M, Cheanvechai C, Loop FD.** Surgical treatment of coronary artery disease: pure graft operations with a study of 741 patients followed 3–7 years. Prog Cardiovasc Dis 1975; 18:237–252.
13. **Siegel W, Lim HS, Proudfit WL, Sheldon WC, Loop FD.** The spectrum of exercise tests and angiographic correlation in myocardial revascularization surgery. Circulation 1975;52:Suppl I:I-156–I-62.
14. **Cannon DS, Miller DC, Shumway NE, Fogarty TJ, Daily PO, Hu M, Brown B, Harrison BC.** The long-term follow-up of patients undergoing saphenous vein bypass surgery. Circulation 1974;49:77–85.

# Antianginal Efficacy and Improved Exercise Performance With Timolol

## Twice-Daily Beta Blockade in Ischemic Heart Disease

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**Antianginal efficacy and improved exercise performance with timolol, a new beta-adrenergic blocking agent, was assessed in 23 patients with chronic stable angina pectoris in an 11-week double-blind, placebo-controlled study. Twenty-two of the 23 subjects completed the open-label phase of this investigation (weeks 0 to 6) while receiving 10 to 30 mg of timolol twice daily to optimize exercise capacity. Weekly anginal episodes and nitroglycerin consumption declined from 8.9 ± 9.1 episodes/week and 8.1 ± 10.6 tablets/week, respectively, with placebo to 2.7 ± 5.2 episodes/week and 2.6 ± 6.0 tablets/week with optimal timolol dose ($p < 0.05$). Resting heart rate (HR) and systolic blood pressure (SBP) also decreased from 75.2 ± 14.0 beats/min and 139.1 ± 15.7 mm Hg with placebo to 55.1 ± 8.9 beats/min and 130.5 ± 15.9 mm Hg with timolol ($p < 0.05$). Peak exercise HR, peak exercise SBP, and peak exercise double product (HR × SBP) were significantly ($p < 0.05$) reduced when evaluated 12 to 13 hours after administration of timolol compared with placebo (101.5 ± 21.1 beats/min versus 193.3 ± 96.2 beats/min, 161.5 ± 26.7 mm Hg versus 175.6 + 20.8 mm Hg, and 16.6 ± 5.1 × $10^{-3}$ versus 21.7 ± 5.4 × $10^{-3}$, respectively). Exercise duration was prolonged from 263.3 ± 90.2 seconds to 330.3 ± 73.9 seconds ($p < 0.05$), while time to onset of 1 mm S-T segment depression was delayed in 15 patients from 231.8 ± 86.4 seconds to 298.7 ± 68.4 seconds ($p < 0.05$).**

**During the double-blind phase (weeks 7 to 10), 8 subjects received timolol and 11 patients received placebo. Nitroglycerin consumption at weeks 8 and 10 and anginal frequency at week 8 were unchanged compared with initial placebo treatment. Resting HR, peak exercise HR, and peak exercise double product were significantly attenuated at weeks 8 and 10 in timolol patients compared with their initial placebo exposure. However, these variables were unchanged in placebo subjects compared with their initial placebo therapy. Exercise duration was again prolonged at week 8 in timolol subjects compared with initial placebo results (315.1 ± 61.2 seconds versus 261.3 ± 68.8 seconds, $p < 0.05$), but not at week 10. Placebo patients demonstrated no difference at week 8 or 10 in exercise performance compared with initial placebo treatment.**

**Timolol twice daily, therefore, is potentially useful in some patients with angina pectoris. Other patients may, however, require a shorter dose interval for optimal angina control and maximal improvement in exercise capacity.**

Beta-adrenergic blocking agents are widely used for the treatment of angina pectoris in patients with coronary heart disease, in whom their beneficial effects on symptoms and exertional capacity have been established.[1] These effects have been reported with beta-blocking agents requiring multiple daily doses[2,3] and recently with drugs of this class which can be administered only once or twice a day to attain the desired therapeutic goal in angina.[4,5] However, due to bothersome and occasionally serious adverse effects,[6] interest continues in the identification of other beta blockers requiring only once- or twice-daily administration for treatment of angina.

Timolol maleate ([-]-L-Tert-butylamino-3-[4-morpholino-1,2,5,thiodiazol-3yloxy]-L-propranolol hydrogen maleate) is a relatively new beta-adrenergic blocking agent which has demonstrated effectiveness in the treatment of mild to moderate hypertension.[7] It has a nonselective effect on beta-adrenergic receptors, little or no membrane stabilizing activity, and no intrinsic sympathomimetic activity.[8] It has a less potent intrinsic negative inotropic effect than that of pro-

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**TABLE I Patient Data**

| Case | Age (yr) & Sex | Timolol Dose BT/DB (mg) | History of MI | MI on ECG | Coronary Angiogram | CABG | Initial Treadmill AP | Initial Treadmill S-T↓ |
|---|---|---|---|---|---|---|---|---|
| 1 | 71M | 60/40 | − | − | 3 VD | + | + | + |
| 2 | 61M | 60/60 | − | − | 1 VD | − | + | + |
| 3 | 54M | 40/40 | + | IMI | 3 VD | − | + | + |
| 4 | 57M | 40/40 | − | − | 2 VD | − | + | + |
| 5 | 69M | 20/20 | − | IMI | 3 VD | − | + | + |
| 6 | 59M | 60/40 | − | − | None | − | + | + |
| 7 | 43M | 40/40 | − | IMI | 3 VD | − | + | − |
| 8 | 54M | 40/40 | + | IMI | 2 VD | + | + | + |
| 9 | 68M | 20/− | − | − | 3 VD | − | + | + |
| 10 | 49M | 40/− | + | AMI | 1 VD | − | + | + |
| 11 | 65M | 20/− | − | − | 1 VD | − | + | + |
| 12 | 57F | 20/20 | − | − | Normal | − | + | + |
| 13 | 54M | 20/− | + | − | 2 VD | + | + | + |
| 14 | 67M | 20/P | − | − | 1 VD | − | + | + |
| 15 | 64M | 20/P | + | − | 2 VD | + | + | + |
| 16 | 44M | 40/P | − | IMI | 1 VD | − | + | + |
| 17 | 54M | 40/P | + | − | 2 VD | − | + | + |
| 18 | 56M | 60/P | − | − | 3 VD | + | + | + |
| 19 | 72M | 40/P | + | − | 3 VD | − | + | + |
| 20 | 62M | 20/P | + | IMI | 3 VD | + | + | − |
| 21 | 63M | 20/P | + | − | 3 VD | + | + | + |
| 22 | 62M | 60/P | − | − | none | − | + | + |
| 23 | 50M | 40/P | − | − | 2 VD | − | + | + |

AMI = anterior myocardial infarction; AP = episode of angina pectoris; BT = best treatment, weeks 3 to 5; CABG = coronary artery bypass graft surgery; DB = double blind, weeks 8 to 10; IMI = inferior myocardial infarction; MI = myocardial infarction; P = placebo; S-T↓ = ≥1 mm S-T segment depression; 1, 2, or 3 VD = 1-, 2-, or 3-vessel coronary artery disease; + = present; − = absent.

pranolol in a dose that produces equipotent beta-adrenergic blockade.[8,9] Recently, timolol reduced long-term mortality in survivors of acute myocardial infarction.[10] Preliminary data indicate that this drug also decreases the frequency of anginal attacks and enhances exercise performance in patients with stable angina pectoris.[11,12] Little information is available, however, on the antianginal efficacy of timolol during long-term maintenance therapy.

We, therefore, evaluated the effect of 10 to 30 mg twice daily timolol upon anginal frequency and exercise capacity over a sustained time interval.

## Methods

**Patients (Table I):** The study group consisted of 23 patients (22 men and 1 woman; mean age 58.9 years, range 43 to 72) with chronic stable angina pectoris from the Cardiology Clinic, University of California, Davis, Medical Center. All subjects had exercise-induced S-T segment depression ≥1.0 mm on the electrocardiogram or significant disease defined as ≥70% narrowing of luminal diameter, or both, in at least 1 major coronary artery documented by coronary angiography. Six patients had a history of myocardial infarction only without electrocardiographic confirmation, while 5 had evidence of previous myocardial infarction on the electrocardiogram alone. Two subjects had both a history of myocardial infarction and electrocardiographic evidence of previous myocardial infarction. Seven patients had had previous coronary artery bypass graft surgery but were receiving treatment for recurrent angina. Nine had significant 3-vessel coronary artery disease, 6 had 2-vessel disease, and 4 had 1-vessel disease. Three patients did not undergo cardiac catheterization and coronary angiography but had exertional chest pain with exercise-induced S-T segment depression. One subject with angina and exercise-induced S-T segment depression (Patient 12) underwent coronary angiography for increasing chest pain after completion of the investigation. She had normal coronary arteries with normal left ventricular function and was therefore excluded from the data analysis.

Twenty-two subjects completed the first 6 weeks of the study protocol while 19 patients finished the entire 11-week investigation. Of those not completing the entire 11-week protocol, 2 were lost to follow-up, 1 discontinued because of headaches and dizziness at week 6, and 1 was removed from the study due to the development of severe hypertension.

Patients were excluded for any of the following criteria: childbearing potential, age <21 years or >75 years, resting supine diastolic blood pressure >100 mm Hg despite diuretic treatment, congestive heart failure, significant cardiomegaly, myocardial infarction within the previous 6 months, valvular or congenital heart disease, second- or third-degree atrioventricular block, Wolff-Parkinson-White syndrome, tachyarrhythmias requiring therapy, cerebrovascular accident within the past year, diabetes mellitus treated with insulin or oral hypoglycemics, bronchospasm, previous adverse reaction to beta-adrenergic blockade, neoplasm, significant renal or hepatic disease, abnormal hemoglobin, abnormal platelet count, hyperthyroidism, or treatment with digitalis, antiarrhythmic drugs, anticoagulants, rauwolfia derivatives, oral contraceptives, or psychotropic drugs.

**Study design (Table II):** The study consisted of a placebo run-in period (weeks 0 to 2), followed by an open-label dose-finding period for all patients (weeks 3 to 5) in which timolol,

**TABLE II Study Design**

| | |
|---|---|
| Weeks 0–2 | Placebo |
| Weeks 3–5 | Open-label: timolol dose titration |
| Week 6 | Down-titration |
| Weeks 7–10 | Double blind: randomization to timolol or placebo treatment |
| Week 11 | Down-titration |

10 to 30 mg twice daily, was administered to determine the optimal dose. A down-titration phase (week 6) followed with randomization to double-blind treatment with placebo or timolol twice daily (weeks 7 to 10) at the previously determined optimal dose. Medication was discontinued in all subjects during week 11 of the investigation.

During this investigation, anginal frequency and nitroglycerin consumption were recorded daily in a diary by each patient. Other than the study drug, only sublingual nitroglycerin was used to treat anginal episodes. No other antianginal medication was administered during any phase of the investigation. Patients underwent symptom-limited exercise testing at weeks 0, 2, 3, 4, 5, 6, 8, and 10. All subjects were treated with 10, 20, and 30 mg of timolol twice daily during weeks 3 to 5 to define the optimal drug dose in terms of maximizing functional capacity. If these individuals achieved a resting heart rate ≤50 beats/min before receiving the last dose level, they were continued on the previous dose of the medication. During the double-blind period of the trial, subjects received either the previously determined optimal dose of timolol or the same number of placebo tablets. Complete physical examinations were performed before entry into the investigation and at week 10. Also at these times, a complete blood count was taken and serum electrolyte measurements, routine blood chemistry determinations, urinalysis, 12-lead electrocardiogram, and chest roentgenograms were obtained.

**Treadmill exercise protocol:** Exercise testing consisted of multistage symptom-limited treadmill exercise according to the standard Bruce[13] protocol. Electrocardiograph leads I, aVF, and $V_5$ were monitored continuously and a complete 12-lead electrocardiogram was recorded every 3 minutes during the test and for 6 minutes after termination of exercise. Blood pressure was determined by sphygmomanometer before exercise, every 3 minutes during exercise, and at the end of the test. Patients were exercised to an end-point of onset of angina, or to the same intensity of angina during each test. Subjects without chest pain on subsequent treadmill testing were exercised to fatigue. All patients had at least 1 prior exposure to this type of exercise before entry into the study in an attempt to negate any habituation to the treadmill. All subjects underwent exercise testing in a fasting state 12 to 13 hours after their last dose of timolol. Parameters assessed were exercise duration, resting and exercise heart rate, resting and exercise systolic blood pressure, resting and exercise double product (heart rate × systolic blood pressure × $10^{-3}$), time to onset of 1 mm S-T segment depression, and estimated myocardial oxygen consumption.

**TABLE III Open-Label Phase: Placebo Versus Optimal Timolol Treatment**

| n = 22 | Placebo | Optimal Timolol* |
|---|---|---|
| Weekly episodes angina pectoris | 8.9 ± 9.1 | 2.7 ± 5.2 |
| Nitroglycerin use (tablets/week) | 8.1 ± 10.6 | 2.6 ± 6.0 |
| Resting HR (beats/min) | 75.2 ± 14.0 | 55.1 ± 8.9 |
| Resting SBP (mm Hg) | 139.1 ± 15.7 | 130.5 ± 15.9 |
| Exercise duration (s) | 263.2 ± 90.2 | 330.3 ± 73.9 |
| Peak exercise HR (beats/min) | 193.3 ± 96.2 | 101.5 ± 21.1 |
| Peak exercise SBP (mm Hg) | 175.6 ± 20.8 | 161.5 ± 26.7 |
| Peak exercise double product (HR × SBP × $10^{-3}$) | 21.7 ± 5.4 | 16.6 ± 5.1 |
| Time to onset 1 mm S-T↓ (s) (n = 15) | 231.8 ± 86.4 | 298.7 ± 69.9 |

* $p < 0.05$ for all of these measurements. S-T↓ = S-T segment depression.

**Statistical analysis:** Student's $t$ test for paired and nonpaired data was used to determine the statistical significance of differences in group mean data. Group data are presented as mean ± 1 standard deviation of the mean.

## Results

Twenty-three patients completed the open-label phase of the study. Nine received 20 mg timolol daily, 9 received 40 mg daily, and 5 received 60 mg daily as the optimal dose. Nineteen of 23 patients entered the double-blind treatment period and completed the entire investigation. These patients continued on the same timolol dose as in the open-label period except for Patients 1 and 6, whose doses were reduced because of HR <50 beats/min after randomization. Patient 12 was excluded from all data analysis.

**Open-label phase (Table III):** *Anginal frequency and nitroglycerin consumption:* Twenty-three patients with chronic angina were treated with timolol for 4 weeks. Weekly anginal frequency declined on optimal timolol dose from 8.9 ± 9.1 eposides/week with placebo to 2.7 ± 5.2 ($p < 0.05$) with timolol. Nitroglycerin consumption also was reduced from 8.1 ± 10.6 tablets/week with placebo to 2.6 ± 6.0 tablets ($p < 0.05$) with timolol.

*Resting hemodynamics and exercise variables:* Resting HR was significantly reduced by timolol from 75.2 ± 14.0 beats/min with placebo to 55.1 ± 8.9 beats/min with the drug ($p < 0.05$). Systolic blood pressure also declined from 139.1 ± 15.7 mm Hg with placebo to 130.5 ± 15.9 mm Hg with optimal timolol ($p < 0.05$). Timolol prolonged exercise capacity before the onset of angina in these patients from 263.2 ± 90.2 seconds with placebo to 330.3 ± 73.9 seconds with optimal timolol ($p < 0.05$). Concomitantly, peak exercise heart rate declined significantly, from 193.3 ± 96.2 beats/min to 101.5 ± 22.1 beats/min ($p < 0.05$) with timolol compared with placebo. Peak exercise SBP was lower with timolol than with placebo (161.5 ± 26.7 mm Hg versus 175.6 ± 20.8 mm Hg, $p < 0.05$). The double product (HR × SBP × $10^{-3}$) was also substantially reduced in these subjects, from 21.7 ± 5.4 with placebo to 16.6 ± 5.1 with timolol therapy ($p < 0.05$).

*S-T segment depression with exercise:* Fifteen (68%) of 22 patients manifested exercise-induced S-T segment depression while receiving both placebo and optimal dose timolol. The appearance of 1 mm S-T segment depression was delayed from 231.8 ± 86.4 seconds with placebo to 298.7 ± 69.9 seconds with timolol ($p < 0.01$). Five subjects had evidence of myocardial ischemia with placebo but not with optimal timolol. Three of these patients exercised to a higher work load while receiving timolol. Two demonstrated no S-T segment change in either period.

**Double-blind phase (Table IV):** Eighteen patients completed the double-blind phase of this investigation. Eight were randomized to timolol treatment at their previous open-label dose while 10 received placebo for this period.

*Anginal frequency and nitroglycerin consumption:* Anginal episodes did not decline at week 8 in timolol subjects (6.5 ± 8.4 episodes/week) compared with initial

**TABLE IV Double-Blind Phase: Timolol or Placebo Treatment (Weeks 8 and 10) Compared With Initial Placebo (Week 2)**

| | Group | Week 2 | Week 8 | Week 10 |
|---|---|---|---|---|
| AP/week | T | 10.4 ± 11.4 | 6.5 ± 8.4 | 6.0 ± 8.0† |
| | P | 4.0 ± 3.0 | 2.2 ± 2.1 | 3.9 ± 6.0 |
| NTG use (tablets/week) | T | 9.9 ± 13.5 | 7.3 ± 10.0 | 6.0 ± 9.5 |
| | P | 3.1 ± 3.6 | 1.9 ± 2.2 | 3.4 ± 6.1 |
| Resting HR (beats/min) | T | 81.5 ± 14.5 | 58.3 ± 10.8* | 57.6 ± 8.5† |
| | P | 73.9 ± 13.0 | 75.3 ± 11.8 | 79.8 ± 12.0 |
| Resting SBP (mm Hg) | T | 134.8 ± 21.0 | 127.5 ± 16.7 | 124.5 ± 15.4 |
| | P | 140.7 ± 10.7 | 139.1 ± 16.8 | 138.2 ± 12.1 |
| Exercise duration (s) | T | 261.3 ± 68.8 | 315.1 ± 61.2* | 302.6 ± 63.2 |
| | P | 264.4 ± 112.3 | 291.7 ± 62.6 | 277.3 ± 65.5 |
| Peak exercise HR (beats/min) | T | 121.4 ± 22.1 | 93.6 ± 15.3* | 92.6 ± 13.6† |
| | P | 127.2 ± 25.8 | 130.7 ± 19.6 | 130.3 ± 17.3 |
| Peak exercise SBP (mm Hg) | T | 174.0 ± 28.8 | 148.3 ± 30.7* | 161.8 ± 27.7 |
| | P | 174.5 ± 18.3 | 167.0 ± 18.2 | 175.0 ± 21.7 |
| Peak exercise DP (HR × SBP × $10^{-3}$) | T | 20.2 ± 7.3 | 13.9 ± 4.1* | 15.1 ± 3.9† |
| | P | 22.2 ± 4.8 | 21.9 ± 4.3 | 22.8 ± 4.1 |

* Week 2 versus 8 ($p < 0.05$); † Week 2 versus 10 ($p < 0.05$). AP = episodes of angina pectoris; DP = double product; NTG = sublingual nitroglycerin; P = placebo (n = 10); T = timolol (n = 8).

placebo treatment (10.4 ± 11.4 episodes/week, not significant [NS]). A significant reduction in anginal frequency occurred in these subjects at week 10, from 10.4 ± 11.4 episodes/week with initial placebo to 6.0 ± 8.0 episodes/week with timolol ($p < 0.05$). This lack of efficacy in group data for anginal occurrence at week 8 for timolol subjects was due mainly to 1 individual who had a marked increase in angina compared with his previous placebo treatment. Nitroglycerin consumption was unaltered at weeks 8 and 10 (7.3 ± 10.0 tablets/week and 6.0 ± 9.5 tablets/week, respectively) compared with the initial placebo phase (9.9 ± 13.5 tablets/week, NS).

Individuals randomized to placebo demonstrated no difference in weekly anginal episodes at weeks 8 and 10 (2.2 ± 2.1 episodes/week and 3.9 ± 6.0 episodes/week, respectively) compared with their initial placebo treatment (4.0 ± 3.0 episodes/week, NS). Nitroglycerin usage was also unchanged in these subjects at weeks 8 and 10 compared with initial placebo exposure (1.9 ± 2.2 tablets/week and 3.4 ± 6.1 tablets/week, respectively, versus 3.1 ± 3.6 tablets/week, NS). One of these 10 placebo subjects was omitted from statistical consideration because of unreliable diaries.

*Heart rate and blood pressure:* In patients receiving timolol resting HR was significantly reduced to 58.3 ± 10.5 beats/min at week 8 and 57.6 ± 8.5 beats/min at week 10 compared to the initial placebo treatment period of 8.5 ± 14.5 beats/min (both $p < 0.05$). Resting SBP did not differ in timolol subjects at week 8 or 10 compared with these same patients receiving placebo (127.5 ± 16.7 mm Hg and 124.5 ± 15.4 mm Hg, respectively, versus 134.8 ± 21.0 mm Hg, both NS). Placebo subjects continued at a similar HR of 75.3 ± 11.8 beats/min at week 8 and 79.3 ± 12.0 at week 10 compared with placebo treatment of 73.9 ± 13.0 beats/min (both NS). Resting SPB was also unchanged in placebo patients at weeks 8 and 10 (139.1 ± 16.8 mm Hg and 138.2 ± 12.1 mm Hg, respectively) compared with their initial placebo phase (140.7 ± 10.7 mm Hg, both NS).

*Exercise variables:* Peak exercise HR was substantially lower with timolol (93.6 ± 15.3 beats/min at week 8 and 92.6 ± 13.6 beats/min at week 10) than with placebo (121.4 ± 22.1 beats/min) (both $p < 0.05$). Placebo subjects maintained a similar exercise HR of 130.7 ± 19.6 beats/min and 130.3 ± 17.3 beats/min at weeks 8 and 10, respectively, compared with initial placebo (127.2 ± 25.8 beats/min, both NS). Peak exercise SBP was lower with timolol treatment at week 8 than with placebo (148.3 ± 30.7 mm Hg versus 174.0 ± 28.8 mm Hg, $p < 0.05$), although there was no significant difference at week 10 (161.8 ± 27.7 mm Hg and 174.0 ± 28.8 mm Hg, NS). The double product was significantly lower at weeks 8 and 10 with timolol than with placebo (13.9 ± 4.1 × $10^{-3}$ and 15.1 ± 3.9 × $10^{-3}$, respectively, versus 20.2 ± 7.3 × $10^{-3}$, $p < 0.05$). Exercise duration at week 8 continued to be improved in the timolol group (315.1 ± 61.2 seconds) compared with that in the placebo treatment phase (261.3 ± 68.8 seconds, $p < 0.05$). However, at week 10 this relation did not persist, as timolol patients' exercise duration declined to 302.6 ± 63.2 seconds, compared with 261.3 ± 68.8 seconds in the placebo treatment period (NS).

Subjects randomized to placebo treatment did not differ in exercise duration at weeks 8 or 10 (291.7 ± 62.6 seconds and 277.3 ± 65.5 seconds, respectively) compared with initial placebo treatment (264.4 ± 112.3 seconds, both NS). Peak exercise HR was similar at weeks 8 and 10 (130.7 ± 19.6 beats/min and 130.3 ± 17.3 beats/min; respectively) in these subjects compared with the initial placebo treatment phase (127.2 ± 25.8 beats/min, both NS). No difference in peak exercise SBP was observed at week 8 or 10 (167.0 ± 18.2 mm Hg and 175.0 ± 21.7 mm Hg, respectively) compared with initial placebo in these subjects (174.5 ± 18.3 mm Hg, both NS). The double product was unchanged in these patients at weeks 8 and 10 compared with initial placebo exposure (21.9 ± 4.3 × $10^{-3}$ and 22.8 ± 4.1 × $10^{-3}$, respectively, versus 22.2 ± 4.8 × $10^{-3}$, NS).

*S-T segment depression:* Fourteen subjects had at least 1 mm exercise-induced S-T segment depression until week 8. This group included 6 patients randomized to timolol and 8 randomized to placebo treatment. The appearance of 1 mm S-T segment depression was insignificantly delayed in timolol subjects at week 8 (261.7 ± 55.6 seconds) compared with their initial placebo period (224.0 ± 54.0 seconds, NS). Placebo patients had 1 mm S-T segment depression at week 8 similar to their initial placebo phase (232 ± 72.7 seconds versus 249.0 ± 106.5 seconds, NS).

*Adverse effects:* One subject had a mild macular rash during week 9 while receiving timolol. Timolol was continued until week 10 with diminution of this condition. One patient had headache and dizziness during weeks 5 and 6 and was discontinued from the study. No abnormalities in serum electrolytes, blood chemistry determinations, or complete blood count were observed at any point in this investigation.

## Discussion

Our study demonstrates the effectiveness of timolol administered twice daily in controlling objective evidence of myocardial ischemia and functional capacity in patients with chronic angina. This result was demonstrated during both the open-label and double-blind phases of this investigation. During the open-label treatment period, anginal frequency and nitroglycerin consumption decreased while exercise capacity was significantly increased compared with placebo control. There was also a reduction in peak exercise HR, in peak exercise SBP, and in the double product (an index of myocardial oxygen demand) in our subjects receiving optimal timolol dosage. Eight subjects randomized to timolol during the double-blind treatment period continued with enhanced exercise performance when first tested at week 8, although this was not maintained at week 10 when compared with placebo treatment in these patients. Reduction of peak exercise HR and double product was maintained in these subjects at weeks 8 and 10 compared with placebo treatment. Ten placebo patients continued at their previous level of exercise performance compared with initial placebo without a difference in cardiac hemodynamic function or exercise variables. Thus, these data support a significant action of timolol administered every 12 hours in the prevention of myocardial ischemia.

Our results with timolol showed a lack of significant improvement in exercise capacity at week 10, in anginal frequency at week 8, and in nitrate consumption at weeks 8 and 10. Thus, we noted a disparity at week 10 between exercise hemodynamics indicating effective beta blockade and exercise capacity. The basis for this finding is unclear but may be related to several factors. Spontaneous variability in the subjective symptom of angina may account for this observation. Another potential explanation is conversion of the exercise endpoint from angina to fatigue by the beta blocker.[14,15] This possibility is supported by the fact that 2 patients, or 25% of the timolol group, terminated exercise at week 10 because of fatigue compared with the exercise endpoint of angina at week 8. Also, some timolol subjects were exercised closer to 13 hours rather than 12 hours after the drug, which may explain in part the lack of prolongation in exercise capacity. The small number of patients randomized to the timolol treatment group may, in addition, preclude the ability to consistently detect significant differences in exercise performance. Although blood level data are not available in our subjects, compliance with the treatment program appeared satisfactory in view of the consistently significant reduction in rest and exercise peak HR and double product at weeks 8 and 10 in the treated individuals compared with the placebo group. Patients randomized to placebo demonstrated no differences in these variables at weeks 8 and 10 compared with their initial placebo phase.

Tolerance to timolol could have developed in the patients receiving this medication; this would explain the differences between exercise performance at weeks 8 and 10 in this group. This possibility is unlikely in view of similar hemodynamic changes observed in timolol subjects at week 10 compared with week 8. Also, tolerance was not observed by us in other subjects receiving timolol long-term to control mild essential hypertension[7] and is not consistent with the previous experience of multiple investigators utilizing various beta-adrenergic blockers to treat angina pectoris.[2,4]

**Absence of training effect:** The possibility of a training effect does not explain the salutary result on exercise capacity demonstrated by timolol subjects at week 8. However, a training effect, namely, a decline in resting HR and improvement in exercise performance over time with multiple episodes of treadmill exercise, does merit consideration as an explanation of our results. All of our subjects had at least 1 treadmill exercise test before entry into this study. Such acclimation to the treadmill is known to result in subsequent reproducibility of the exercise test.[16] Also, our placebo patients had no decrease in resting heart rate or significant improvement in exercise capacity from initial placebo treatment through completion of the double-blind treatment period. Thus, the presence of any training effect influencing the exercise performance of our patients is unlikely.

**Other investigations:** Our data are consistent with those of other investigators evaluating other beta-adrenergic blocking agents in angina pectoris as well as with previous observations concerning timolol.[11,12,17,18] Thus, Villa et al[19] studied 16 patients with chronic stable angina pectoris by treadmill exercise at peak drug effect in a double-blind crossover investigation. Twelve of 16 subjects had improved exercise tolerance, with an 11% increase in exercise duration and a 20% improvement in total work on timolol. Aronow et al[20] evaluated 23 patients with chronic angina pectoris in a placebo-controlled, double-blind randomized crossover study utilizing bicycle ergometry. Two hours after drug administration, timolol prolonged exercise duration 51% compared with placebo while it substantially decreased the mean maximal amount of exercise-induced ischemic S-T segment depression. Anginal frequency and nitroglycerin consumption were also significantly reduced. Again, as seen in our subjects, timolol reduced resting

HR, peak exercise HR, peak SBP, and double product. In addition, Aronow et al[21] demonstrated an increase in exercise duration of ≥25% in only 3 of 7 coronary patients with timolol when tested 12 hours after drug administration; all 7 patients in this study achieved this degree of improved exercise capacity 2 hours after drug administration. These data are concordant with our findings and suggest an effective action for twice daily timolol in the control of angina pectoris for a certain proportion of these patients.

**Adverse effects:** Beta-adrenergic blockade can produce a number of adverse effects. Few of these are potentially serious; most are bothersome and may be alleviated by adjustment in dose or drug withdrawal.[22] Timolol maleate twice daily was well tolerated in our patients. No serious adverse effects were observed. One subject experienced a macular rash during timolol treatment which resolved in 1 week with continuation of the drug. It is unclear at present whether this reaction is related to the compound. Headaches and dizziness developed in another subject during timolol treatment, and continued into the down-titration phase of the investigation (week 6) before the double-blind phase. No other patient had adverse effects thought to be drug-related.

**Conclusions:** Timolol maleate is an effective agent which can decrease anginal frequency and improve exercise capacity in patients with coronary heart disease and stable angina pectoris. This action can be demonstrated for up to 12 hours after drug administration in some subjects with chronic angina by an increased exercise capacity as well as a decrease in anginal frequency. Resting HR and SBP, peak exercise HR and SBP, and double product are significantly altered by twice-daily administration of this drug. The occurrence of myocardial ischemia as reflected by exercise-induced S-T segment depression can be delayed in some anginal patients receiving twice-daily timolol. Timolol, therefore, can be potentially useful in at least some patients for the treatment of angina pectoris when administered twice daily. However, other patients may require a more frequent dose interval for optimal control of angina pectoris and maximal improvement in exercise performance.

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## References

1. **Miller RR, Olson HG, Pratt CM, Amsterdam EA, Mason DT.** Efficacy of beta adrenergic blockade in coronary heart disease: propranolol in angina pectoris. Clin Pharmacol Ther 1975;18:598–605.
2. **Alderman EL, Davies RO, Crowley JJ, Lopes MG, Brooker JZ, Friedman JP, Graham AF, Matlof HJ, Harrison DC.** Dose response effectiveness of propranolol for the treatment of angina pectoris. Circulation 1975;51: 964–975.
3. **Thadani U, Parker JO.** Propranolol in angina pectoris: comparison of therapy given two and four times daily. Am J Cardiol 1980;46:117–123.
4. **Thadani U, Davidson C, Singleton W, Taylor SH.** Comparison of five beta-adrenoreceptor antagonists with different ancillary properties during sustained twice daily therapy in angina pectoris. Am J Med 1980;68: 243–250.
5. **Jackson G, Schwartz J, Kates RE, Winchester M, Harrison DC.** Atenolol: once daily cardioselective beta blockade in angina pectoris. Circulation 1980;61:555–560.
6. **Frishman W, Silverman R, Strom J, Elkayam U, Sonnenblick E.** Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 4. Adverse effects. Choosing a beta-adrenoreceptor blocker. Am Heart J 1979;98: 256–262.
7. **Harris FJ, Tonkin M, Pratt C, DeMaria AN, Amsterdam EA, Mason DT.** Short- and long-term therapy of mild essential hypertension with timolol. Clin Pharmacol Ther 1981;30:765–772.
8. **Scriabne A, Torchiana ML, Stauroski JM, Ludden CT, Minsker DH, Stone CA.** Some cardiovascular effects of timolol, a new β-adrenergic blocking agent. Arch Int Pharmacodyn Ther 1973;205:76–93.
9. **Graham RM, Oates HF, Weber MA, Stores GS.** Suppression of renin release by timolol. Arch Int Pharmacodyn Ther 1976;219:205–210.
10. Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801–807.
11. **Leary WP, Coleman AJ.** The treatment of angina pectoris with Blocadren® (timolol maleate, MSD). In: Magnani B, ed. Beta-Adrenergic Blocking Agents in the Management of Hypertension and Angina Pectoris. New York: Raven Press, 1974:139–146.
12. **Brallovsky D.** Timolol maleate (MK-950): a new beta-blocking agent for the prophylactic management of angina pectoris. A multicenter, multinational, cooperative trial. In Ref 11:117–137.
13. **Bruce RA.** Methods of exercise testing. Step test, bicycle, treadmill, isometrics. Am J Cardiol 1974;33:715–720.
14. **Epstein S, Robinson B, Kahler R, Braunwald E.** Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man. J Clin Invest 1965;44:1745–1783.
15. **Kannel WB, Sorlie PD.** Remission of clinical angina pectoris: the Framingham study. Am J Cardiol 1978;42:119–123.
16. **Smokler PE, MacAlpin RN, Alvardo A, Kattus AA.** Reproducibility of a multi-stage near maximal treadmill test for exercise tolerance in angina pectoris. Circulation 1973;48:346–351.
17. **Hamer J, Souton E.** Effects of propranolol on exercise tolerance in angina pectoris. Am J Cardiol 1966;18:354–360.
18. **Wolfson S, Heinle RA, Herman MV, Kemp HG, Sullivan JM, Gorlin R.** Propranolol and angina pectoris. Am J Cardiol 1966;18:345–353.
19. **Villa I, Gilles RD, Dorian WP, Burford PG.** Effects of timolol on exercise tolerance in patients with angina pectoris. In Ref 11:153–166.
20. **Aronow WS, Turbow M, VanCamp S, Curie M, Whittaker K.** The effect of timolol vs placebo on angina pectoris. Circulation 1980;61:66–69.
21. **Aronow WS, Plasencia G, Wong R, Landa D.** Exercise duration to angina at two and twelve hours after timolol. Am Heart J 1981;29:155–159.
22. **Greenblatt DJ, Koch-Weser J.** Adverse reactions to propranolol in hospitalized medical patients: a report from the Boston Collaborative Drug Surveillance Program. Am Heart J 1973;86:478–484.

# Regional Coronary Blood Flow During Relief of Pacing-Induced Angina by Nitroglycerin

## Implications for Mechanism of Action

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**The mechanism for the therapeutic effect of nitroglycerin in stress-induced angina remains controversial; it has been attributed to both increased blood supply to the ischemic myocardium and decreased myocardial oxygen demand. To investigate the contribution of each of these mechanisms, systemic pressures and great cardiac vein flow were measured in 14 patients with single-vessel disease involving the left anterior descending (LAD) coronary artery during the development of pacing-induced angina and after the administration of nitroglycerin while continuing pacing at the angina-provoking rate. Great cardiac vein flow, measured by thermodilution, represents the venous efflux from the LAD territory and therefore provided an index of flow to the poststenotic myocardium. In 11 patients, nitroglycerin was administered systemically (400 to 800 μg sublingually or 200 μg intravenously); angina was relieved in 10, concomitant with a decrease in both great cardiac vein flow (from 123 ± 29 to 98 ± 29 ml/min, $p < 0.001$) and mean aortic pressure (from 118 ± 22 to 104 ± 22 mm Hg, $p < 0.001$). In contrast, when 75 μg of nitroglycerin was administered directly into the left main coronary artery of 7 patients, it produced a small increase in great cardiac vein flow (from 108 ± 32 to 125 ± 31 ml/min, $p = 0.059$), no change in aortic pressure, and no relief of angina. This study suggests that nitroglycerin's major beneficial action in pacing-induced angina is unrelated to direct effects on the coronary circulation and is likely related to its cardiac unloading effect.**

Since Brunton[1] first attributed the antianginal effect of nitrates to decreased "arterial tension" in 1867, the mechanism of their therapeutic action has been the subject of controversy.[2] The debate has centered on the relative importance of reduced myocardial oxygen demand due to cardiac unloading[3–12] and improved myocardial blood supply due to dilation of epicardial coronary arteries (including stenotic regions),[13–18] increased collateral blood flow,[19–24] and redistribution of coronary flow toward ischemic regions.[25–27] Most studies addressing the mechanism of nitrates' action have examined systemic hemodynamic function and coronary blood flow after administration of nitroglycerin to animals with acute coronary ligations or to patients with coronary artery disease at rest; they have not generally examined the effect of nitroglycerin in patients during episodes of symptomatic ischemia. Acute coronary ligation in the dog may not be an appropriate model for stress-induced ischemia in man, and the effect of nitroglycerin on patients in the resting, asymptomatic state may not necessarily reflect the mechanism of its antianginal action. In the one classic study in which coronary blood flow *was* measured in patients after administration of nitroglycerin during episodes of angina, Ganz and Marcus[7] showed that pacing-induced angina could be relieved by intravenous but not by intracoronary nitroglycerin; unfortunately, during these interventions they measured total coronary sinus blood flow, rather than flow to the specific coronary bed that was ischemic.

To examine the mechanism of nitroglycerin's therapeutic effect in patients with stress-induced angina pectoris, it is necessary to administer nitroglycerin during an episode of angina and to determine how it affects symptoms, systemic hemodynamics, and that portion of coronary blood flow directed to the ischemic myocardium. Therefore, we produced angina by incre-

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mental atrial pacing in patients with single-vessel disease involving the proximal LAD coronary artery and administered nitroglycerin by 1 or more of 3 routes (sublingual, intravenous, and intracoronary) while continuing to pace at the angina-provoking rate. Great cardiac vein flow, representing blood flow to the poststenotic myocardium, was determined in the basal state, during pacing-induced angina, and after administration of nitroglycerin. Systemic pressure responses and great cardiac vein flow measurements were related to the symptomatic response to nitroglycerin.

## Methods

**Patient selection:** The subjects were selected from patients undergoing diagnostic cardiac catheterization and coronary angiography at the Johns Hopkins Hospital. All subjects had >50% arteriographic narrowing of the LAD coronary artery proximal to the origin of its first major diagonal branch, without significant narrowing in the right or circumflex coronary artery. Patients were excluded if they had significant valvular or congenital heart disease, previous cardiac surgery, previous myocardial infarction, congestive heart failure, cardiomegaly visible on chest roentgenography, or an abnormal resting electrocardiogram. Informed consent was obtained in each case.

**Procedure:** All patients were studied in the fasting state after premedication with diazepam, diphenhydramine, and atropine. All precatheterization medications were continued. Routine diagnostic cardiac catheterization, coronary angiography, and left ventriculography were performed using the Judkins technique. A triple thermistor thermodilution pacing catheter (Wilton Webster Laboratories, Altadena, California) was then placed through a right brachial vein incision and inserted into the coronary sinus with the distal sampling thermistor advanced to the great cardiac vein. The patient's heart rate was progressively increased by atrial pacing in increments of 10 to 20 beats/min, according to a protocol previously described.[28] Great cardiac vein flow, representing the venous efflux from the myocardium supplied by the LAD coronary artery, was determined[28–30] at rest, during pacing-induced angina, and after the administration of nitroglycerin. Phasic and mean aortic pressure and 12-lead electrocardiogram were monitored throughout. In 7 patients, 400 to 800 μg of nitroglycerin was administered sublingually during pacing-induced angina, and great cardiac vein flow was determined 1 to 3 minutes later; in 4 of these patients left ventricular pressure was monitored continuously as well. In an additional 7 patients, nitroglycerin was administered as a 75 μg bolus injection into the left main coronary artery during pacing-induced angina, and great cardiac vein flow was determined continuously for the next 30 to 60 seconds; the greatest alteration in flow was recorded. In 4 of these patients, a 200 μg dose of nitroglycerin was then rapidly injected intravenously while pacing at the same rate with persistence of angina pectoris, and great cardiac vein flow was determined 15 to 60 seconds later. Four of the patients who received intracoronary injections of nitroglycerin during pacing-induced

**TABLE 1 Effects of Systemic Nitroglycerin (NTG) on Pacing-Induced Angina**

| Patient | Location & Severity of Coronary Stenoses | GCV Flow (ml/min) At Rest | GCV Flow (ml/min) During Angina | GCV Flow (ml/min) After NTG | Aortic Pressure (mm Hg) At Rest | Aortic Pressure (mm Hg) During Angina | Aortic Pressure (mm Hg) After NTG | Did NTG Relieve Angina? |
|---|---|---|---|---|---|---|---|---|
| Sublingual Nitroglycerin, 400–800 μg | | | | | | | | |
| 1 | 99% proximal LAD* | 108 | 147 | 127 | 122/80 (100) | 136/105 (118) | 123/96 (104) | Yes |
| 2 | Total occlusion proximal LAD 30% RCA* | 34 | 69 | 58 | 150/90 (116) | 170/20 (142) | 158/100 (128) | No |
| 3 | 90% proximal LAD, 40% RCA | 51 | 150 | 134 | 135/64 (108) | 190/116 (144) | 180/110 (136) | Yes |
| 4 | 80% proximal LAD | 66 | 107 | 80 | 120/84 (100) | 130/100 (114) | 105/82 (90) | Yes |
| 5 | 60% proximal LAD | 93 | 117 | 93 | 132/70 (106) | 120/85 (104) | 110/76 (90) | Yes |
| 6 | 99% proximal LAD* | 59 | 143 | 96 | 160/80 (110) | 190/110 (150) | 150/100 (126) | Yes |
| 7 | 70% proximal LAD | 45 | 133 | 124 | 150/70 (100) | 195/95 (128) | 186/92 (123) | Yes |
| Mean | ... | 65 | 124 | 102 | 138/77 (106) | 162/102 (129) | 145/94 (114) | ... |
| SD | ... | 27 | 29 | 28 | 15/9.2 (6.2) | 32/12 (17) | 33/12 (19) | ... |
| Intravenous Nitroglycerin, 200 μg | | | | | | | | |
| 8 | 80% proximal LAD | 70 | 120 | 73 | 102/72 (84) | 100/78 (85) | 80/62 (70) | Yes |
| 9 | 90% proximal LAD, 30% LCXM | 108 | 159 | 140 | 125/65 (85) | 145/85 (105) | 135/80 (95) | Yes |
| 10 | 90% proximal LAD, 60% LAD diagonal | 58 | 126 | 84 | 160/80 (115) | 148/105 (125) | 140/90 (110) | Yes |
| 11 | 70% proximal LAD, 95% mid-LAD | 56 | 77 | 68 | 107/70 (84) | 100/75 (86) | 86/68 (76) | Yes |
| Mean | ... | 73 | 121 | 91 | 124/72 (92) | 123/86 (100) | 110/75 (88) | ... |
| SD | ... | 24 | 34 | 33 | 26/6.2 (15) | 27/14 (19) | 32/12 (18) | ... |

*Angiographically visible right to left collateral vessels. Numbers in parentheses indicate values for mean aortic pressure. GCV = great cardiac vein; LCXM = left circumflex marginal coronary artery; NTG = nitroglycerin; RCA = right coronary artery; SD = standard deviation.

**TABLE II Effects of Intracoronary Nitroglycerin on Pacing-Induced Angina**

| Patient | Location & Severity of Coronary Stenosis | GCV Flow (ml/min) At Rest | GCV Flow (ml/min) During Angina | GCV Flow (ml/min) After NTG | Aortic Pressure (mm Hg) At Rest | Aortic Pressure (mm Hg) During Angina | Aortic Pressure (mm Hg) After NTG | Did NTG Relieve Angina? |
|---|---|---|---|---|---|---|---|---|
| 8 | 80% proximal LAD | 70 | 120 | 120 | 102/72 (84) | 100/78 (85) | 95/76 (82) | No |
| 9 | 90% proximal LAD, 30% LCXM | 108 | 159 | 173 | 125/65 (85) | 145/85 (105) | 145/88 (107) | No |
| 10 | 90% proximal LAD, 60% LAD diagonal | 58 | 126 | 130 | 160/80 (115) | 148/105 (125) | 148/105 (125) | No |
| 11 | 70% proximal LAD, 95% mid LAD | 56 | 77 | 135 | 107/70 (84) | 100/75 (86) | 100/75 (86) | No |
| 12 | 90% proximal LAD | 86 | 119 | 142 | 114/75 (92) | 90/70 (78) | 90/70 (78) | No |
| 13 | 90% proximal LAD | 49 | 74 | 83 | 120/68 (92) | 115/84 (97) | 110/84 (95) | No |
| 14 | 80% proximal LAD | 68 | 79 | 91 | 122/65 (90) | 102/72 (86) | 102/72 (86) | No |
| Mean | ... | 71 | 108 | 125 | 121/71 (92) | 114/81 (95) | 113/81 (94) | ... |
| SD | ... | 20 | 32 | 31 | 19/5.5 (11) | 23/12 (16) | 24/12 (17) | ... |

Format and abbreviations as in Table I.

angina had flow measurements repeated after turning off the pacemaker (with return to baseline heart rate and complete resolution of angina) and again after a 75 μg intracoronary bolus injection of nitroglycerin at this baseline heart rate.

**Statistical analysis:** A paired-samples *t* test was used to assess changes in aortic pressure, left ventricular end-diastolic pressure (LVEDP), and great cardiac vein flow with each method of administration of nitroglycerin. All data are presented as mean ± standard deviation. Differences were considered significant when the p value was <0.05.

## Results

**Patient characteristics:** Eleven of the 14 patients were male; mean age was 54 years (range 36 to 64). All had significant narrowing of the proximal left anterior descending coronary artery (Tables I and II) without significant narrowing in other coronary arteries. Three patients had angiographically visible right to left collateral vessels.

**Effect of incremental atrial pacing:** During incremental atrial pacing, all 14 patients developed typical angina pectoris with electrocardiographic S-T segment depression; peak heart rate averaged 140 beats/min. Mean aortic pressure rose from 98 ± 11 mm Hg to 112 ± 24 mm Hg ($p = 0.01$), and great cardiac vein flow rose from 68 ± 23 to 116 ± 30 ml/min ($p < 0.001$) (Tables I and II). Eleven of the 13 patients in whom sequential flow measurements were performed demonstrated the flow limitation phenomenon we have previously described[28]: each increment in heart rate led to an increase in great cardiac vein flow until a certain point was reached; further increase in heart rate beyond that point led to no further augmentation of flow but did lead to angina and electrocardiographic signs of ischemia. In the 4 patients in whom LVEDP was measured, there was no significant change with pacing (15 ± 3.6 mm Hg at rest and 14 ± 13 mm Hg at peak heart rate).

**Effect of systemic nitroglycerin (Table I, Fig. 1):** In 10 of the 11 cases in which nitroglycerin was administered systemically (sublingually or intravenously) during pacing-induced angina, the angina was wholly or partially relieved despite continuation of atrial pacing at the same rate at which angina was produced. S-T segment depression decreased in 8 of these cases. The antianginal effect of sublingual nitroglycerin was usually

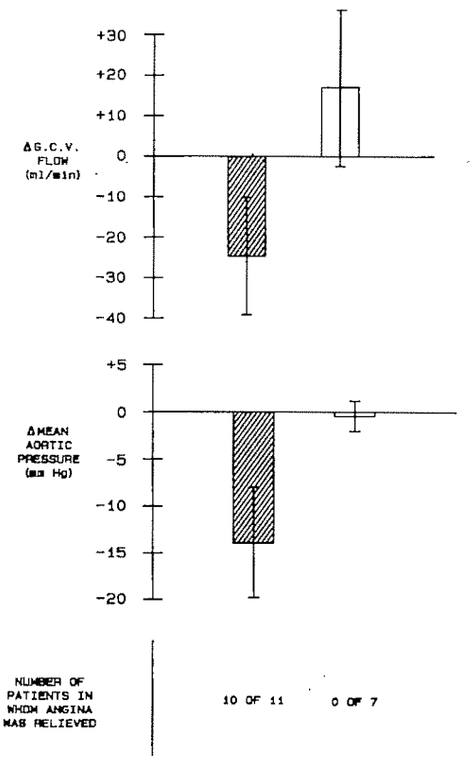



**FIGURE 1.** The effects of nitroglycerin administered during pacing-induced angina on great cardiac vein (G.C.V.) flow, mean aortic pressure, and clinical symptoms. The **hatched bars** indicate the response to systemic (sublingual or intravenous) nitroglycerin; the **open bars** indicate the response to intracoronary nitroglycerin. **Brackets** indicate standard deviations.

manifest in 1 to 3 minutes, that of intravenous nitroglycerin in 30 to 90 seconds. In every case, relief of symptoms was preceded by a fall in aortic pressure and a fall in great cardiac vein flow. In response to sublingual nitroglycerin, mean aortic pressure fell from 129 ± 17 to 114 ± 19 mm Hg ($p = 0.002$) and great cardiac vein flow fell from 124 ± 29 to 102 ± 28 ml/min ($p = 0.004$); in each of the 4 cases in which it was measured, LVEDP fell—from a mean of 14 ± 13 to 6.0 ± 5.0 mm Hg (not significant). The responses of great cardiac vein flow, aortic pressure, and LVEDP in a representative patient are illustrated in Figure 2.

In response to intravenous nitroglycerin, mean aortic pressure fell from 100 ± 19 to 88 ± 18 mm Hg ($p = 0.003$) and great cardiac vein flow fell from 121 ± 34 to 91 ± 33 ml/min ($p = 0.049$).

**Effect of intracoronary nitroglycerin (Table II, Fig. 1):** In contrast to the relief of ischemia with systemic nitroglycerin, when the drug was administered by the intracoronary route during pacing-induced angina, no patient had relief of symptoms and no patient showed improvement of ischemic changes on electrocardiography, despite a modest increase in great cardiac vein flow in most cases (108 ± 32 to 125 ± 31 ml/min, $p = 0.059$). In all cases, great cardiac vein flow returned to prenitroglycerin levels by 60 seconds after injection. There was no discernible effect of the intracoronary nitroglycerin on aortic pressure. To assess the responsiveness of these patients' coronary arteries to this dose of nitroglycerin, the same dose was administered to 4 patients (Patients 9, 11, 12, and 13) at the end of the study, after pacing had been discontinued. In these 4 patients, whose great cardiac vein flow had risen by 26 ± 22 ml/min in response to intracoronary nitroglycerin administered during peak pacing, great cardiac vein flow increased by 57 ± 29 ml/min in response to the same dose administered at the basal, nonanginal heart rate ($p = 0.009$).

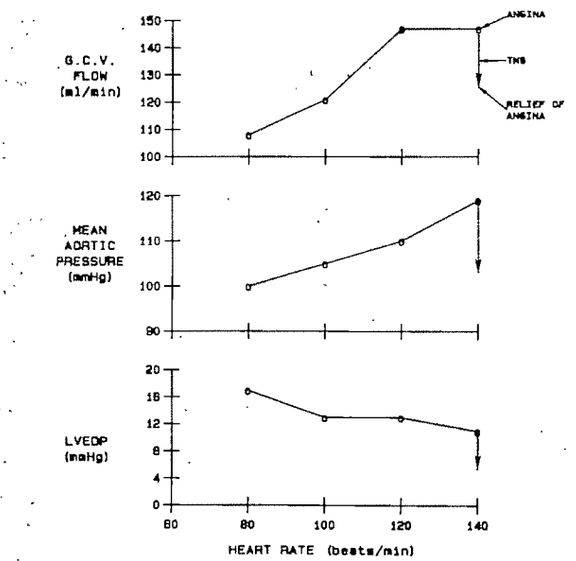



**FIGURE 2.** The effects of incremental atrial pacing and sublingual nitroglycerin (TNG) on great cardiac vein (G.C.V.) flow, mean aortic pressure, and LVEDP in a representative patient with single-vessel LAD disease. The **solid line and open circles** indicate the effects of incremental atrial pacing; note the development of flow limitation as the heart rate was increased from 120 to 140 beats/min. Angina and S-T segment changes occurred at a heart rate of 140 beats/min. The **dotted line and arrow** indicate the effects of 400 μg of nitroglycerin administered sublingually while continuing pacing at 140 beats/min: great cardiac vein flow, aortic pressure, and LVEDP decreased, and angina was relieved.

## Discussion

The present study demonstrates that (1) sublingual and intravenous nitroglycerin are capable of relieving pacing-induced angina pectoris concomitant with reductions in systemic pressure and despite reductions in blood flow to the poststenotic coronary bed, and (2) intracoronary nitroglycerin does not relieve pacing-induced angina despite a modest increase in blood flow to the poststenotic coronary bed. The use of patients with single-vessel disease is crucial, because only for such patients can one be reasonably certain in which coronary bed ischemia is occurring. The use of thermodilution flow measurements in the great cardiac vein provides a measure of the flow, both direct and collateral, to the LAD territory.[28,30–33]

The thermodilution technique enables one to measure transmural flow to the LAD territory but does not allow differentiation of regional blood flow within the LAD bed. Thus, it is possible that nitroglycerin-induced relief of angina might be associated with a relative preservation of blood flow to the subendocardium. Such an effect has been observed in dogs[12] and has been attributed to nitroglycerin's cardiac unloading effect with consequent reductions in diastolic left ventricular pressure and in intramyocardial pressure surrounding small subendocardial coronary vessels. An *absolute* increase in flow to the subendocardium seems quite unlikely, given the simultaneous decrease in perfusion pressure, myocardial demand, and transmural flow.

Although systemic hemodynamics during exercise are not identical to those during incremental atrial pacing, increased myocardial oxygen demand due to increased heart rate-blood pressure product has been implicated in the pathogenesis of angina in both situations.[34,35] Furthermore, administration of nitroglycerin in both situations leads to a reduction in systemic blood pressure.[36] Thus, it is likely, although unproven, that the results we obtained after administration of nitroglycerin during pacing-induced angina apply to most cases of exertional angina as well.

The decrease in blood flow to the poststenotic myocardium we observed after systemic administration of nitroglycerin is probably due to the combination of decreased coronary perfusion pressure and reduced myocardial oxygen demand. In spite of this decrease in flow to the poststenotic vascular territory, objective and subjective signs of ischemia were almost invariably improved. Although there are suggestions that nitroglycerin may have a direct depressant effect on myocardial metabolism[37–39] and may increase oxygen availability to the myocardium by altering the oxyhemoglobin dissociation curve,[39] reduced oxygen de-

mand due to cardiac unloading seems the most likely mechanism for its therapeutic effect.[6–8,10,11] The decrease in aortic and left ventricular pressures we observed after systemic administration of nitroglycerin are certainly compatible with decreased ventricular wall tension associated with cardiac unloading. However, other possible noncoronary effects of nitroglycerin (such as depression of oxygen demand unassociated with cardiac unloading) have not been excluded.

We have previously shown that incremental atrial pacing in patients with isolated LAD disease leads to progressive increases in great cardiac vein flow until a point of flow limitation is reached; angina and S-T segment changes occur at that point.[28] After the development of flow limitation and ischemia during incremental pacing in the present study, intracoronary nitroglycerin produced a small increase in flow to the LAD territory in most patients. This increase in flow after intracoronary nitroglycerin may be due to dilation of the coronary stenosis,[13–18] increase in collateral flow to the LAD bed, or further vasodilation in nonischemic (for example, subepicardial) regions within the LAD bed. Indeed, animal experiments have suggested that, in the presence of a critical coronary artery stenosis, some vasodilational reserve is present but that it is limited to the subepicardium.[40] Thus, it is not surprising that a moderate ability to augment transmural flow exists in patients during angina but that such augmentation is not associated with relief of the angina; presumably, it is directed principally to nonischemic regions. The failure of intracoronary nitroglycerin to relieve angina despite increased coronary flow, in other studies[7,41] as well as in ours, strongly suggests that increased perfusion of poststenotic beds does not play a major role in nitroglycerin's therapeutic action in pacing-induced angina.

The present study does not negate the fact that nitroglycerin improves both symptoms and myocardial perfusion in some cases by relieving coronary artery spasm; nor does it imply that nitroglycerin is not capable of increasing subendocardial perfusion or collateral flow under certain circumstances. However, it does suggest that nitroglycerin's major beneficial action in most cases of stress-induced angina pectoris is unrelated to direct effects on the coronary circulation and is likely related to its cardiac unloading effect.

## References


1. **Brunton TL.** On the use of nitrate of amyl in angina pectoris. Lancet 1867;2:97–98.
2. **Feldman RL, Conti CR.** Relief of myocardial ischemia with nitroglycerin: what is the mechanism? Circulation 1981;64:1098–1100.
3. **Mason DT, Braunwald E.** The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. Circulation 1965;32: 755–766.
4. **Williams JF, Glick G, Braunwald E.** Studies on cardiac dimensions in intact unanesthetized man. V. Effects of nitroglycerin. Circulation 1965;32: 767–771.
5. **Bernstein L, Friesinger GC, Lichtlen PR, Ross RS.** The effect of nitroglycerin on the systemic and coronary circulation in man and dogs. Circulation 1966;33:107–116.
6. **Mason DT, Zelis R, Amsterdam EA.** Actions of the nitrites on the peripheral circulation and myocardial oxygen consumption: significance in the relief of angina pectoris. Chest 1971;59:296–305.
7. **Ganz W, Marcus HS.** Failure of intracoronary nitroglycerin to alleviate pacing-induced angina. Circulation 1972;46:880–889.
8. **Ganz W, Marcus HS.** Changes in myocardial oxygen consumption during relief of pacing-induced angina by nitroglycerin (abstr). Am J Cardiol 1973;31:133.
9. **Burggraf GW, Parker JO.** Left ventricular volume changes after amyl nitrate and nitroglycerin in man as measured by ultrasound. Circulation 1974; 49:136–143.
10. **Greenberg H, Dwyer EM, Jameson AG, Pinkernell BH.** Effects of nitroglycerin on the major determinants of myocardial oxygen consumption. Am J Cardiol 1975;36:426–432.
11. **Fantini F, Dabizzi RP, Franchi F, Michelucci A, Padeletti L.** Hemodynamic effects of nitroglycerin. Int J Clin Pharmacol Biopharm 1979;17:449–452.
12. **Gerry JL, Schaff HV, Kallman CH, Flaherty JT.** Effects of nitroglycerin on regional myocardial ischemia induced by atrial pacing in dogs. Circ Res 1981;48:569–576.
13. **Likoff W, Kasparian H, Lehman JS, Segal BL.** Evaluation of "coronary vasodilators" by coronary arteriography. Am J Cardiol 1964;13:7–9.
14. **Feldman RL, Pepine CJ, Curry RC, Conti CR.** Coronary arterial response to graded doses of nitroglycerin. Am J Cardiol 1979;43:91–97.
15. **Brown BG, Bolson E, Petersen RB, Pierce CD, Dodge HT.** The mechanisms of nitroglycerin action: stenosis vasodilation as a major component of drug response. Circulation 1981;64:1089–1097.
16. **Macho P, Vatner SF.** Effects of nitroglycerin and nitroprusside on large and small coronary vessels in conscious dogs. Circulation 1981;64:1101–1107.
17. **Fam WM, McGregor M.** Effect of nitroglycerin and dipyridamole on regional coronary resistance. Circ Res 1968;22:649–659.
18. **Cohen MV, Kirk ES.** Differential response of large and small coronary arteries to nitroglycerin and angiotension. Circ Res 1973;33:445–453.
19. **Fam WM, McGregor M.** Effect of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia. Circ Res 1964;15:355–365.
20. **Goldstein RE, Stinson EB, Scherer JL, Seninger RP, Grehl TM, Epstein SE.** Intraoperative coronary collateral function in patients with coronary occlusive disease. Nitroglycerin responsiveness and angiographic correlations. Circulation 1974;49:298–308.
21. **Becker LC.** Effect of nitroglycerin and dipyridamole on regional left ventricular blood flow during coronary artery occlusion. J Clin Invest 1976; 58:1287–1296.
22. **Capurro NL, Kent KM, Epstein SE.** Comparison of nitroglycerin-, nitroprusside-, and phentolamine-induced changes in coronary collateral function in dogs. J Clin Invest 1977;60:295–301.
23. **Jugdutt BI, Becker LC, Hutchins GM, Bulkley BH, Reid PR, Kallman CH.** Effect of intravenous nitroglycerin on collateral blood flow and infarct size in the conscious dog. Circulation 1981;63:17–28.
24. **Bache RJ.** Effect of nitroglycerin and arterial hypertension on myocardial blood flow following acute coronary artery occlusion in the dog. Circulation 1978;57:557–562.
25. **Horwitz LD, Gorlin R, Taylor WJ, Kemp HG.** Effects of nitroglycerin on regional myocardial blood flow in coronary artery disease. J Clin Invest 1971;50:1578–1584.
26. **Cohn PF, Maddox D, Holman BL, Markis JE, Adams DF, See JR.** Effect of sublingually administered nitroglycerin on regional myocardial blood flow in patients with coronary artery disease. Am J Cardiol 1977;672–678.
27. **Mehta J, Pepine CJ.** Effect of sublingual nitroglycerin on regional flow in patients with and without coronary disease. Circulation 1978;58:803–807.
28. **Fuchs RM, Brinker JA, Maughan WL, Weisfeldt ML, Yin FCP.** Coronary flow limitation during the development of ischemia. Effect of atrial pacing in patients with left anterior descending coronary artery disease. Am J Cardiol 1981;48:1029–1036.
29. **Ganz W, Tamura K, Marcus HS, Donoso R, Toshida S, Swan HJC.** Measurements of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971;44:181–195.
30. **Pepine CJ, Mehta J, Webster WW, Nichols WW.** In vivo validation of a thermodilution method to determine regional left ventricular blood flow in patients with coronary artery disease. Circulation 1978;58:795–802.
31. **Hood WB.** Regional venous drainage of the human heart. Br Heart 1968; 30:105–109.
32. **Gensini GG, DiGiorgi S, Coskun O, Papacio A, Kelly AE.** Anatomy of the coronary circulation in living man: coronary venography. Circulation 1965;31:778–784.
33. **Roberto DR, Nakazawa HK, Klocke FJ.** Origin of great cardiac vein and coronary sinus drainage within the left ventricle. Am J Physiol 1976;230: 486–492.
34. **O'Brien KP, Higgs LN, Glancy DL, Epstein SE.** Hemodynamic accompaniments of angina: a comparison during angina induced by exercise and by atrial pacing. Circulation 1969;39:735–743.
35. **Bahler RC, Macleod CA.** Atrial pacing and exercise in the evaluation of patients with angina pectoris. Circulation 1971;43:407–419.
36. **Najmi M, Griggs DM, Kasparian H, Novack P.** Effects of nitroglycerin on hemodynamics during rest and exercise in patients with coronary insufficiency. Circulation 1967;35:46–54.
37. **Somani P, Bachand RT, Hardman HF, Laddy AR.** Nutritional circulation in the heart. II. A reappraisal of the effect of nitroglycerin on myocardial hemodynamics, oxygen consumption and nutritional blood flow in the isolated supported heart preparation. Eur J Pharmacol 1969;8:1–13.
38. **Coulson RL, Borrow KM, Rusy BF, Bove AA, Spann JF.** Direct reduction of myocardial oxygen requirement by nitroglycerin (abstr). Pharmacologist 1974;16:224.
39. **Grose GJ, Hardman HF.** Alteration in oxyhemoglobin equilibrium (P-50) and myocardial oxygen consumption (MV02) by nitroglycerin (GTN). J Pharmacol Exp Ther 1975;193:346–355.
40. **Gould KL, Lipscomb K, Calvert C.** Compensatory changes of the distal coronary vascular bed during progressive coronary constriction. Circulation 1975;51:1085–1094.
41. **Pepine CJ, Feldman RL, Conti CR.** Observations on the role of coronary artery spasm in stress-induced angina (abstr). Circulation 1980;62:Suppl III:III-312.

# Implications of Increased Myocardial Isoenzyme Level in the Presence of Normal Serum Creatine Kinase Activity

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**Although increased serum creatine kinase (CK) activity in the presence of an increased level of myocardial-specific isoenzymes (CKMB) has been strongly associated with acute myocardial infarction, the significance of an increased serum CKMB level in the presence of a normal total CK level is uncertain. In 335 consecutive patients suspected of having an acute myocardial infarction and 71 control subjects, peak serum CKMB and CK levels were correlated with the presence of other clinical criteria for acute myocardial infarction: (1) typical chest pain, (2) increased myocardial lactate dehydrogenase ($LDH_1/LDH_2$), (3) acute electrocardiographic changes (new or ST-T wave changes with evolution), and (4) an elevated CKMB level on 2 or more determinations or a typical CK curve. No control subject had an increase in CK or CKMB or any of the 4 criteria for myocardial infarction. Of the 176 subjects with normal CK and normal CKMB (Group 1), only 11% had more than a single criterion, and none had more than 2 criteria consistent with myocardial injury. In contrast, of the 83 with elevated CK and CKMB levels (Group 2), 93% had 2 or more and 81% had 3 or more of the 4 criteria. Of the 63 patients with elevated CKMB but a persistently normal CK (Group 3), 65% had 2 or more criteria for acute myocardial infarction and 77% had subendocardial electrocardiographic changes; these patients resembled those with both elevated CK and MB. The phenomenon of elevated CKMB with normal CK occurred in 20% of the patients aged ≥70 years but in only 10% of the younger group ($p < 0.01$). These findings suggest that elevated CKMB with normal CK likely represents definite myocardial injury, is more common in the elderly, and should be considered part of the spectrum of nontransmural myocardial infarction.**

The irreversible disruption of myocardial cell membranes results in the release into the serum of specific intracellular constituents, among which are CK and its isoenzymes. The application of techniques for the measurement of these myocardial enzymes of CK has enhanced the physician's ability to distinguish patients with frank myocardial injury from those with reversible ischemia or noncardiac symptoms.[1-3] The definition of unequivocal infarction has been based on an increase in the CK activity above the normal range, the simultaneous appearance of CKMB, and a characteristic disappearance curve.[4] Because it is now possible to sensitively measure CKMB, a group of patients has been identified in whom CKMB is elevated but total CK remains within normal limits.[5] The significance of this finding has not been clearly established, and it remains uncertain whether or not this represents a subtle form of myocardial injury.[1,6-8] It was hypothesized that, were this finding to represent cell death, other evidence indicative of myocardial injury should be present. Conversely, the constellation of normal CK and elevated CKMB should not occur in asymptomatic patients. The present study was undertaken to clarify the nature of the relation between these enzymatic findings and myocardial infarction.

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## Methods

**Patients:** The charts of 1,021 consecutive patients admitted to the Beth Israel Hospital between March and November 1980 in whom CK and CKMB determinations had been requested were reviewed. Patients in whom a potential noncardiac source of CK had been documented were excluded: those with seizure, trauma, intercurrent surgery, or musculoskeletal disorders. Patients with the electrocardiographic finding of left bundle branch block and without previous tracings were also excluded. All patients with the diagnosis of myocardial infarction in whom multiple enzyme determinations were available were included; 10 patients with only 1 CK measurement were not included.

Three hundred thirty-five patients comprised the study group. In all, a minimum of 3 enzyme determinations within 36 hours of admission were available; the first of these was obtained at the time of symptomatic presentation and the second was generally obtained within 12 to 18 hours of the first. Seventy-one asymptomatic patients hospitalized for elective surgery, of a similar age distribution, and with a remote history of coronary artery disease served as control subjects; these patients had at least 1 determination of cardiac enzymes while in the hospital. In each patient, the following clinical and laboratory data were obtained: age, sex, presenting symptoms, the admitting physicians' initial clinical impression, serial 12-lead electrocardiograms, admission chest

**TABLE I Clinical Characteristics***

| | Study Patients | | | | Control Patients | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group A | Group B |
| Enzyme pattern | CK−MB− | CK+MB+ | CK−MB+ | CK+MB− | CK−MB− | CK+MB+ |
| Patients (n) | 173 | 83 | 63 | 16 | 66 | 5 |
| Age (yr) | 66.7 ± 1.3 | 71.8 ± 1.2 | 75.5 ± 1.2* | 66.6 ± 3.7 | 60.2 ± 3.5 | 70.8 ± 6.8 |
| Chest pain | 94 (54%)† | 71 (86%) | 32 (51%) | 9 (56%) | 0 | 0 |
| ECG (new changes) | 29 (17%) | 72 (87%) | 41 (65%) | 8 (50%) | 0 | 0 |
| Transmural | 2 (7%) | 49 (67%) | 8 (20%) | 0 | 0 | 0 |
| Nontransmural | 27 (93%) | 24 (33%) | 33 (80%) | 8 (100%) | 0 | 0 |

* Numbers in parentheses represent percentages of the total number of patients in each group. † $p < 0.05$ versus all other groups. Age is average ±1 standard error of the mean.

CK− = creatine kinase within normal laboratory range 200 IU; CK+ = creatine kinase >200 IU; MB− = creatine kinase myocardial enzyme <6% of total (considered normal range); MB+ = creatine kinase myocardial enzyme >6%.

roentgenogram, serum glutamic oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH), and isoenzymes, as well as CK and its isoenzymes. In the text and analysis, the term *typical chest pain* is used to summarize the following general descriptions on the patient's record: ischemic pain, angina, crushing substernal pain, and substernal pressure or aching in the chest, back, or jaws with radiation into the left or both arms. All electrocardiograms were reviewed by at least one of us; the few discrepancies with official readings were settled by consensus. Evidence of transmural infarction was considered present if a new Q-wave or characteristic evolution, or both, was observed on serial tracings. Subendocardial infarction or ischemia was diagnosed if new S-T segment depression or T-wave inversion, or both, persisted for >24 hours. Nonspecific S-T segment and T-wave changes were considered significant if they represented an interval change in the electrocardiogram, were localized in distribution, and persisted for >24 hours. The interpretation of the chest roentgenogram was the official reading made by the radiology department.

Laboratory data were processed routinely in the clinical laboratory at the Beth Israel Hospital. Myocardial isoenzymes were measured with agar gel electrophoresis (Corning). Before densitometric quantification, a visual inspection of the agar plate was performed, and only those with a visible CKMB band underwent further analysis. CKMB results are reported as percentages and not in international units, because accurate measurement of international units of MB using this technique would require eluting the MB band after it is removed from the agarose plate,[9] a procedure not performed in the laboratory. A CKMB level of ≤5% is considered within normal limits. In the clinical laboratory LDH isoenzymes are quantitated routinely when the total LDH level exceeds 220 IU. In all 147 of 249 patients in Group 1 and the control group, all patients in Group 2, 55 of 63 patients in Group 3 and 18 of 21 patients in Group 4 had at least 1 LDH isoenzyme measurement. For the purposes of this study, when LDH isoenzymes were not measured it was assumed that the myocardial isoenzyme/liver isoenzyme ($LDH_1/LDH_2$) did *not* reveal evidence of myocardial necrosis. This assumption may well have resulted in the incorrect classification of some patients with myocardial injury as normal. If an estimated 15% of patients with no LDH isoenzyme determinations were assumed to have $LDH_1 \geq LDH_2$, this would have resulted in approximately 3 patients in Group 1 and 2 patients in Group 3 being reclassified on the basis of our criteria for myocardial injury (see Table III).

Results throughout are expressed as the mean ± standard error of the mean. Where statistical methods are applied, the specific test is indicated.

## Results

The study was designed to evaluate the significance of a particular enzymatic profile. The initial identification of subjects was based only on the requirement that CKMB determination had been requested by the physician and performed by our laboratory. We were therefore initially unaware of the clinical indication for the test. Patient groups were identified on the basis of the CK and CKMB levels falling within or exceeding normal limits for the laboratory. This resulted in 4 identifiable groups: Group 1 had normal CK and CKMB (CK−MB−; n = 173); Group 2 had elevated CK and CKMB (CK+MB+; n = 83); Group 3 had a normal CK and elevated CKMB (CK−MB+; n = 63); and Group 4 had elevated CK and normal CKMB (CK+MB−; n = 16).

Five patients in the control group and all Group 4 patients had CK elevation with normal MB that defied explanation on the basis of available data. These patients will not be characterized further.

Table I lists the clinical characteristics of the 4 groups and control subjects. Group 1 consisted of patients in whom infarction was clinically excluded by history, physical examination, electrocardiography, and enzymatic analysis. In contradistinction, Group 2 included patients in whom the clinician believed unequivocally that myocardial infarction had occurred. Group 3 included patients in whom the diagnosis of infarction was uncertain. This last group was significantly older than the other ($p < 0.01$, one-way analysis of variance). The incidence of typical chest pain and electrocardiographic changes consistent with transmural or nontransmural infarction was highest in Group 2 (86% and 87%, respectively). The percentage of patients with chest pain was almost identical in Group 1 and Group 3 patients, but electrocardiographic changes were much more common in Group 3 (65% versus 17%). Not surprisingly, patients in Group 2 more frequently had electrocardiographic findings compatible with a transmural event, whereas those in Group 3 had predominantly nontransmural changes. Chest pain and electrocardiographic changes were absent in the control group (Group A, Table I).

Enzymatic data are listed in Table II. In Group 2, CKMB% averaged 18 ± 5% and all other enzymatic in-

**TABLE II Enzyme Profile**

| | Study Patients | | | Control Patients: Group A |
|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | |
| Enzyme pattern | CK−MB− | CK+MB+ | CK−MB+ | CK−MB− |
| CK Peak | 73.9 ± 3.0 | 983.4 ± 96.5 | 98.0 ± 5.4 | 68.9 ± 5.3 |
| LDH Peak | 280.6 ± 15.6 | 778.3 ± 80.7 | 315.5 ± 26.9 | 309.9 ± 28.0 |
| SGOT Peak | 35.9 ± 4.8 | 125.5 ± 14.5 | 27.5 ± 3.6 | 54.3 ± 14.3 |
| $LDH_1/LDH_2$* | 2 (1%) | 66 (80%) | 12 (20%) | 0 |

* Entry indicates number of patients and percentage of the total in each group with the finding.
CK = serum creatine kinase, normal ≤200 IU/liter; LDH = serum lactate dehydrogenase activity, normal ≤220 IU/liter; $LDH_1/LDH_2$ = ratio of cardiac to liver isoenzymes of lactic dehydrogenase; MB = myocardial specific isoenzyme of DK; (+) if ≥6% of total CK; SGOT = serum glutamic oxalacetic transaminase activity, normal ≤40 IU/liter.

dexes were higher than in all other groups and the control group. In Group 3, although the peak CK total was well within normal limits, it was significantly higher than in Group I and the control group ($p < 0.05$, analysis of variance); CKMB% was 12 ± 6% in this group, a value well above the upper limits of normal (5%) in our laboratory. In Group 3, the peak CK level (98.0 ± 11.3 IU) was more than double the basal CK level (47.0 ± 9.5 IU; $p < 0.01$, paired $t$ test) measured either on admission or at discharge. These data suggest that any CKMB level >5 IU is abnormal (98.0 × 5%). Although neither total peak SGOT nor LDH effectively discriminated among control, Group 1, and Group 3 patients, 20% (12 of 63) of Group 3 patients did demonstrate reversal of LDH isoenzymes. Thus, examination of clinical and enzymatic data suggested that Group 3 represented a population with characteristics more closely resembling Group 2 than Group 1 or control patients.

To further characterize the study group and determine the occurrence of clinically significant events in this group, a set of criteria were identified other than a single elevated CK or CKMB level which most clearly differentiated patients in whom myocardial infarction had been clinically excluded (Group 1) from those in whom infarction was evident (Group 2). These criteria were typical chest pain, new electrocardiographic changes, and $LDH_1/LDH_2 \geq 1$. In order to minimize the likelihood of increased CKMB+ occurring as a random event, we also considered the presence of increased CKMB+ on more than 1 occasion or the presence of a characteristic CK curve to be a criterion. A patient could thus have a maximum of 4 positive criteria. These results are presented in Table III. Eighty-nine percent of patients in Group 1 had a maximum of a single criterion; none had more than 2 criteria. In contrast, 93% of patients in Group 2 had 2 or more criteria. Therefore, in the evaluation of Group 3, a minimum of 2 criteria were required to qualify as strong evidence for myocardial injury. Sixty-five percent of the patients in this group had 2 or more criteria. In sharp contrast, no patient in the control group had a single positive criterion.

**TABLE III Diagnostic Criteria***

| Criteria Number | Study Patients | | | Control Patients |
|---|---|---|---|---|
| | Group 1: CK−MB−† | Group 2: CK+MB+ | Group 3: CK−MB+ | Group A: CK−MB− |
| 0 | 43 | 1 | 6 | 100 |
| 1 | 46 | 6 | 29 | 0 |
| 2 | 11 | 12 | 33 | 0 |
| 3 | 0 | 27 | 24 | 0 |
| 4 | 0 | 54 | 3 | 0 |

* Diagnostic criteria = typical chest pain, new ECG changes, $LDH_1/LDH_2 \geq 1$, CKMB+ more than once or typical CK curve; maximum of 4 criteria per patient. † Percentage of total in each group with designated number of criteria.

We sought to clarify the relation between the clinical criteria for acute myocardial infarction and the peak percentage of CKMB in Group 3 patients. All the patients in Group 3 were subclassified into 4 groups based on the number of positive clinical criteria for infarction. For the patients with no criteria (n = 4), mean CKMB was 7.5 ± 0.3%, whereas those with 1 criterion (n = 16) mean CKMB was 9.6 ± 1.1%. The means for those with 2 (n = 29) and 3 (n = 13) criteria were 10.2 ± 1.5% and 13.5 ± 1.5%, respectively. In 1 patient with 4 positive criteria, peak CKMB was 29%. Although there is some overlap in the range of CKMB for the different numbers of diagnostic criteria, the mean percentage of CKMB increases as the number of positive criteria for acute infarction increases ($p < 0.05$, one-way analysis of variance).

## Discussion

In our study, patients with an enzymatic profile characterized by the presence of an elevation in CKMB on at least 1 determination without an increase in total CK above normal had a high incidence of new nontransmural electrocardiographic changes and a 20% incidence of LDH isoenzyme reversal. Laboratory evaluation often demonstrated an increase in CK to twice basal levels during the hospital course. In contrast, new electrocardiographic changes, CK fluctuations, and reversed LDH ratio were distinctly unusual in Group 1 patients and absent among control subjects. We interpret these data to indicate that patients with positive CKMB but without elevation of total CK had clinical features similar to those with transmural infarction and should be considered to have had nontransmural myocardial injury.

Reports bearing directly on such patients are scarce. D'Souza et al[10] examined a clinically similar group of patients, describing details of CK and LDH isoenzymes. In all, 24 patients were identified in whom the highest

recorded total CK was within normal limits but in whom CKMB was detected. Eleven of these patients had a reversed LDH ratio, 5 of whom had electrocardiographic evidence of nontransmural injury. In another recent study,[5] 20% of 724 consecutive patients admitted to coronary care unit for chest pain had a normal CK but elevated CKMB level utilizing a laboratory method similar to that used in our study. Of these 69 patients, 17% had electrocardiographic evidence of new transmural infarction and 28% had an LDH isoenzyme reversal, figures similar to those in our corresponding patients (20% and 20%, respectively). However, our study differs in that it was designed to determine whether patients with normal CK and elevated CKMB had a clinical and biochemical profile consistent with myocardial injury. Thus, we required only that patients have CK isoenzymes measured without prior knowledge of their clinical presentation or other objective data. On the basis of a composite measure that discriminated patients with transmural infarction from those in whom myocardial infarction was clinically excluded, Group 3 closely resembled those with myocardial infarction. It seems reasonable, therefore, to consider them as having had some myocardial necrosis.

Another aim of the study was to make a preliminary characterization of this group of patients. Group 3 patients were, on the average, older than those in other groups (Table I). Their relative senescence may have a bearing on the low incidence (51%) of presentation with typical chest pain; many patients presented with shortness of breath, syncope, weakness, or abdominal symptoms. This tendency for older patients to present in an atypical fashion has been reported in several studies.[11,12] The increased incidence of this more subtle form of injury in the elderly (20% in patients over age 70, 9% in patients under age 70) may be due to several factors: the distribution of atheromatous lesions, the presence of more abundant collateral vessels, a lower rate of of myocardial oxygen consumption or a lower basal CK activity in the elderly, and perhaps a delay in obtaining therapy because of the atypical nature of the symptoms.

In light of the paucity of information on this enzymatic profile, it seems appropriate to speculate on its place in the clinical spectrum of active coronary disease. In previous clinical descriptions, prolonged or frequent episodes of pain unresponsive to nitroglycerin and associated with localized ST-T wave changes identified patients with nontransmural necrosis.[13] In other studies, these descriptions indicated impending infarction or even a poor prognosis,[14–16] and it is likely that recent reports of positive infarct scintigrams in patients with unstable angina[17,18] include this group of patients. In a recent clinical study, Neill et al[19] performed coronary angiography in patients with coronary insufficiency at the time of hospitalization for the acute episode and 4 months later. Reversible ST-T wave changes frequently corresponded to the anatomic distribution of a severely stenosed vessel. Of 30 electrocardiographic/angiographic correlations, 9 vessels progressed to complete occlusion during the follow-up period. Taken in concert with these studies, our data seem to identify Group 3 patients as a subset of those with an acute coronary syndrome in whom nontransmural necrosis has occurred and who may be at future risk for morbid and mortal events.

In summary, in this study the patients with a CK−MB+ profile have clinical and laboratory characteristics similar to those with typical infarction and distinct from those in whom infarction is excluded. This profile often occurs in an elderly population with a relatively high incidence of atypical ischemic symptoms but with electrocardiographic changes and other laboratory data consistent with necrosis. Our data also suggest that each patient's basal level of CK serve as his reference, because an elevation to at least twice basal levels was observed in the majority of Group 3 patients, even though the maximal CK level remained normal. One may state with a fair degree of confidence that the presence of an elevated CKMB level with a normal CK level, especially in elderly patients, is frequently accompanied by several other criteria associated with myocardial infarction and should be interpreted as definite myocardial damage.

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## References

1. **Wagner GS.** Optimal use of serum enzyme levels in the diagnosis of acute myocardial infarction. Arch Intern Med 1980;140:317–318.
2. **Grande P, Christiansen C, Pedersen A, Christensen MS.** Optimal diagnosis in acute myocardial infarction: a cost effectiveness study. Circulation 1980;61:723–728.
3. **Roberts R, Gowda KS, Ludbrook PA, Sobel BE.** Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction. Am J Cardiol 1975;36:433–437.
4. **Sobel BE, Shell WE.** Serum enzyme determinations in the diagnosis and assessment of myocardial infarction. Circulation 1972;45:471–480.
5. **Dillon MC, Calbreath DF, Dixon AM, Rivin BE, Roark SF, Ideker RE, Wagner GS.** Diagnostic problem in acute myocardial infarction: CK-MB in the absence of abnormally elevated total creatine kinase levels. Arch Intern Med 1982;142:33–38.
6. **Strauss HD, Roberts R.** Plasma MB creatine kinase activity and other conventional enzymes: comparison in patients with chest pain and tachyarrhythmias. Arch Intern Med 1980;140:336–339.
7. **Irvin RG, Cobb FR, Roe CR.** Acute myocardial infarction and MB creatine phosphokinase: relationship between onset of symptoms of infarction and appearance and disappearance of enzyme. Arch Intern Med 1980;140: 329–334.
8. **Przyjemski CJ.** Prognosis after hospitalization for suspected myocardial infarction. N Engl J Med 1980;303:1364.
9. **Navin TR, Hagen DW.** Creatine kinase MB isoenzyme in the evaluation of myocardial infarction. Curr Probl Cardiol 1979;3:7–32.
10. **D'Souza JP, Stne HE, Horvitz RA, Kubasik NP, Brody BB, Barold SS.** The significance of the MB isoenzyme in patients with acute cardiovascular disease with a normal or borderline total CPK activity. Clin Biochem 1978;11:204–209.
11. **Uretsky BF, Farquhar DS, Berezin AF, Hood WB Jr.** Symptomatic myocardial infarction without chest pain: prevalence and clinical course. Am J Cardiol 1977;40:498–503.
12. **Latting CA, Silverman MA.** Acute myocardial infarction in hospitalized patients over age 70. Am Heart J 1980;100:311–318.
13. **Madias JE, Gorlin R.** The myth of acute "mild" myocardial infarction. Ann Intern Med 1977;86:347–352.
14. **Fischl SJ, Herman MV, Gorlin R.** The intermediate coronary syndrome. Clinical, angiographic and therapeutic aspects. N Engl J Med 1973;288: 1193–1198.
15. **Harris PJ, Lee KL, Harrell FE, Behar VS, Rosati RA.** Outcome in medically treated coronary artery disease. Ischemic events: nonfatal infarction and death. Circulation 1980;62:718–725.
16. **Gazes PC, Mobley EM Jr, Faris HM Jr, Duncan RC, Humphries GB.** Preinfarctional (unstable) angina. A prospective study. Ten year follow-up. Prognostic significance of electrocardiographic changes. Circulation 1973;43:331–336.
17. **Jaffe AS, Klein MS, Patel BR, Siegel BA, Roberts R.** Abnormal technitium-99m pyrophosphate images in unstable angina: ischemia versus infarction? Am J Cardiol 1979;43:1035–1038.
18. **Olson HG, Lyons KP, Aronow WS, Stinson PI, Kuperus J, Waters HJ.** The high-risk angina patient. Identification by clinical features, hospital course, electrocardiography and technetium-99m stannous pyrophosphate scintigraphy. Circulation 1981;64:674–683.
19. **Neill WA, Wharton TP Jr, Fluri-Lundeen J, Cohen IS.** Acute coronary insufficiency—coronary occlusion after intermittent ischemic attacks. N Engl J Med 1980;302:1157–1162.

# Spectrum of Global Left Ventricular Responses to Supine Exercise

## Limitation in the Use of Ejection Fraction in Identifying Patients With Coronary Artery Disease

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**Left ventricular function was evaluated with rest and supine bicycle exercise-multigated blood pool scans in 53 patients who had previously undergone coronary angiography for evaluation of a chest pain syndrome. There were 21 normal patients (<25% stenosis in any coronary artery, left ventricular end-diastolic pressure ≤12 mm Hg, and normal left ventriculography) and 32 patients with coronary artery disease (CAD) (>50% narrowing in 1 or more major coronary arteries). Thirty-two (60%) were receiving propranolol at the time of the study. The normal patient group had a significant increase in mean ejection fraction (EF) during exercise (+0.08 ± 0.09), while the CAD group had no increase (0 ± 0.11; p <0.05). Mean end-systolic volume decreased significantly in the normal group (−5 ± 8 ml/m$^2$) but demonstrated no significant change in the CAD group (1 ± 12 ml/m$^2$; p <0.05 compared with normal patients). There was no significant change in mean end-diastolic volume in either group. Mean ejection rate, mean peak systolic pressure/end-systolic volume ratio, and mean pulmonary blood volume ratio also differed in the normal versus CAD patients. Despite mean differences, there was considerable overlap in both groups of individual EF responses: 8 of 21 (38%) of the normal group did not have an increase in EF of 0.05 with exercise, while 15 of 32 (47%) of the CAD group did have an increase in EF of 0.05 with exercise. However, the addition of peak systolic pressure/end-systolic volume ratio and pulmonary blood volume (exercise/rest) ratio improved the sensitivity for detecting CAD from 53 to 84% without adversely affecting specificity. Thus, there is a wide spectrum of left ventricular EF responses to supine exercise. In our patient population, EF alone was an insensitive and nonspecific marker of CAD. The addition of other parameters of global left ventricular function, which may be generated using radionuclide angiography, helps distinguish patients with CAD from normal subjects.**

Radionuclide blood pool imaging offers a noninvasive means of assessing left ventricular function at rest and during maximal exercise. The adequacy of left ventricular function during exercise has been proposed as a reliable method for identifying patients with CAD.[1-13] Although this measurement assesses the adequacy of the coronary circulation only indirectly, it appears to have diagnostic value because many patients with significant coronary stenosis have an impaired left ventricular contractile response to exercise compared with normals. The ejection fraction is the most widely used objective measure of left ventricular contractile function because it is easily and accurately measured.[14,15] Normal patients reportedly have an increase in EF during exercise of ≥0.05.[5] However, because it is a ratio of 2 physiologic parameters, stroke volume and end-diastolic

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volume; because it may be affected by changes in heart rate, preload, or afterload; and because exercise is a complex intervention, changes in EF alone may not completely define the adequacy of left ventricular performance during exercise stress.[16,17] Although EF is often the only parameter quantitated during exercise-multigated blood pool scanning, its relation to the presence of coronary disease has not been clarified. Furthermore, other parameters of global left ventricular function may be derived, such as ejection rate,[2] end-diastolic volume,[3,4,9] the ratio of peak systolic pressure to end-systolic volume,[11] and pulmonary blood volume ratio,[6] and their usefulness in relation to EF in the evaluation of CAD has not been clearly defined. In this study, the changes in left ventricular EF during supine bicycle exercise were compared with changes in end-diastolic volume, end-systolic volume, and pulmonary blood volume ratio in patients with or without CAD. The data help to clarify the changes in global left ventricular function to be anticipated in patients with coronary disease.

## Methods

**Patient population:** Fifty-three patients undergoing cardiac catheterization for a stable chest pain syndrome had rest and exercise-multigated blood pool scanning.[12] Patients with unstable or refractory angina pectoris, congestive heart failure, or left ventricular aneurysm were excluded. Twenty-one patients with <25% stenosis measured in at least 2 angiographic projections in all coronary vessels and with left ventricular end-diastolic pressure ≤12 mm Hg at rest were defined as normal; this group was comprised of 10 males and 11 females with a mean age of 47 ± 12 years (mean ± 1 standard deviation). None had mitral valve prolapse. Thirty-two patients with >50% diameter luminal narrowing measured in at least 2 angiographic projections in 1 or more major coronary vessel were defined as having CAD and included 26 males and 6 females with a mean age of 53 ± 9 years. Four patients had single-vessel disease, 16 double-vessel disease, and 12 triple-vessel disease. Eleven patients had a documented previous myocardial infarction. Thirty-two patients were receiving propranolol and included 8 of 21 (38%) normal and 24 of 32 (75%) CAD patients. Propranolol was not routinely discontinued before exercise because of reluctance of the patients' physicians in our institution. Nitrates were withheld for 4 hours before the performance of the stress test. No patient was receiving digoxin.

**Scan acquisition:** Each patient was given an intravenous injection of stannous pyrophosphate (Pyrolite, New England Nuclear, North Billerica, Massachusetts) followed within 30 minutes with 20 mCi of technetium-99m pertechnetate for in vivo labeling of the red blood cells.[18] After 10 minutes of tracer equilibration, supine multigated blood pool images were acquired in the anterior and the left anterior oblique view for optimal visualization of the interventricular septum. An Ohio Nuclear Series 420 Anger Camera with a medium sensitivity all-purpose parallel hole collimator (Technicare, Cleveland, Ohio) interfaced to a computer (MUGA-CART, Medical Data Systems, Ann Arbor, Michigan) was used for image acquisition and data analysis. Images were recorded in 14 frames from the end of diastole through two thirds of the cardiac cycle and approximately 200,000 counts were obtained in each frame.

**Exercise protocol:** Supine exercise studies were performed with a bicycle ergometer table (Engineering Dynamic, Lowell, Massachusetts) during continuous 12-lead electrocardiographic monitoring (Hewlett Packard, Waltham, Massachusetts). Exercise was begun at a pedal speed of 50 rpm and a work load of 150 kpm/min and increased by 150 kpm/min every 3 minutes to a symptom-limited maximum (fatigue, shortness of breath, or angina). Images were obtained in the left anterior oblique projection starting 1 minute after each exercise level was begun and continued until approximately 200,000 counts/frame were acquired (1.5 to 2 minutes). Heart rate and blood pressure were recorded at each exercise level. The maximal heart rate was expressed as a fraction of the predicted maximal heart rate to be anticipated based on patient age (220 minus age). A significant abnormal electrocardiographic response to exercise was ≥1 mm of horizontal S-T segment depression, 0.08 second after the J point.

**Catheterization data:** Each patient underwent routine cardiac catheterization which included right- and left-sided pressure measurements, selective coronary arteriography, and radiographic contrast left ventriculography. Coronary angiograms were reviewed by 2 observers and disagreements settled by consensus. Coronary stenoses were measured using calipers in relation to the proximal normal-appearing segment in 2 or more angiographic projections. Greater than 50% narrowing in any vessel was considered to be significant stenosis.

**Ejection fraction analysis:** EF was determined from the rest and peak exercise left anterior oblique images. A semiautomated edge detection algorithm was used to determine counts within the left ventricular region of interest (Medical Data Systems, MUGE Program). EF was the difference between background-corrected end-diastolic and end-systolic counts divided by end-diastolic counts. EF was reported as the average of 2 separate determinations. Previous data from our laboratory indicate that the intraobserver variability for EF (±2 standard deviations) is ±6% at rest, ±9% with exercise, and ±11% for the change between rest and exercise.[18] In this study, the EF was determined by 1 observer at 2 separate times (2 months apart) without knowledge of clinical or catheterization data or the 2 values averaged.

**Ejection rate analysis:** The average ejection rate was the change in counts in the left ventricle from end-diastole to end-systole with respect to time, normalized for end-diastolic counts (stroke counts/ejection time/end-diastolic counts).[2] Because the counts within the left ventricular region of interest are proportional to volume, this measurement is comparable to the change of volume over time relation normalized for end-diastolic volume which has been obtained from the contrast ventriculogram (dV/dt/end-diastolic volume). Ejection rates were determined by 1 observer on 2 separate occasions without knowledge of clinical or catheterization data and the 2 values averaged.

**Left ventricular volume analysis:** End-diastolic volume was calculated using a previously reported geometric approach.[19,20] This involves (1) calibration of the camera system for actual square centimeters per picture element, (2) computer derivation of the area in square centimeters, (3) computer derivation of the longest chord in centimeters within the left ventricular region of interest, and (4) trigonometric correction to orthogonal biplane views. For this study, the calculation was modified so that end-diastolic volumes were derived from the left anterior oblique view alone, allowing a measurement of end-diastolic volume during rest and peak exercise (without having to change the position of the camera). This was accomplished by using the computer-derived left anterior oblique area and length and the single-plane area-length equation of Sandler and Dodge[21,22]: Volume = 4/3 long axis × short axis$^2$, where short axis = 4 area/$\pi$ long axis.

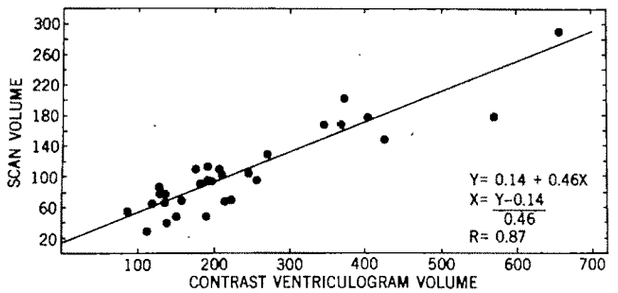



**FIGURE 1.** Linear regression curve of contrast left ventriculographic end-diastolic volume (right anterior oblique) and radionuclide ventriculographic end-diastolic volume (left anterior oblique); Y = scan volume, X = contrast ventriculographic volume. Rearrangement of equation for use in our patient study where scan volumes were measured and related to catheterization volumes (considered true volumes): X = (Y/0.46 − 0.14)/0.46. The standard error of the estimate was 13 ml/m$^2$.

To determine the validity of using this single-plane geometric approach, 30 other patients (7 normal patients and 23 with coronary disease) undergoing both contrast left ventriculography and multigated blood pool scans were analyzed. Left anterior oblique end-diastolic volumes were compared with volumes derived from anterior oblique single-plane left ventriculography and biplane-multigated blood pool scanning. The individual paired data points for right anterior oblique contrast ventriculograms and left anterior oblique multigated blood pool scans are shown in Figure 1. The values correlate closely ($r = 0.87$, $p < 0.0001$). There was also a close correlation between left anterior oblique and biplane-multigated blood pool scan values ($r = 0.91$, $p < 0.0001$). For both correlations, the slope of the regression line was substantially less than unity (left anterior oblique absolute volumes were smaller). This may be partly due to the fact that the left ventricle is more foreshortened in the left anterior oblique compared to the right anterior oblique view. For this study, all scan end-diastolic volumes derived from the gated blood pool scan were corrected to angiographic volume using the regression equation and were then divided by the body surface area to derive an index value.

Stroke volume was calculated as EF multiplied by the end-diastolic volume and cardiac output was stroke volume times heart rate. End-systolic volume was the difference between end-diastolic volume and stroke volume. This approach avoided assuming a left ventricular end-systolic geometry. Volumes were determined by 1 observer on 2 separate occasions without knowledge of clinical or catheterization data, and the 2 results were averaged.

**Peak systolic pressure/end-systolic volume analysis:** Peak systolic pressure was determined by blood pressure cuff at rest and at each stage of exercise. The ratio of peak systolic pressure to end-systolic volume index was calculated as an average of the 2 derived values.[11]

**Pulmonary blood volume ratio:** The ratio of pulmonary blood volume during exercise compared with rest was derived from multigated blood pool scanning. This parameter has been shown of value in differentiating patients with and without CAD.[6] A region of interest was placed over the lung in both rest and exercise end-diastolic images. The count ratio of exercise to rest activity, normalized for study collection time, was calculated. From previous work, a ratio of 1.05 was found to be 2 standard deviations above the normal mean and was defined as the upper limit of normal. Pulmonary blood volume ratios were determined by 2 observers and then averaged.

**TABLE I Clinical Data on Normal Patients and Patients With CAD**

| | Normal (n = 21) | Coronary Disease (n = 32) | P |
|---|---|---|---|
| Age (yr) | 47 ± 12 | 53 ± 9 | ... |
| Number of males | 10 (48%) | 26 (81%) | <0.05 |
| Number with exercise-induced S-T depression | 2 (10%) | 19 (59%) | <0.001 |
| Number receiving propranolol | 8 (38%) | 24 (75%) | <0.05 |
| Number achieving 85% of maximal predicted heart rate | 15 (71%) | 8 (25%) | <0.001 |
| Heart rate | | | |
| Rest | 71 ± 12 | 66 ± 11 | ... |
| Exercise | 141 ± 23* | 111 ± 24* | <0.001 |
| Difference | +71 ± 23 | +45 ± 17 | <0.001 |
| Systolic blood pressure | | | |
| Rest | 130 ± 17 | 127 ± 19 | ... |
| Exercise | 177 ± 28* | 165 ± 22* | <0.05 |
| Difference | +47 ± 32 | +38 ± 23 | ... |

Values are mean ± 1 standard deviation.
* $p < 0.001$, compared with rest value.

**Statistical analysis:** The differences between rest and exercise values of each variable were derived. Group values were expressed as mean ± 1 standard deviation. Differences among group means were compared using an unpaired $t$ test. Changes between rest and exercise values were compared using a paired $t$ test. Frequency differences were compared using chi-square analysis. A 2-way analysis of variance was performed on the duplicate values for each scan-determined variable which were determined on the 2 occasions. This was done to calculate experimental plus operator error in an attempt to assess the significance of individual differences with respect to random error, which is important when data from individual patients are being considered. However, when group means are used, random error in both directions negates this problem and thus the individual variations may be less important in data analysis.

## Results

**Clinical data (Table I):** Patients with CAD were significantly more frequently male, more likely to be receiving propranolol, and had a lower maximal heart rate and systolic blood pressure with exercise than pa-

**TABLE II Intraobserver Variance (+2 Standard Deviations) for Parameters of Global Left Ventricular Function for the Individual Resting, Peak Exercise, and Difference Between Resting and Peak Exercise Measurements**

| | Resting | Exercise | Difference |
|---|---|---|---|
| EF* | 0.06 | 0.09 | 0.11 |
| Ejection rate | 0.6 | 0.7 | 0.6 |
| End-diastolic volume (ml/m$^2$) | 18 | 14 | 17 |
| Stroke volume (ml/m$^2$) | 9 | 9 | 14 |
| End-systolic volume (ml/m$^2$) | 16 | 13 | 17 |
| Pulmonary blood volume ratio* | 0.10 | ... | ... |

* Previously reported.[6,11]

tients without CAD. Within each group, there was no relation between taking propranolol and peak exercise heart rate.

**Intraobserver variability:** The intraobserver variance (±2 standard deviations) for the variables studied are summarized in Table II.

**Overall scan data (Table III):** At rest, patients with CAD could not be differentiated from normal patients. With exercise, EF, ejection rate, and the peak systolic pressure/end-systolic volume ratio were significantly lower and end-systolic volume was significantly higher in patients with CAD than in normal patients. The exercise/rest pulmonary blood volume ratio was greater in patients with CAD. Differences in end-diastolic volume were not statistically significant.

**Scan data in normal patients:** Among the 21 normal patients, EF increased by ≥0.05 during exercise in 13 patients (62%) and failed to increase by 0.05 in 8 patients. The 2 groups of normal patients did not differ in any clinical variable except for peak exercise heart rate. Patients who increased EF by ≥0.05 during exercise had a lower peak heart rate than patients who increased EF by <0.05 (134 ± 24 versus 153 ± 18, p <0.05). Five of the 13 and 3 of the 8 patients in the 2 normal groups were receiving propranolol (difference not significant).

Mean values for scan-derived variables of left ventricular performance are shown in Table IV and illustrated in Figure 2. The 2 groups of normal patients did not differ in any parameter at rest. However, the group with a ≥0.05 increase in EF during exercise accomplished this with a significant increase in stroke volume and a significant decrease in end-systolic volume. On the other hand, the group with a <0.05 increase in EF had no change in stroke volume or end-systolic volume with exercise. The peak exercise values did not differ significantly in the 2 groups except for the peak systolic pressure/end-systolic volume during exercise, which was higher in patients with a ≥0.05 increase in EF.

**Scan data in patients with coronary disease:** Among the 32 patients with CAD, the EF increased by ≥0.05 during exercise in 15 patients (47%) and failed to

**TABLE III Scan Data in Normal Patients and Patients With CAD**

| | Normal (n = 21) | Coronary Disease (n = 32) | p |
|---|---|---|---|
| HR (beats/min) | | | |
| Rest | 72 ± 13 | 66 ± 11 | ... |
| Exercise | 142 ± 23* | 111 ± 24* | <0.001 |
| Difference | +70 ± 25 | +45 ± 20 | <0.001 |
| SPB (mm Hg) | | | |
| Rest | 130 ± 17 | 127 ± 19 | ... |
| Exercise | 177 ± 28* | 165 ± 22* | <0.05 |
| Difference | +47 ± 34 | +38 ± 21* | ... |
| EF | | | |
| Rest | 0.65 ± 0.07 | 0.62 ± 0.12 | ... |
| Exercise | 0.73 ± 0.08† | 0.62 ± 0.13 | <0.01 |
| Difference | +0.08 ± 0.09 | 0 ± 0.11 | <0.05 |
| Ejection rate (dV/dt) | | | |
| Rest | 1.9 ± 0.4 | 1.8 ± 0.5 | ... |
| Exercise | 2.6 ± 0.5† | 2.1 ± 0.6* | <0.01 |
| Difference | +0.7 ± 0.5 | 0.3 ± 0.6 | <0.01 |
| EDV (ml/m²) | | | |
| Rest | 63 ± 4 | 75 ± 26 | ... |
| Exercise | 64 ± 5 | 79 ± 25‡ | ... |
| Difference | +1 ± 9 | +4 ± 1 | ... |
| ESV (ml/m²) | | | |
| Rest | 22 ± 8 | 35 ± 22 | ... |
| Exercise | 17 ± 8* | 34 ± 21 | <0.01 |
| Difference | −5 ± 9 | +1 ± 11 | <0.05 |
| Stroke volume (ml/m²) | | | |
| Rest | 41 ± 9 | 44 ± 16 | ... |
| Exercise | 47 ± 11* | 50 ± 22* | ... |
| Difference | +6 ± 9 | +5 ± 11 | ... |
| Cardiac output (liters/min/m²) | | | |
| Rest | 3.0 ± 1.1 | 2.8 ± 1.2 | ... |
| Exercise | 6.6 ± 2.1* | 5.5 ± 2.8* | ... |
| Difference | +3.6 ± 1.8 | +2.6 ± 2.8 | ... |
| PSP/ESV ratio | | | |
| Rest | 6.5 ± 2.6 | 5.6 ± 2.8 | ... |
| Exercise | 11.8 ± 4.7† | 6.5 ± 2.6 | <0.01 |
| Difference | +5.3 ± 3.7 | 0.9 ± 3.4 | <0.01 |
| Pulmonary blood volume ratio | 0.99 ± 0.13 | 1.16 ± .35 | <0.01 |

* p <0.05, † p <0.001, and ‡ p <0.01, compared with resting value. Values are mean ± 1 standard deviation. EDV = end-diastolic volume; ESV = end-systolic volume; HR = heart rate; PSP = peak systolic pressure; SDP = systolic blood pressure.

**TABLE IV Scan Data in Normal Patients With and Without ≥0.05 Increase in EF During Exercise**

| | EF Increase | | |
|---|---|---|---|
| | ≥0.05 (n = 13) | <0.05 (n = 8) | p |
| HR (beats/min) | | | |
| Rest | 73 ± 9 | 70 ± 18 | ... |
| Exercise | 134 ± 24* | 153 ± 18* | ... |
| Difference | +61 ± 25 | +83 ± 21 | <0.05 |
| SBP (mm Hg) | | | |
| Rest | 131 ± 13 | 126 ± 23 | ... |
| Exercise | 175 ± 26* | 181 ± 31* | ... |
| Difference | 44 ± 27 | +55 ± 23 | ... |
| EF | | | |
| Rest | 0.63 ± 0.07 | 0.69 ± 0.08 | ... |
| Exercise | 0.76 ± 0.07 | 0.68 ± 0.08 | <0.05 |
| Difference | +0.13 ± 0.07 | −0.01 ± 0.03 | <0.001 |
| Ejection rate (dV/dt) | | | |
| Rest | 1.8 ± 0.4 | 2.0 ± 0.3 | ... |
| Exercise | 2.6 ± 0.4† | 2.7 ± 0.6* | ... |
| Difference | +0.8 ± 0.4 | +0.7 ± 0.3 | ... |
| EDV (ml/m²) | | | |
| Rest | 64 ± 14 | 64 ± 14 | ... |
| Exercise | 63 ± 14 | 66 ± 23 | ... |
| Difference | −1 ± 11 | +2 ± 11 | ... |
| ESV (ml/m²) | | | |
| Rest | 24 ± 7 | 20 ± 8 | ... |
| Exercise | 15 ± 4† | 21 ± 11 | ... |
| Difference | −9 ± 7 | +1 ± 3 | <0.001 |
| Stroke volume (ml/m²) | | | |
| Rest | 40 ± 7 | 44 ± 11 | ... |
| Exercise | 48 ± 11* | 45 ± 11 | ... |
| Difference | +8 ± 11 | +1 ± 8 | ... |
| Cardiac output (liters/min/m²) | | | |
| Rest | 2.9 ± 0.7 | 3.2 ± 0.4 | ... |
| Exercise | 6.4 ± 1.8† | 6.8 ± 0.2* | ... |
| Difference | +3.5 ± 2.2 | +3.6 ± 1.7 | ... |
| PSP/ESV ratio | | | |
| Rest | 6.2 ± 2.5 | 7.0 ± 2.8 | ... |
| Exercise | 13.1 ± 4.7† | 9.7 ± 3.7* | <0.05 |
| Difference | +6.9 ± 12.3 | +2.7 ± 8.8 | <0.01 |
| Pulmonary blood volume ratio | 0.92 ± 0.07 | 0.98 ± 0.06 | ... |

* p <0.01, † p <0.001, compared with resting value. Values are mean ± 1 standard deviation. Abbreviations as in Table III.

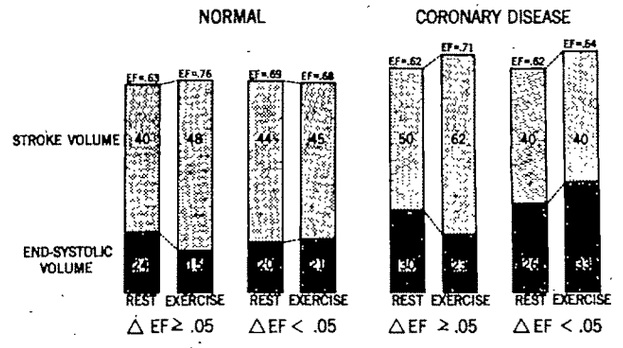



**FIGURE 2.** Mean radionuclide volumes and EF data collected during rest and exercise for normal and CAD patients grouped according to whether EF increased with exercise.

increase by 0.05 in 17 patients. Only 2 of 15 patients (13%) with a normal EF during exercise had a previous myocardial infarction compared with 9 of 17 patients (53%) with an abnormal response to exercise ($p < 0.05$). There was no difference in any other clinical variable, including propranolol use or the number of diseased vessels in either group. Ten of the 15 and 14 of the 17 patients in the 2 coronary disease groups were receiving propranolol (difference not significant). Mean resting heart rate and resting and exercise systolic blood pressure were similar in the 2 coronary disease groups and did not differ significantly from normal. The peak heart rate was comparably reduced in both groups (116 ± 20 and 107 ± 27, difference not significant), which was significantly below the peak heart rate in normals (142 ± 23, $p < 0.01$). The patients with a ≥0.05 increase in EF included 3 with single-vessel left anterior descending disease, 9 with double-vessel disease, and 3 with triple-vessel disease. The patients with a <0.05 increase in EF included 3 with single-vessel left anterior descending disease, 8 with double-vessel disease, and 6 with triple-vessel disease. These distributions did not differ significantly.

The mean values for the scan variables of left ventricular performance in patients with CAD with a ≥0.05 increase versus <0.05 increase in EF are shown in Table V and illustrated in Figure 2. Patients with an increase ≥0.05 in EF demonstrated an increase in ejection rate, stroke volume, and peak systolic pressure/end-systolic volume ratio and a decrease in end-systolic volume during exercise. This group differed significantly from the normal group only in having a lower peak systolic pressure/end-systolic volume ratio during exercise (7.8 ± 2.7 versus 11.8 ± 4.6, $p < 0.01$), and a higher pulmonary blood volume ratio (1.06 ± 0.17 versus 0.99 ± 0.13, $p < 0.05$). Ejection rate, EF end-diastolic volume, stroke volume, end-systolic volume, and cardiac output did not differ significantly from that in the normal group.

Coronary disease patients with an EF increase <0.05 were characterized by a significant increase in end-diastolic and end-systolic volumes during exercise and no change in ejection rate, stroke volume, and the peak systolic pressure/end-systolic volume ratio. These patients did not differ from normal subjects at rest; however, with exercise the heart rate, ejection rate, cardiac index, and peak systolic pressure/end-systolic volume were lower than in normal subjects ($p < 0.01$) and pulmonary blood volume was higher than in normal patients ($p < 0.01$).

**TABLE V Scan Data in CAD Patients With and Without ≥0.05 Increase in EF During Exercise**

| | EF Increase | | |
|---|---|---|---|
| | ≥0.05 (n = 15) | <0.05 (n = 17) | p |
| HR (beats/min) | | | |
| Rest | 67 ± 81 | 66 ± 13 | ... |
| Exercise | 116 ± 2* | 107 ± 27* | ... |
| Difference | +49 ± 17 | +41 ± 22 | ... |
| SBP (mm Hg) | | | |
| Rest | 122 ± 17 | 132 ± 20 | ... |
| Exercise | 168 ± 26* | 163 ± 17* | ... |
| Difference | +46 ± 22 | +31 ± 19 | <0.05 |
| EF | | | |
| Rest | 0.62 ± 0.12 | 0.62 ± 0.12 | ... |
| Exercise | 0.71 ± 0.08† | 0.54 ± 0.08* | <0.01 |
| Difference | +0.09 ± 0.04 | −0.08 ± 0.08 | <0.001 |
| Ejection rate | | | |
| Rest | 1.8 ± 0.4 | 1.9 ± 0.8 | ... |
| Exercise | 2.4 ± 0.8* | 1.9 ± 0.4 | <0.05 |
| Difference | +0.6 ± 0.8 | 0 ± 0.4 | <0.01 |
| EDV (ml/m²) | | | |
| Rest | 80 ± 23 | 66 ± 25 | ... |
| Exercise | 85 ± 23 | 73 ± 25* | ... |
| Difference | +5 ± 15 | 7 ± 8 | ... |
| ESV (ml/m²) | | | |
| Rest | 30 ± 12 | 26 ± 16 | ... |
| Exercise | 23 ± 8* | 33 ± 16* | ... |
| Difference | −7 ± 12 | +7 ± 8 | <0.001 |
| Stroke volume (ml/m²) | | | |
| Rest | 50 ± 15 | 40 ± 16 | ... |
| Exercise | +62 ± 23* | 40 ± 16 | <0.01 |
| Difference | +12 ± 12 | 0 ± 8 | <0.05 |
| Cardiac output (liters/min/m²) | | | |
| Rest | 3.3 ± 1.2 | 2.6 ± 1.2 | ... |
| Exercise | 6.9 ± 1.9* | 4.4 ± 2.9* | <0.01 |
| Difference | +3.6 ± 1.5 | +1.6 ± 2.1 | ... |
| PSP/ESV ratio | | | |
| Rest | 4.6 ± 1.5 | 6.6 ± 3.3 | ... |
| Exercise | 7.8 ± 2.7† | 5.6 ± 2.1 | ... |
| Difference | +3.2 ± 1.9 | −1.0 ± 2.9 | <0.001 |
| Pulmonary blood volume ratio | 1.06 ± 0.23 | 1.21 ± 0.45 | ... |

* $p < 0.01$, † $p < 0.001$, compared with resting value. Values are mean ± 1 standard deviation. Abbreviations as in Table III.

Among all coronary disease patients, there was no difference in rest or exercise values in patients with and without electrocardiographic ischemia during exercise except for a smaller exercise increase in peak systolic pressure/end-systolic volume ratio in ischemic patients (+0.3 ± 0.8 versus + 2.4 ± 0.6, $p < 0.05$). However, when patients with and without previous myocardial infarction were compared, the 13 patients with previous myocardial infarction had (1) a lower rest and exercise EF (rest = 0.54 ± 0.13 versus 0.67 ± 0.08, $p < 0.05$; exercise = 0.56 ± 0.11 versus 0.66 ± 0.12, $p < 0.05$); (2) a lower rest and exercise stroke volume (ml/m²) (rest = 34 ± 11 versus 50 ± 16, $p < 0.05$; exercise = 39 ± 14 versus 58 ± 25, $p < 0.05$); (3) a lower rest and exercise cardiac output (liters/min/m²) (rest = 2.4 ± 0.7 versus 3.2 ±1.3, $p < 0.05$; exercise = 4.4 ± 1.4 versus 6.4 ± 3.1, $p < 0.05$).

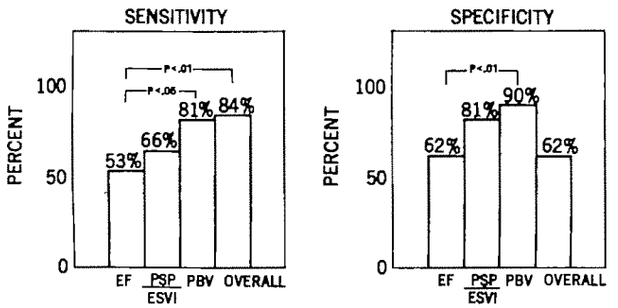



**FIGURE 3.** Comparison of the sensitivities and specificities of EF, peak systolic pressure (PSP)/end-systolic volume (ESVI) ratio, and pulmonary blood volume (PBV) ratio (see text).

**Sensitivity and specificity:** An EF increase during exercise of ≥0.05 had a sensitivity for detecting coronary disease of 53% (17 of 32) and a specificity of 62% (13 of 21). When normal was defined as a peak systolic pressure/end-systolic volume index increase with exercise of ≥2, the sensitivity was higher than for EF, 66% (21 of 32) as was the specificity, 81% (17 of 21). However, these increases did not reach statistical significance. When normal was defined by an exercise/rest pulmonary blood volume ratio of <1.06, the sensitivity increased to 78% (25 of 32), $p < 0.05$, and the specificity increased to 90% (19 of 21), $p < 0.01$. Using peak systolic pressure/end-systolic volume ratio and exercise/rest pulmonary blood volume ratio in conjunction with EF significantly increased overall sensitivity from 53 to 84% (27 of 32), $p < 0.01$, with no change in specificity compared with EF alone (Fig. 3).

## Discussion

Cardiologists have long sought a simple yet accurate method to noninvasively predict the presence or absence of CAD. The development of exercise radionuclide angiography has generated hope that such a method might be available. However, EF is often the only objective parameter of left ventricular function derived by many laboratories performing radionuclide ventriculography, and EF can be influenced by cardiac loading conditions and heart rate and is not purely related to myocardial contractile function.[11,23,24] Optimally, the EF response to exercise would be abnormal in all patients with CAD and normal in patients without CAD. However, the present study demonstrates that the response of EF to exercise was neither sensitive nor specific in differentiating patients with and without significant CAD. One limitation of the present study is the relatively large number of patients receiving propranolol. This was not by design but was related to the reluctance of most physicians at our institution to discontinue propranolol. Although this may contribute to false-positive and false-negative studies,[25,26] this group of patients is likely to be representative of routine patients encountered at many clinical facilities.

In our study, the sensitivity (53%) was considerably lower than previously reported values.[12] This may be explained in part by the fact that many patients in our group had clinically less severe coronary disease (that is, no unstable angina, congestive heart failure, or aneurysms). In addition, most of the coronary patients were receiving propranolol which may have "normalized" the EF during exercise in some patients with CAD.[25,26]

Among the coronary disease patients, 1 subset was strikingly similar to normal patients in that EF increased ≥0.05 during exercise. These patients did differ from normal in having a lower exercise heart rate, peak systolic pressure/end-systolic volume ratio, and a higher pulmonary blood volume ratio. In addition, fewer patients in this group had had a myocardial infarction compared to the remainder of the coronary disease patients. The latter patients (those with an "abnormal" EF response to exercise) with a <0.05 increase in EF with exercise, differed from normal in nearly all parameters studied, which is consistent with data reported in previous studies.[17,25–30]

The relatively low specificity (62%) of the 0.05 increase in EF with exercise in the "normal" population also warrants explanation. All of the patients in this group underwent coronary angiography to evaluate a chest pain syndrome. Such patients may have had disease involving the smaller vessels or the substance of the myocardium even though abnormalities were not evident at rest,[31–33] which might result in a depressed left ventricular reserve as evidenced by a lack of increase in EF during exercise. Alternatively, this observation may be explained by factors other than contractile reserve influencing EF in this group of patients, such as age, high contractile state of the myocardium at rest, abnormal responsiveness of the peripheral vascular system or autonomic nervous system, or both, and altered ventricular loading conditions.[17,31–33] Some patients in this group were receiving propranolol and nitrates, which may affect the EF, although the mean EF response was similar in the patients who were not receiving these agents.

**Quantitation of end-diastolic volume:** Other parameters of potential value in detection of exercise-induced left ventricular dysfunction can be derived from radionuclide cineangiography, and we were interested in determining what further pathophysiologic insight these might provide. To accomplish this goal, it was necessary to measure end-diastolic volume. In our study a geometric approach to derivation of end-diastolic volume was employed,[19,20] although reliable volumes may also be obtained using a counts method.[3,4,7,9,34] Our method has several potential limitations when compared with the "gold standard": biplane contrast left ventriculography. First, for both contrast ventriculography and the blood pool studies, only a single view was used. A single-plane volume analysis may provide misleading data because coronary disease is known to affect left ventricular systolic function regionally, and therefore evaluation of the 2 views would be more desirable than just a single view.[35] Unfortunately, only a single-view contrast ventriculogram during catheterization and a single-view gated scan during exercise was available. Nevertheless, there is ample evidence in the literature that a single-plane geometric assessment of

end-diastolic volume using x-ray contrast left ventriculography is adequate.[21,22] This is because the impact of an intervention on end-diastolic volume alone is likely to be global and similar in different projections. Only changes in systole are likely to be regional. Furthermore, nearly all methods for radionuclide EF and counts-based end-diastolic volume measurements use a single view of the left ventricle.

The second limitation may be the use of a geometric compared with a counts-based method. A previous study suggested that reliable data may be derived using either method with no significant difference in correlation coefficients or standard errors of the estimate.[34] In the previous study, the area-length data were derived primarily from analog (Polaroid®) images, whereas our data were analyzed using digitized images and a computer algorithm to determine area and length. One advantage of the geometric approach is that assumptions about variations in tracer attenuation from activity in basal compared with apical portions of the left ventricle are avoided.[35] Once again, geometric assumptions were used to derive only end-diastolic volume and not EF. End-systolic volume and stroke volume were derived from EF and end-diastolic volume, and no assumptions about the shape or motion of the left ventricle during systole were necessary. Furthermore, no patients with left ventricular aneurysm were included and all but 4 patients had resting EF values >0.50. Therefore, our patients were unlikely to have end-diastolic left ventricular outlines that differed markedly from an ellipsoidal shape, which might be source of error using a geometric estimate of end-diastolic volume.

The third potential limitation is that the single view used to quantitate end-diastolic volumes was the left anterior oblique instead of the more commonly used single-plane right anterior oblique view. Although a right anterior oblique view should be more desirable because more left ventricular wall is exposed,[36] this view is not available using equilibrium blood pool imaging due to superimposition of right ventricular activity. All exercise equilibrium approaches to derive EF or end-diastolic volume utilize the left anterior oblique view alone. For these reasons, our approach to end-diastolic volume measurement appears reasonable, and its accuracy and limitations are comparable to those of other methods.[34]

**Observer variability:** In addition to errors inherent in the methodologic assumptions used to derive the 8 variables evaluated, inconsistency in data may also occur due to observer variability. The present data support previous data from this laboratory[18] indicating that measurement of these variables is complex and has considerable intraobserver variability. Furthermore, the observation that intraobserver variance (±2 standard deviations) for the change in EF from rest to exercise is 0.11 may be partly responsible for some of the apparent inconsistencies between the EF response to exercise and the presence or absence of CAD. The 0.05 increase in EF with exercise criteria may be within the individual error due to observer variability. This probably does not explain the entire inconsistency, however, because the other variables (derived in part from EF) appeared to have less inconsistency. The observer variability leads to difficulties in comparing data from different institutions, and therefore the range of normal used in this study is unlikely to be useful in patients studied elsewhere. However, it is unlikely to present a problem in comparing patient groups in this study because mean values were employed, thereby reducing differences due to individual observer variability and allowing statistical comparison of different groups.

**Other variables measured during exercise:** As with EF, variable responses of ejection rate (dV/dt), cardiac index, and absolute volumes to exercise did not differentiate patients with and without CAD. However, 2 measurements of global left ventricular function, the peak systolic pressure/end-systolic volume ratio response to exercise and pulmonary blood volume (exercise/rest ratio), were consistently different in patients with CAD and normal patients. The pressure/volume ratio, a parameter which may be less influenced by cardiac loading conditions,[11,37–39] showed a smaller increase with exercise in patients with coronary heart disease. The pulmonary blood volume ratio, a parameter which may be related to left ventricular filling pressure,[40] was greater in patients with CAD than in normal patients. The use of these 2 parameters in addition to EF significantly increased sensitivity from 53 to 84% without worsening specificity. Therefore, these parameters appear to be helpful adjuncts to EF in detecting CAD. Our study confirms other reports which indicate that analysis of other aspects of left ventricular function besides EF is useful in defining ventricular performance.

**Clinical implications:** Although the left ventricular EF response to exercise is "abnormal" in many patients with CAD, this parameter alone is not a reliable indicator of coronary disease. Normal patients may not have an increase in EF with exercise and some CAD patients may have an EF increased by ≥0.05. Furthermore, in the present study no parameter of global left ventricular function invariably detected or excluded CAD. Therefore, inferences concerning the presence or absence of CAD from rest and exercise global left ventricular function parameters should be made with caution. This study considered only parameters of global left ventricular function; previous data have shown that the sensitivity and specificity of radionuclide cineangiography as a technique in the evaluation of CAD are considerably improved when regional wall motion is also analyzed.[5,12] Further studies which include regional wall motion (not performed in this study) might even indicate that no additional advantage is gained in terms of sensitivity and specificity with the use of these other parameters. However, in most clinical settings regional wall motion assessment is subjective. This study suggests that objective parameters can be derived from careful analysis of radionuclide images and are helpful in defining cardiac function more precisely, as well as in improving the diagnostic yield of the radionuclide EF.

## References


1. **Frischknecht J, Steele P, Kirck D, Jensen D, Vogel R.** Effect of exercise on left ventricular ejection fraction in men with coronary artery disease. Am Heart J 1979;97:494–498.
2. **Bacharach SL, Green MV, Borer JS, Hyde JE, Farkas SP, Johnson GS.** Left ventricular peak ejection rate, filling rate, and ejection fraction—frame rate requirements at rest and exercise: concise communication. J Nucl Med 1979; 20: 189–193.
3. **Slutsky R, Karliner J, Ricci D, Kaiser R, Pfisterer M, Gordon D, Peterson K, Ashburn W.** Left ventricular volumes by gated equilibrium radionuclide angiography: a new method. Circulation 1979;60:556–564.
4. **Slutsky R, Karliner J, Ricci D, Schuler G, Pfisterer M, Peterson K, Ashburn W.** Response of left ventricular volume to exercise in man assessed by radionuclide equilibrium angiography. Circulation 1979;60:565–571.
5. **Borer JS, Kent KM, Bacharach SL, Green MV, Rosing DR, Siedes SF, Epstein SE, Johnson GS.** Sensitivity, specificity, and predictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease. Comparison with exercise electrocardiography. Circulation 1979;60:572–580.
6. **Okada RD, Pohost GM, Kirshenbaum HD, Kushner FG, Boucher CA, Block PC, Strauss HW.** Radionuclide determined change in pulmonary blood volume with exercise: improved sensitivity of multigated blood pool scanning in detecting coronary artery disease. N Engl J Med 1979;301:569–576.
7. **Sorenson SG, Ritchie JL, Caldwell JH, Hamilton GW, Kennedy JW.** Serial exercise radionuclide angiography: validation of count-derived changes in cardiac output and quantitation of maximal exercise ventricular volume change after nitroglycerin and propranolol in normal men. Circulation 1980;61:600–609.
8. **Becker LC.** Diagnosis of coronary artery disease with exercise radionuclide imaging: state of the art. Am J Cardiol 1980;45:1301–1304.
9. **Caldwell JH, Hamilton GW, Sorenson SG, Ritchie JL, Williams DL, Kennedy JW.** The detection of coronary artery disease with radionuclide techniques: a comparison of rest-exercise thallium imaging and ejection fraction response. Circulation 1980;61:610–619.
10. **Slutsky R, Karliner J, Gerber K, Battler A, Froelicher V, Gregoratos G, Peterson K, Ashburn W.** Peak systolic blood pressure/end-systolic volume ratio: assessment at rest and during exercise in normal subjects and patients with coronary heart disease. Am J Cardiol 1980;46:813–820.
11. **Okada RD, Boucher CA, Strauss HW, Pohost GM.** Exercise radionuclide imaging approaches to coronary artery disease. Am J Cardiol 1980;46: 1188–1204.
12. **Poltner LR, Dehmer GT, Lewis SE, Parkey RW, Blomquist CG, Willerson JT.** Left ventricular performance in normal subjects: a comparison of the responses to exercise in the upright and supine position. Circulation 1980;62:528–534.
13. **Brady TJ, Thrall JH, Keyes JW, Brymer JF, Walton JA, Pitt B.** Segmental wall-motion analysis in the right anterior oblique projection: comparison of exercise equilibrium radionuclide ventriculography and exercise contrast ventriculography. J Nucl Med 1980;21:617–621.
14. **Ashburn WL, Schelbert HR, Verba JW.** Left ventricular ejection fraction—a review of several radionuclide angiographic approaches using the scintillation camera. Prog Cardiovasc Dis 1978;20:267–284.
15. **Pfisterer ME, Battler A, Swanson SM, Slutsky R, Froelicher V, Ashburn WL.** Reproducibility of ejection-fraction determinations by equilibrium radionuclide angiography in response to supine bicycle exercise: concise communication. J Nucl Med 1980;20:491–495.
16. **Krayenbuehl HD, Hess OM, Turina J.** Assessment of left ventricular functions. Cardiovasc Med 1978;3:883–908.
17. **Slutsky R.** Response of the left ventricle to stress: effects of exercise, atrial pacing, afterload stress and drugs. Am J Cardiol 1981;47:357–364.
18. **Okada RD, Kirshenbaum HD, Kushner FG, Strauss HW, Dinsmore RE, Newell JB, Boucher CA, Block PC, Pohost GM.** Observer variance in the quantitative evaluation of left ventricular wall motion and the quantitation of left ventricular ejection fraction using rest and exercise multigated blood pool imaging. Circulation 1980;61:128–136.
19. **Bingham JB, Tarolli EJ, Alpert N, Boucher CA, Okada RD, McKusick KA, Pohost GM, Strauss HW.** Determination of left ventricular end-diastolic volume from gated cardiac images: comparison with contrast ventriculography (abstr). J Nucl Med 1979;20:667.
20. **Boucher CA, Bingham JB, Osbakken MD, Okada RD, Strauss HW, Block PC, Levine FH, Phillips HR, Pohost GM.** Early changes in left ventricular size and function following correction of left ventricular volume overload. Am J Cardiol 1981;47:991–1004.
21. **Dodge HT, Sandler H, Baxley WA, Hawley RR.** Usefulness and limitations of radiographic methods for determining left ventricular volume. Am J Cardiol 1966;18:10–24.
22. **Sandler H, Dodge HT.** The use of single plane angiocardiograms for the calculation of left ventricular volume in man. Am Heart J 1968;75:325–334.
23. **Hammermeister KE, Brooks RC, Worbasse JR.** The rate of change of left ventricular volume in man. I. Validation and peak systolic ejection rate in health and disease. Circulation 1974;49:729–738.
24. **Bevegard S, Holmgren A, Jonsson B.** The effect of body position on the circulation at rest and during exercise with special reference to the influence of stroke volume. Acta Physiol Scand 1960;49:279–285.
25. **Battler A, Ross J, Slutsky R, Pfisterer M, Ashburn W, Froelicher V.** Improvement of exercise-induced left ventricular dysfunction with oral propranolol in patients with coronary heart disease. Am J Cardiol 1979;44: 318–324.
26. **Sorenson SG, Ritchie JL, Caldwell JH, Hamilton GW, Kennedy JW.** Serial exercise radionuclide angiography: validation of count-derived changes in cardiac output and quantitation of maximal exercise ventricular volume change after nitroglycerine and propranolol in normal men. Circulation 1980;61:600–609.
27. **Gorlin R, Cohen LS, Elliot WC, Klein MD, Fane FJ.** Effect of supine exercise on left ventricular volume and oxygen consumption in man. Circulation 1965;32:361–371.
28. **Sharma B, Goodwin JF, Raphael MJ, Steiner RE, Rainbow RG, Taylor SH.** Left ventricular angiography on exercise. A new method of assessing left ventricular function in ischemic heart disease. Br Heart J 1976;38:59–70.
29. **Thadani I, West RO, Matthew TM, Parker JO.** Hemodynamics at rest and during supine and sitting bicycle exercise in patients with coronary artery disease. Am J Cardiol 1977;39:776–783.
30. **Caldwell JH, Stewart DK, Dodge HT, Frimer M, Kennedy JW.** Left ventricular volume during maximal supine exercise: a study using metallic epicardial markers. Circulation 1978;58:732–738.
31. **Port S, Cobb FR, Coleman RE, Jones RH.** Effect of age on the response of left ventricular ejection fraction to exercise. N Engl J Med 1980;303: 1133–1138.
32. **Berger HJ, Sands MJ, Davies RA, Wackers FJTH, Alexander J, Lachman AS, Williams BW, Zaret BL.** Exercise left ventricular performance in patients with chest pain, ischemic-appearing exercise electrocardiograms, and angiographically normal coronary arteries. Ann Intern Med 1981;94: 186–191.
33. **Gibbons RJ, Lerry KL, Cobb F, Jones RH.** Ejection fraction response to exercise in patients with chest pain and normal coronary arteriograms. Circulation 1981;64:952–957.
34. **Massie BM, Kramer BL, Gertz EW, Henderson SG.** Radionuclide measurements of left ventricular volume: comparison of geometric and counts methods. Circulation 1982;65:725–730.
35. **Strauss HW, McKusick KA, Bingham JB.** Cardiovascular nuclear imaging: principles, instrumentation, and pitfalls. Am J Cardiol 1980;46:1109–1116.
36. **Cohn PF, Gorlin R, Adams DF, Chahine RA, Vokonas PS, Herman MV.** Comparison of biplane and single plane left ventriculograms in patients with coronary artery disease. Am J Cardiol 1974;33:1–6.
37. **Sagawa, Suga H, Shoukas AA, Bakalar KM.** End-systolic pressure/volume ratio: a new index of ventricular contractility. Am J Cardiol 1977;40: 748–753.
38. **Nivatpumin T, Katz S, Scheuer J.** Peak left ventricular systolic pressure/end-systolic volume ratio: a sensitive detector of left ventricular disease. Am J Cardiol 1979;43:969–974.
39. **Grossman W, Braunwald E, Mann T, McLaurin L, Green L:** Contractile state of the left ventricle in man as evaluated from end-systolic pressure volume relation. Circulation 1977;56:845–852.
40. **Okada RD, Osbakken MD, Boucher CA, Strauss HW, Block PC, Pohost GM.** Pulmonary blood volume ratio response to exercise: a noninvasive determination of exercise-induced changes in pulmonary capillary wedge pressure. Circulation 1982;65:126–133.

# Left and Right Ventricular Function at Rest and During Bicycle Exercise in the Supine and Sitting Positions in Normal Subjects and Patients With Coronary Artery Disease

## Assessment by Radionuclide Ventriculography

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**To assess the hemodynamic influence of posture during radionuclide cardiac studies, rest and exercise electrocardiographically gated blood pool cardiac scintigraphy was performed in the supine and sitting positions in 22 normal subjects and in 20 patients with coronary artery disease (CAD). In normal subjects, left ventricular ejection fraction was higher in the sitting position both at rest (67 ± 6% versus 64 ± 5%, $p < 0.01$) and during exercise (79 ± 9% versus 76 ± 6%, $p < 0.05$). Left ventricular end-diastolic volume in the sitting position was smaller at rest (by 19 ± 26%, $p < 0.001$), but this variable was similar in both positions during exercise ($p > 0.05$). Left ventricular end-systolic volume was smaller in the sitting position both at rest, by 26 ± 31 percent, and during exercise, by 14 ± 20% ($p < 0.001$). Left ventricular end-diastolic volume increased from rest to exercise, in the sitting position by 31 ± 23% ($p < 0.001$) and in the supine position by 6 ± 22% ($p > 0.05$).**

**In patients with CAD, similar left ventricular ejection fractions in both postures were found at rest and during exercise. Left ventricular end-diastolic volume in the sitting posture was smaller at rest by 16 ± 22% ($p < 0.01$) and during exercise by 8 ± 18% ($p < 0.05$). Sitting left ventricular end-systolic volume was smaller by 18 ± 20% ($p < 0.001$) at rest and by 14 ± 21% ($p < 0.01$) during exercise. Left ventricular end-diastolic volume increased from rest to exercise, in the sitting position by 45 ± 36% ($p < 0.001$) and in the supine position by 32 ± 51% ($p < 0.01$). Despite significant hemodynamic differences, the value of rest-exercise radionuclide cardiac studies to detect CAD was similar in the 2 positions.**

Radionuclide ventriculography is being used extensively as a noninvasive method to assess ventricular function at rest and during exercise in both the supine and the sitting positions.[1–7] In normal subjects, left ventricular ejection fraction increases during bicycle ergometer exercise. In contrast, ejection fraction fails to increase at peak exercise in patients with coronary artery disease.[1–7] Although previous studies have determined the rest and exercise hemodynamic differences between the supine and sitting positions,[8–17] limited information is available regarding comparative scintigraphic studies in the 2 postures.[18–20] Furthermore, the few studies available thus far report conflicting results.

This investigation was undertaken to compare left ventricular ejection fraction and volume patterns and right ventricular ejection fraction, at rest and during bicycle exercise, in both the supine and sitting postures, in subjects without demonstrable heart disease and in patients with angiographic CAD and normal left ventricular function. The electrocardiographically gated blood pool cardiac scintigraphy, a noninvasive technique useful for serial determinations of quantitative ventriculograms,[1–4,19–23] was used.

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### Methods

**Patient population:** Twenty-two normal subjects included in the first group consisted of 16 men and 6 women aged 19 to 59 years (mean ± standard deviation 44 ± 12). Fourteen patients had atypical chest pain with normal hemodynamic function and coronary artery anatomy at cardiac catheterization and selective coronary artery cineangiography. No patient had clinical or electrocardiographic evidence of variant angina.[24] The remaining 8 were asymptomatic volunteers without evidence of cardiac disease. All control subjects had normal findings on physical examination, chest X-ray, and resting and exercise electrocardiography. None was an athlete or had performed regular exercise training in the recent or remote past.

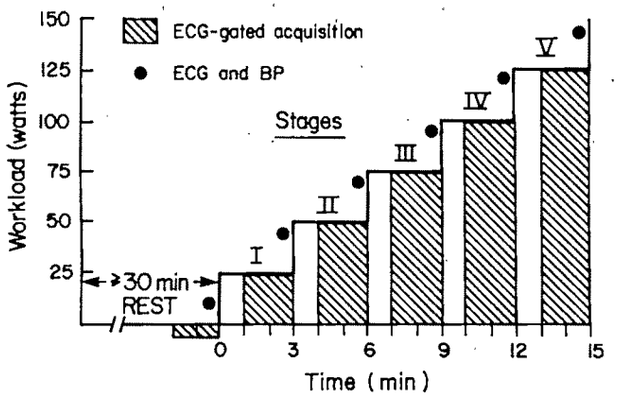



**FIGURE 1.** Exercise protocol. Subjects were often exercised to more than 5 stages. There was a rest period of ≥30 minutes before exercise in the first position, and at least a 60-minute rest period before exercise in the second position. Acquisition was performed twice at rest in each posture immediately before starting exercise. BP = blood pressure; ECG = electrocardiogram.

The second group consisted of 20 patients with CAD, as defined by at least a 50% reduction in diameter of ≥1 major coronary arteries. There were 15 men and 5 women aged 30 to 62 years (mean 47 ± 11). All had stable angina pectoris without evidence of associated cardiac conditions other than coronary heart disease. Patients with a history of acute myocardial infarction, abnormal Q waves (≥40 ms) on the electrocardiogram, or abnormal wall motion on contrast left ventricular cineangiography were excluded. Likewise, patients with valvular heart disease, systemic hypertension, diabetes mellitus, or intermittent claudication were excluded from the study.

All participants were leading a sedentary life, had normal sinus rhythm, and on request, manifested their willingness to participate. Physical examination, except for the occasional patient with an $S_4$ gallop, showed nothing abnormal and none had clinical, electrocardiographic, radiographic, or echocardiographic evidence of cardiomegaly, cardiac failure, left ventricular hypertrophy, or mitral valve prolapse.

Cardiac catheterization, biplane left ventricular angiography, and selective coronary cineangiography, using standard techniques, were carried out within 8 days before the radionuclide study. All participants had normal left ventricular function at rest as determined by an ejection fraction ≥65% on contrast ventriculography or a radionuclide ejection fraction ≥55%, or both, and normal wall motion.

**Radionuclide studies:** Electrocardiographically gated blood pool cardiac imaging was used to assess global and regional ventricular function and volume changes. Each study consisted of 2-minute acquisition in the modified left anterior oblique projection that best separated both ventricles and left atrium. A conventional Anger type scintillation camera with 37 photomultiplier tubes equipped with a high-sensitivity parallel-hole collimator interfaced to a dedicated medical computer system was used. Data were collected in a continuous electrocardiographic synchronized mode with 16 frames spanning the cardiac cycle. With this method, approximately 180,000 to 220,000 counts per frame were obtained. Acquisitions were made at rest and during the last 2 minutes of exercise at each work load (Fig. 1).

After retrieval, the raw data underwent 3-point spatial smoothing and background subtraction. A rectangular region of interest was then placed around the ventricle at end-diastole, taking special care to define the aortic and mitral valve planes and the interventricular septum. The left ventricular time activity curve was then generated by an automated edge-detection program which defined new left ventricular regions of interest for each frame of the composite cardiac cycle. From the time-activity curve, left ventricular ejection fraction was calculated by standard methods.[1–3] Right ventricular ejection fraction was calculated by similar methods but using manually defined right ventricular regions of interest at end-diastole and end-systole.[25] All ejection fraction determinations were performed by a single blinded operator.

Two observers who had no knowledge of the patient's

**TABLE I Summary of Hemodynamic Data on Normal Subjects and Patients With Coronary Artery Disease in Both Postures: Effect of Exercise**

| | Normal Subjects | | CAD | |
|---|---|---|---|---|
| | Rest | Exercise | Rest | Exercise |
| Supine | | | | |
| HR (beats/min) | 76 ± 13 | 147 ± 16 | 77 ± 9 | 128 ± 21 |
| SBP (mm Hg) | 120 ± 9 | 191 ± 19 | 119 ± 15 | 176 ± 18 |
| RPP (mm Hg × beats/min ×$10^2$) | 92 ± 20 | 283 ± 51 | 87 ± 17 | 227 ± 51 |
| LV EF (%) | 63.6 ± 5 | 76.3 ± 6 | 64.1 ± 8 | 62.0 ± 11 |
| RV EF (%) | 51.4 ± 7 | 65.8 ± 10 | 49.1 ± 6 | 58.3 ± 9 |
| %LV-EDV change | ... | 6 ± 22 | ... | 32 ± 51 |
| %LV-ESV change | ... | −33 ± 27 | ... | 38 ± 50 |
| Ex D (min) | ... | 10.1 ± 3.9 | ... | 7.0 ± 2.5 |
| Sitting | | | | |
| HR (beats/min) | 80 ± 9 | 164 ± 15* | 74 ± 10 | 141 ± 23* |
| SBP (mm Hg) | 119 ± 12 | 180 ± 20† | 116 ± 10 | 170 ± 16 |
| RPP (mm Hg × beats/min ×$10^2$) | 95 ± 11 | 295 ± 47† | 86 ± 14 | 240 ± 47† |
| LV EF (%) | 67.1 ± 6‡ | 78.9 ± 9† | 64.7 ± 7 | 63.6 ± 11 |
| RV EF (%) | 53.0 ± 8 | 67.2 ± 11 | 50.3 ± 8 | 61.3 ± 10 |
| %LV-EDV change | ... | 31 ± 23* | ... | 45 ± 36 |
| %LV-ESV change | ... | −22 ± 33† | ... | 48 ± 52 |
| Ex D (min) | ... | 10.9 ± 3.9 | ... | 7.6 ± 2.6 |

* $p < 0.001$, versus supine; † $p < 0.05$, versus supine; ‡ $p = < 0.01$, versus supine.
ED = exercise duration; HR = heart rate; LV-EF = left ventricular ejection fraction; %LV-EDV change = relative left ventricular end-diastolic volume change from rest to peak exercise; %LV-ESV change = relative left ventricular end-systolic volume change from rest to peak exercise; RPP = rate-pressure product; RV EF = right ventricular ejection fraction; SBP = systolic blood pressure.

**TABLE II Group and Individual Values of Left Ventricular Ejection Fraction and Wall Motion Scores at Rest and During Exercise in Normal Subjects**

| | Supine | | | | Sitting | | | |
|---|---|---|---|---|---|---|---|---|
| | Rest | | Exercise | | Rest | | Exercise | |
| Case | EF | WMS | EF | WMS | EF | WMS | EF | WMS |
| 1 | 63 | 0 | 83 | 0 | 65 | 0 | 84 | 0 |
| 2 | 55 | 0 | 81 | 0 | 64 | 0 | 87 | 0 |
| 3 | 71 | 0 | 88 | 0 | 62 | 0 | 75 | 0 |
| 4 | 73 | 0 | 84 | 0 | 84 | 0 | 92 | 0 |
| 5 | 61 | 0 | 76 | 0 | 65 | 0 | 88 | 0 |
| 6 | 64 | 0 | 84 | 0 | 76 | 0 | 86 | 0 |
| 7 | 67 | 0 | 66 | 0 | 64 | 0 | 68 | 1 |
| 8 | 64 | 0 | 84 | 0 | 66 | 0 | 89 | 0 |
| 9 | 74 | 0 | 81 | 0 | 72 | 0 | 90 | 0 |
| 10 | 65 | 0 | 80 | 0 | 71 | 0 | 78 | 0 |
| 11 | 59 | 0 | 71 | 0 | 63 | 0 | 70 | 0 |
| 12 | 68 | 0 | 76 | 0 | 74 | 0 | 82 | 0 |
| 13 | 63 | 0 | 74 | 0 | 69 | 0 | 76 | 0 |
| 14 | 70 | 0 | 68 | 1 | 67 | 0 | 60 | 2 |
| 15 | 56 | 0 | 77 | 0 | 61 | 0 | 73 | 0 |
| 16 | 63 | 0 | 71 | 0 | 58 | 0 | 64 | 0 |
| 17 | 55 | 0 | 73 | 0 | 65 | 0 | 80 | 0 |
| 18 | 60 | 0 | 67 | 0 | 55 | 0 | 70 | 0 |
| 19 | 61 | 0 | 69 | 0 | 67 | 0 | 76 | 0 |
| 20 | 67 | 0 | 82 | 0 | 76 | 0 | 87 | 0 |
| 21 | 56 | 0 | 70 | 0 | 69 | 0 | 83 | 0 |
| 22 | 64 | 0 | 73 | 0 | 64 | 0 | 78 | 0 |
| Mean | 63.6 | 0.00 | 76.3 | 0.05 | 67.1 | 0.00 | 78.9 | 0.14 |
| SD | 5.6 | 0.00 | 6.5 | 0.21 | 6.5 | 0.00 | 8.8 | 0.47 |
| p | ... | ... | * | ... | ... | ... | * | ... |

* = $p < 0.001$, versus rest. EF = left ventricular ejection fraction ×100; WMS = wall motion score.

clinical or angiographic data systematically analyzed regional wall motion in 5 segments—high septal, low septal, inferoapical, posterolateral, and superolateral—by subjective assessment of the endless-loop movie format and static mode[1] and with the aid of computer manipulation of images including the stroke volume image,[7,26] the ejection fraction image,[7] and the superimposition of the end-diastolic and end-systolic isocontours.[27] Each segment was classified as normal, hypokinetic, akinetic, or dyskinetic (scored 0, 1, 2, and 3, respectively). The scores of all segments were then added to obtain a numerical expression of wall motion for each study; this figure was then averaged to the nearest whole number between the 2 observers. In our laboratory, the intra- and interobserver variability of wall motion interpretation had correlation coefficients of 0.97 and 0.92, respectively. Radionuclide wall motion and left ventricular ejection fraction correlated closely with contrast studies.[26] An increase in the right and left ventricular ejection fraction of ≥7% and no change in wall motion score was considered the normal response to exercise.[3] Variations in ejection fraction ≤6% may be attributed to physiologic or statistical noise.

Left ventricular volume changes from rest to exercise were determined for end-diastole and end-systole using the same background-subtracted regions of interest as those utilized to calculate ejection fraction, as follows: Percent volume change = $100 \times [(\text{LVC Ex}/e^{-\lambda t}) - (\text{LVC R})]/\text{LVC R}$, where LVC = normalized (that is, corrected for the actual frame time and the number of processed cycles) left ventricular end-diastolic or end-systolic counts at peak exercise (Ex) or rest (R) (average of the 2 radionuclide studies at rest); and $e^{-\lambda t}$ = general equation for isotope decay where t = absolute time difference (in minutes) between the midpoints of rest and exercise studies and $\lambda$ = decay constant for technetium-99m. A negative value indicates a decrease, whereas a positive one indicates an increase in left ventricular volume from rest to exercise. There was a high degree of correlation between the 2 resting values for left ventricular end-diastolic and end-systolic counts, corrected for background and beats processed, in the supine (r = 0.96) and sitting (r = 0.93) positions.

Similarly, left ventricular volume differences between the 2 postures were calculated for end-diastole and end-systole, both at rest and during peak exercise, as follows: sitting/supine LVV ratio = $100 \times (\text{LVC Sit} \times \text{ID})/(\text{LVC Sup} \times \text{ID})$, where LVV = left ventricular end-diastolic or end-systolic volume; LVC = normalized left ventricular end-diastolic or end-systolic counts at rest or at peak exercise in the sitting (Sit) or supine (Sup) position; ID = correction for isotope decay (ID = 1 for the study performed in the second position and ID = $e^{-\lambda t}$ for the study carried out in the initial position, where t = time [in minutes] between corresponding studies in the supine and sitting positions). An LVV ratio value <100% implies a greater volume supine.

Actual volumes are not measured by this count-derived technique, but because photon attenuation factors such as body build remain constant for each person, relative changes in ventricular volumes produced by exercise and by changes in body position can be compared for each subject. This technique, which has the inherent advantage of making no geometric assumptions about left ventricular shape, has been used to measure left ventricular volume responses to interventions such as exercise, nitroglycerin administration, and atrial and ventricular pacing.[19–23]

**Study design:** Before the investigation was begun, the administration of beta-blocking agents and oral nitrates was discontinued for at least 72 and 24 hours, respectively, in patients receiving these medications. None took sublingual glyceryl trinitrate in the last 6 hours before or during the study.

Studies were carried out at rest and during bicycle exercise in both the supine and the sitting positions, following the protocol depicted in Figure 1. A rest period of 30 minutes preceded the first radionuclide acquisition, and a 60 minute rest period was interspaced between the 2 exercise tests. The order of the position was alternated in consecutive subjects,

**TABLE III Group and Individual Values of Left Ventricular Ejection Fraction and Wall Motion Scores at Rest and During Exercise in Patients With CAD**

| | Supine | | | | | Sitting | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Rest | | Exercise | | | Rest | | Exercise | | |
| Patient | EF | WMS | EF | WMS | ECG | EF | WMS | EF | WMS | ECG |
| 1-Vessel Disease | | | | | | | | | | |
| 1 | 74 | 0 | 80 | 1 | − | 77 | 0 | 78 | 2 | − |
| 2 | 56 | 0 | 65 | 2 | − | 66 | 0 | 79 | 0 | − |
| 3 | 77 | 0 | 73 | 5 | + | 67 | 0 | 69 | 4 | + |
| 4 | 55 | 0 | 62 | 0 | − | 59 | 0 | 68 | 0 | − |
| 5 | 70 | 0 | 72 | 3 | − | 61 | 0 | 57 | 4 | + |
| 6 | 82 | 0 | 74 | 4 | + | 85 | 0 | 86 | 2 | − |
| 7 | 64 | 0 | 56 | 2 | + | 64 | 0 | 59 | 4 | + |
| 2-Vessel Disease | | | | | | | | | | |
| 8 | 57 | 0 | 54 | 4 | + | 58 | 0 | 58 | 3 | + |
| 9 | 59 | 0 | 61 | 3 | − | 56 | 0 | 63 | 0 | − |
| 10 | 56 | 0 | 46 | 6 | + | 57 | 0 | 45 | 7 | + |
| 11 | 60 | 0 | 72 | 0 | − | 70 | 0 | 76 | 2 | − |
| 12 | 64 | 0 | 68 | 2 | − | 66 | 0 | 66 | 1 | − |
| 13 | 75 | 0 | 55 | 4 | + | 66 | 0 | 68 | 5 | + |
| 3-Vessel Disease | | | | | | | | | | |
| 14 | 56 | 0 | 44 | 5 | + | 59 | 0 | 61 | 3 | + |
| 15 | 61 | 0 | 50 | 3 | + | 64 | 0 | 46 | 5 | + |
| 16 | 66 | 0 | 67 | 1 | − | 57 | 0 | 59 | 1 | − |
| 17 | 58 | 0 | 53 | 4 | − | 59 | 0 | 52 | 2 | + |
| 18 | 65 | 0 | 71 | 2 | − | 68 | 0 | 70 | 6 | − |
| 19 | 65 | 0 | 69 | 1 | − | 64 | 0 | 66 | 2 | − |
| 20 | 62 | 0 | 48 | 6 | + | 71 | 0 | 46 | 8 | + |
| Mean | 64.1 | 0.00 | 62.0 | 2.90 | ... | 64.7 | 0.00 | 63.6 | 3.08 | ... |
| SD | 7.8 | 0.00 | 10.6 | 1.83 | ... | 7.3 | 0.00 | 11.3 | 2.31 | ... |
| p | ... | ... | ... | * | ... | ... | ... | ... | * | ... |

* = $p < 0.001$, versus rest. ECG = electrocardiogram; EF = left ventricular ejection fraction X100; WMS = wall motion score; + = ischemic; − = nonischemic.

so that one half the control subjects and one half the patients with CAD exercised first in the supine position, the other half exercised first in the sitting position. During supine exercise, the ergometer was positioned at the foot of a horizontal table, the axle being 34 cm (13.4 inches) above the table. All participants were exercised to maximal capacity, that is, angina or exhaustion. Symptoms, cuff-blood pressure, and a 9-lead electrocardiogram (standard, limb, and precordial $V_1$ and modified $V_5$ and $V_6$ leads) were recorded throughout the investigation.

**Statistical analysis:** All rest values in a given subject were defined as the average of the 2 resting radionuclide studies. Ejection fraction, heart rate, and blood pressure changes were analyzed by 2-way analysis of variance followed by the Tuckey test when appropriate. Student's $t$ test for paired data was used to compare results, including volume changes induced by exercise, in the supine and sitting positions. To compare the data at a given stage between the 2 groups, the unpaired student's $t$ test was utilized. To determine the statistical significance of sitting to supine left ventricular volume ratio, group values were analyzed with a 2-sided 1-sample $t$ test, where the hypothetical mean equals 100. Results are given as mean ± standard deviation.

## Results

**Normal subjects:** In no subject in this group did angina or an abnormal electrocardiogram develop during or after exercise. At rest, there were no significant differences in heart rate, rate-pressure product, right ventricular ejection fraction, or systolic blood pressure between the 2 postures although the first 3 variables were somewhat higher in the sitting position; however, mean left ventricular ejection fraction was significantly higher in the sitting position (Table I). On exercise in the sitting position, heart rate, rate-pressure product, and left ventricular ejection fraction were significantly higher and systolic blood pressure lower than in the supine position. The difference of right ventricular ejection fraction between the 2 postures did not reach statistical significance.

For both postures there was a significant increase, from rest to peak exercise, in mean heart rate, systolic blood pressure, rate-pressure product, and right and left ventricular ejection fraction ($p < 0.001$). All subjects but 1 in each position had an increase in right ventricular ejection fraction of ≥7%.

Individual and group left ventricular ejection fractions and segmental wall motion scores are shown in Table II. The mean ejection fraction increased on exercise by 12.7% (±7.0) in the supine position, with 20 of the 22 subjects having an increase of ≥7%. In the sitting position, ejection fraction increased during exercise by a mean of 11.8% (±7.2), with 19 subjects having an increase of ≥7%. In 21 subjects the left ventricular ejection fraction response to exercise was concordant in the 2 postures. As per our protocol, all subjects had normal wall motion scores at rest, and in no individual did wall motion score change with body position. During exercise 1 subject supine and 2 sitting had abnormal segmental wall motion scores, concordance being present in 21.

When ejection fraction plus wall motion scores were taken into consideration, discordant results were present in only 1 of the 22 subjects with 2 classified as "abnormal" in the supine (1 man and 1 woman) and 3 in the sitting position (1 man and 2 women).

The mean exercise duration was longer by 0.8 minutes in the sitting position, but this difference was not statistically significant.

**Patients with CAD:** Coronary cineangiography demonstrated single-vessel disease in 7, 2-vessel disease in 6, and 3-vessel disease in 7 patients. Angina developed at peak exercise in 13 patients in the supine and in 11 patients in the upright position. Nine patients in the supine and 10 in the upright position had abnormal S-T segment depression at peak exercise (Table III).

At rest, there were no significant differences in mean heart rate, systolic blood pressure, rate-pressure product, or right and left ventricular ejection fraction between the 2 postures (Table I). In both positions, mean heart rate, systolic blood pressure, rate-pressure product, and right ventricular ejection fraction increased ($p < 0.001$) from rest to peak exercise whereas left ventricular ejection fraction did not. Twelve patients in the supine and 13 in the upright posture had an increase in the right ventricular ejection fraction by ≥7%, concordance being present in 17 patients. During exercise, mean heart rate and rate-pressure product were higher in the sitting than in the supine position. Postural differences in exercise systolic blood pressure and exercise right ventricular ejection fraction did not reach statistical significance (Table I).

Individual and group left ventricular ejection fraction and segmental wall motion scores are presented in Table III. The mean ejection fraction decreased by 2.1% (±8.7) in the supine position, with 17 of the 20 patients failing to have an increase of ≥7%, whereas in the sitting position, ejection fraction decreased by a mean of 1.1% (±8.9), with 17 patients failing to have an increase of ≥7%. In 18 patients, left ventricular ejection fraction response to exercise was concordant in the 2 postures. Mean wall motion scores were similar in both positions at rest and during exercise, with 17 patients showing concordant results. When both ejection fraction plus wall motion scores were taken into consideration, concordance was present in 17 of the 20 patients, with 2 classified as "normal" in the supine and 3 in the sitting position.

**TABLE IV Prediction of the Extent of CAD by Radionuclide Exercise Studies**

| Radionuclide Studies | Coronary Arteriography | | |
|---|---|---|---|
| | No Disease (14) | SVD (7) | MVD (13) |
| Supine | | | |
| No disease | 13 | 1 | 1 |
| SVD | 1 | 3 | 4 |
| MVD | 0 | 3 | 8 |
| Sitting | | | |
| No disease | 12 | 2 | 1 |
| SVD | 2 | 2 | 5 |
| MVD | 0 | 3 | 7 |

MVD = multiple-vessel disease; SVD = single-vessel disease.

Mean exercise duration was 0.6 minutes longer in the sitting posture, but this difference did not reach statistical significance (Table I). However, exercise duration computed for all 42 participants was 8.6 minutes (±3.6) in the supine and 9.4 minutes (±3.6) in the sitting position, the difference being significant at the 1% level.

Details regarding the prediction of the extent of CAD are shown in Table IV in the 34 patients who underwent invasive studies. A correct prediction was made in 24 patients during supine radionuclide studies and in 21 during studies in the sitting position. The presence or absence of CAD was correctly predicted in 31 patients in the supine and in 29 patients in the sitting position.

**Relative left ventricular volume changes during exercise:** In normal subjects exercise-induced changes in left ventricular end-diastolic and end-systolic volumes were significantly different in the 2 postures (Table I). End-diastolic volume increased by 6% in the supine and by 31% in the sitting position, but only in the latter was this increase statistically significant ($p < 0.001$). End-systolic volume decreased in both postures ($p < 0.001$). In patients with CAD (Table I), exercise produced a significant increase ($p < 0.001$) in left ventricular end-diastolic and end-systolic volumes in the 2 positions.

**Relative volume differences between the 2 positions:** Left ventricular end-diastolic volume (Table V) was smaller in the sitting posture at rest in both normal subjects and patients with CAD. During peak exercise, patients with CAD had a smaller end-diastolic volume in the sitting position, whereas normal subjects showed similar end-diastolic volumes in the 2 positions. Left ventricular end-systolic volume (Table V) was significantly smaller in the sitting position in both groups at rest as well as during peak exercise.

## Discussion

Blood pool cardiac scintigraphy at rest and during exercise was carried out in both the supine and the sitting positions in normal subjects and in patients with CAD. The results indicated that (1) the usefulness of rest-exercise radionuclide studies in detecting subjects with CAD is similar in both postures; (2) in patients with CAD left ventricular end-diastolic volume increased from rest to exercise in both positions; (3) in normal subjects left ventricular end-diastolic volume increased from rest to exercise in the sitting but not in the supine

**TABLE V Relative Volume Differences Between the 2 Positions**

| | Sit/Sup LVEDV Ratio ×100 | | Sit/Sup LVESV Ratio ×100 | |
|---|---|---|---|---|
| | Normal Subjects | CAD | Normal Subjects | CAD |
| Rest | 81 ± 26* | 84 ± 22† | 74 ± 31* | 82 ± 20* |
| Ex | 97 ± 17 | 92 ± 18‡ | 86 ± 20* | 86 ± 21† |

* = $p < 0.001$; † = $p < 0.01$; ‡ = $p < 0.05$.
Ex = peak exercise; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; Sit = sitting; Sup = supine.

posture; (4) at rest, sitting left ventricular end-diastolic and end-systolic volumes were smaller than those supine in both groups; and (5) during exercise, sitting left ventricular end-systolic volume in both groups and sitting end-diastolic volume in patients with CAD were smaller than those supine, whereas end-diastolic volumes in normal subjects were similar in the 2 postures.

**Effect of posture on left ventricular function:** In normal subjects, the higher sitting left ventricular ejection fraction at rest and during exercise found in the present study may represent an increased contractile state (relative to that in the supine position) to compensate for the smaller sitting left ventricular end-diastolic volume. We thus concur with Poliner et al,[18] who suggested that changes in myocardial contractility are of greater relative importance in the upright than in the supine position. Our results are at variance with those of Freeman et al,[20] who reported that exercise left ventricular ejection fraction was similar in the 2 positions. Because the methods used were similar, this discrepancy may be attributable to different study populations.

Previous reports[5] have suggested that "abnormal" left ventricular function response to exercise may be found more frequently in normal women than in normal men. It is thus of interest that 2 of the 3 "abnormal" responses in our group of normal subjects were in women. However, because of the small number of subjects tested, no statistically valid conclusions regarding sex differences can be drawn from our data.

In patients with CAD, left ventricular ejection fraction and segmental wall motion score, at rest and during exercise, were similar in both positions. Therefore, for diagnostic purposes, upright and supine rest-exercise radionuclide ventriculography were equally effective in detecting subjects with CAD and in predicting its extent. These findings agree with those reported by Freeman et al.[20] Despite this generalization, individual variations of more than 6% between left ventricular ejection fraction in 1 position and the other do occur (Tables II and III), which suggest that during longitudinal follow-up radionuclide studies only 1 position should be used throughout.

Patients with electrocardiographic signs of myocardial ischemia during exercise more often developed an abnormal left ventricular function response, whereas all patients with "normal" ejection fraction and wall motion response to exercise showed no electrocardiographic signs of myocardial ischemia (Table III). These observations are in keeping with previous reports.[5,6]

**Effect of posture on left ventricular volume:** Two major physiologic effects of changes in body position are alterations in systemic venous return and in the sympathetic-parasympathetic predominancy.[28,29] A greater effect of posture on left ventricular volume at rest than during exercise is therefore expected because both venous return and sympathetic tone are markedly enhanced by muscular exercise itself,[28,29] regardless of body position. Indeed, our results and those of previous studies[8,18] showed that resting end-diastolic volume in both groups was lower in the sitting than in the supine position.

The smaller sitting left ventricular end-diastolic volume during exercise in patients with CAD may allow them to achieve a higher rate-pressure product in this position. Thus, at peak exercise patients with CAD achieved a similar level of left ventricular stress in the 2 positions. Freeman et al[20] did not compare rest or exercise left ventricular volumes in the 2 postures, but indirect observations led them to postulate a similar hypothesis. Thadani et al[9] found that left ventricular end-diastolic pressure during exercise-induced myocardial ischemia was lower in the upright than in the supine position, and attributed their findings to a relatively lower sitting left ventricular end-diastolic volume. Our results confirm their assumptions.

The sitting/supine left ventricular end-systolic volume ratio at rest was smaller in normal subjects than in patients with CAD despite similar sitting/supine end-diastolic volume ratios. These observations suggest that an increased contractility as a response to the diminished venous return in the sitting posture is present only in normal subjects and not in patients with CAD. This inability to increase myocardial contractility may be secondary to their limited oxygen supply, although an altered sympathetic-parasympathetic response cannot be discarded.

**Effect of exercise on left ventricular volume:** End-diastolic volume in normal subjects did not change significantly from rest to exercise in the supine position, but it increased when they exercised in the sitting position. These results reflect a lack of utilization of the Frank-Starling mechanism during exercise in the supine position and the use of this mechanism during upright exercise. Our observations further support the remarks made by Parker and Case[30] who, based on invasive studies, concluded that normal subjects do not make use of the Frank-Starling mechanism when exercising in the supine posture. These findings are in keeping with some previous studies[8,11,20,21,30–32] but not with others.[4,18] In patients with CAD, end-diastolic volume increased from rest to exercise in both positions, implying that the Frank-Starling mechanism was operational in the 2 postures. Similar findings were reported by some[4,20,21] but not by other[31] investigators.

It is difficult to reconcile the disparate reported results regarding exercise-induced ventricular volume changes. Different study populations or leg position may in part account for them. The level of physical conditioning, age, or other factors[33–36] may render physiologically heterogeneous a group of seemingly homogeneous individuals. Weiss et al[37] showed that normal subjects have an increase in left ventricular end-diastolic diameter from rest to exercise in the semisupine position. They attributed those findings to the higher intensity of exertion attained by their participants, but body position may have been the most important factor. In our study the legs were elevated relative to the chest. Poliner et al[18] and Slutsky et al,[31] whose findings were not entirely concordant with ours, did not specify the position of the legs during supine studies.

Finally, despite these generalizations, the effects of both posture and exercise over left ventricular end-diastolic and end-systolic volumes cannot be predicted in the individual subject. Some participants showed no

changes or changes in the opposite direction to those given by the group mean. These observations are not surprising. During invasive studies Thadani et al[9,10,16] and others[38–42] made similar observations and described marked individual variations in left ventricular end-diastolic pressure, stroke index, and stroke work index during exercise. Left ventricular end-diastolic pressure changes may possibly correlate with changes in left ventricular end-diastolic volume. Further studies combining invasive and radionuclide methods will be needed to assess this possibility.

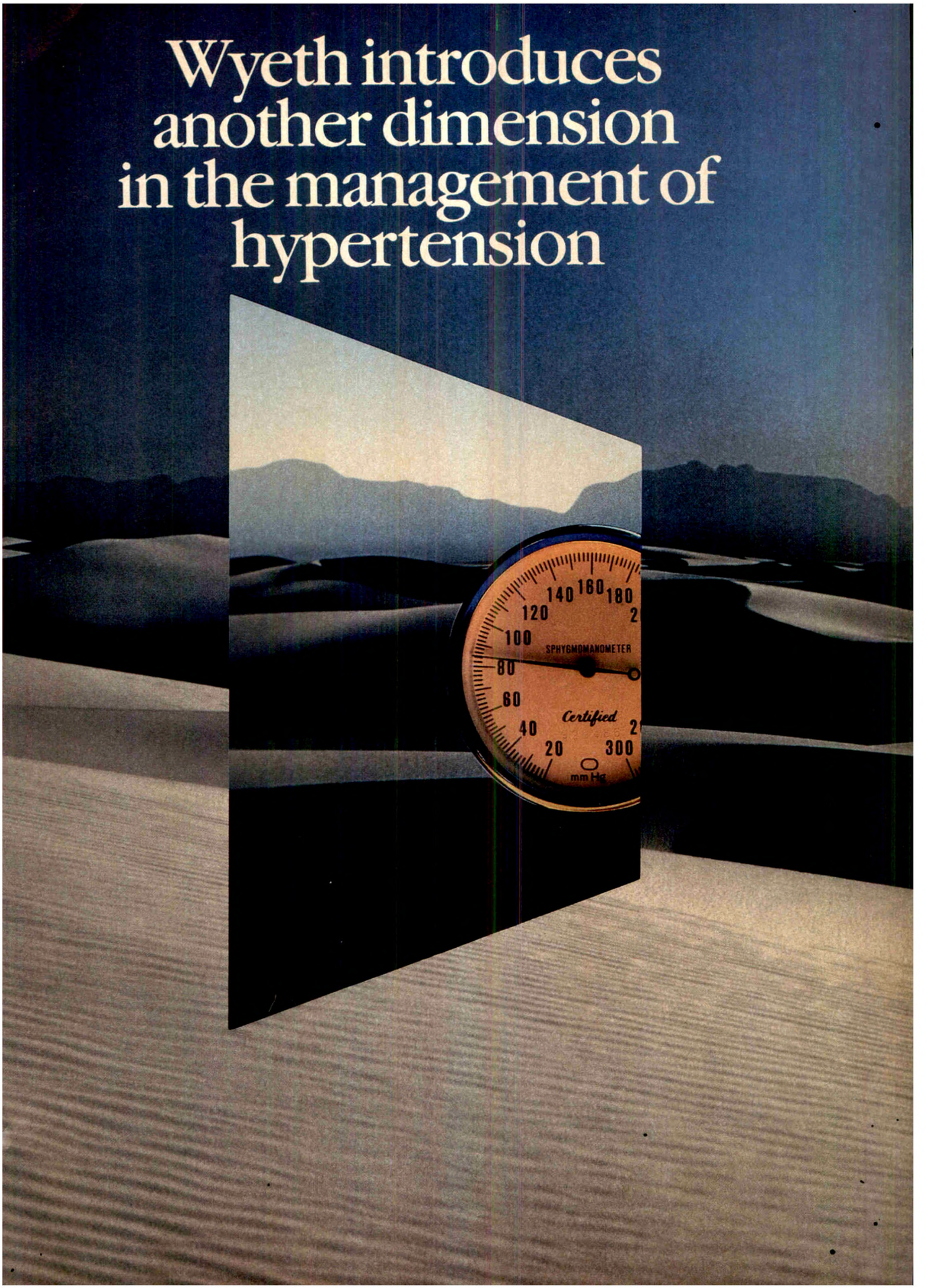
**Implications:** Despite significant differences between the hemodynamic responses at rest and during exercise in the sitting and supine positions, the usefulness of rest-exercise radionuclide studies in detecting subjects with CAD is similar in both postures. Our results suggest that during longitudinal studies, absolute values of quantitative radionuclide ventriculography in 1 position should not be compared with those in the other position either at rest or during peak exercise in the individual patient. In patients with CAD, estimated variables of myocardial oxygen consumption at peak exercise indicate similar metabolic demands in both postures, with the heart rate being higher in the sitting position and the end-diastolic volume being higher in the supine position. Finally, our data support the proposition that during supine exercise normal subjects do not use the Frank-Starling mechanism, whereas this mechanism is evident in patients with CAD during supine exercise and in both groups during upright exercise.

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## References

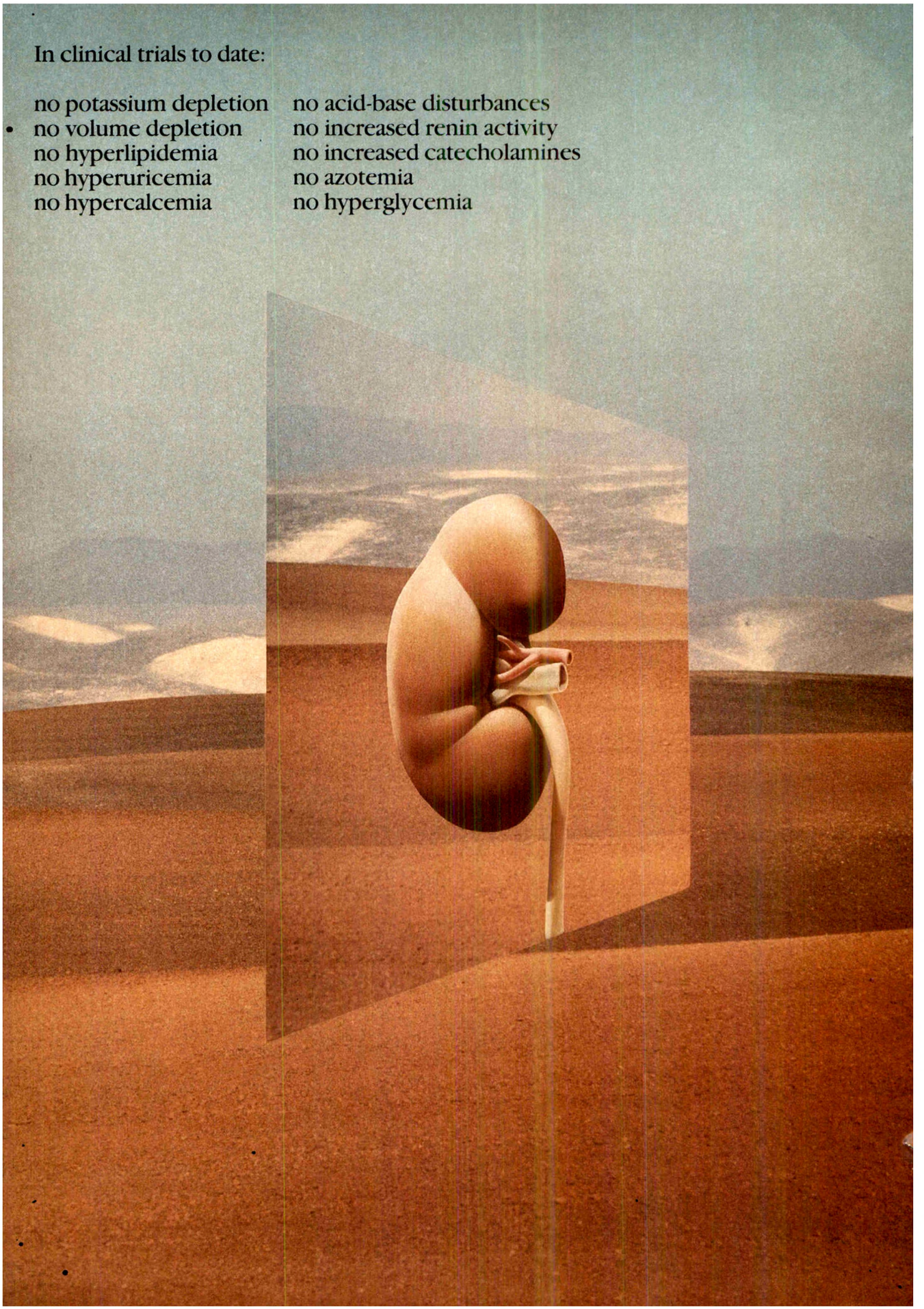

1. **Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS.** Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary artery disease. N Engl J Med 1977;296:839–844.
2. **Borer JS, Kent KM, Bacharach SL, Green MV, Rosing DR, Seides SF, Epstein SE, Johnston GS.** Sensitivity, specificity and predictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease: comparison with exercise electrocardiography. Circulation 1979;60:572–580.
3. **Manyari DE, Nolewajka A, Purves P, Donner A, Kostuk WJ.** Comparative value of the cold-pressor test and supine bicycle exercise to detect subjects with coronary artery disease using radionuclide ventriculography. Circulation 1982;65:571–579.
4. **Greenberg PS, Ellestad MH, Berge R, Johnson K, Hayes M, Bible M, Morales-Ballejo H.** Radionuclide angiographic correlation of the R wave, ejection fraction, and volume response to upright bicycle exercise. Chest 1981;80:459–464.
5. **Jones R, McEwan P, Newman G, Port S, Rerych S, Scholz P, Upton M, Peter C, Austin E, Leong K, Gibbons R, Cobb F, Coleman R, Sabiston D.** Accuracy of diagnosis of coronary artery disease by radionuclide measurement of left ventricular function during rest and exercise. Circulation 1981;64:586–601.
6. **Berger HJ, Reduto LA, Johnston DE, Borkowski H, Sands M, Cohen LS, Langou RA, Gottschalk A, Zaret BL.** Global and regional left ventricular response to bicycle exercise in coronary artery disease. Assessment by quantitative radionuclide angiocardiography. Am J Med 1979;66:13–21.
7. **Bodenheimer MM, Banka VS, Fooshe CM, Gillespie JA, Helfant RH.** Detection of coronary heart disease using radionuclide determined regional ejection fraction at rest and during handgrip exercise. Correlation with coronary arteriography. Circulation 1978;58:640–648.
8. **Holmgren A, Ovenfors CO.** Heart volume at rest and during muscular work in the supine and the sitting position. Acta Med Scand 1960;167:267–277.
9. **Thadani U, West RO, Mathew TM, Parker JO.** Hemodynamics at rest and during supine and sitting bicycle exercise in patients with coronary artery disease. Am J Cardiol 1977;39:776–783.
10. **Thadani U, Parker JO.** Hemodynamics at rest and during supine and sitting bicycle exercise in normal subjects. Am J Cardiol 1978;41:52–59.
11. **Crawford MH, White DH, Amon KW.** Echocardiographic evaluation of left ventricular size and performance during handgrip and supine and upright bicycle exercise. Circulation 1979;59:1188–1196.
12. **Bevegard S, Holmgren A, Jonsson B.** The effect of body position on the circulation at rest and during exercise with special reference to influence on stroke volume. Acta Physiol Scand 1960;49:279–298.
13. **Granath A, Jonsson B, Strandell T.** Circulation in healthy old men studied by right heart catheterization at rest and during exercise in supine and sitting positions. Acta Med Scand 1964;176:425–446.
14. **Lacerof H.** Influence of body position on exercise tolerance, heart rate, blood pressure and respiratory rate in coronary insufficiency. Br Heart J 1971; 33:78–83.
15. **Bygdeman S, Wahren J.** Influence of body position on the anginal threshold during leg exercise. Eur J Clin Invest 1974;4:201–206.
16. **Thadani U, Parker JO.** Influence of glyceryl trinitrate during supine and upright exercise in patients with angina pectoris. Br Heart J 1978;40: 1229–1236.
17. **Epstein SE, Beiser GD, Stampfer M, Braunwald E.** Exercise in patients with heart disease. Effects of body position and type and intensity of exercise. Am J Cardiol 1969;23:572–576.
18. **Pollner LR, Dehmer GJ, Lewis SE, Parkey RW, Blomqvist CG, Willerson JT.** Left ventricular performance in normal subjects: a comparison of the responses to exercise in the upright and supine positions. Circulation 1980;62:528–534.
19. **Manyari DE, Nolewajka A, Purves P, Kostuk WJ.** Right and left ventricular function and volume changes at rest and during exercise in the supine and sitting positions (abstr). Circulation 1980;62:Suppl III:III–228.
20. **Freeman MR, Berman DS, Staniloff H, Elkayam U, Maddahi J, Swan HJ, Forrester J.** Comparison of upright and supine bicycle exercise in the detection and evaluation of extent of coronary artery disease by equilibrium radionuclide ventriculography. Am Heart J 1981;102:182–189.
21. **Manyari DE, Melendez LJ, Driedger AA, Cradduck TD, MacDonald AG, Kostuk WJ.** Left ventricular function and volume during supine exercise in subjects with coronary artery disease. J Appl Physiol 1981;50:636–642.
22. **Ritchie JL, Sorensen SG, Kennedy JW, Hamilton GW.** Radionuclide angiography: noninvasive assessment of hemodynamic changes after administration of nitroglycerin. Am J Cardiol 1979;43:278–284.
23. **Hung J, Kelly DT, Hutton BF, Uther JB, Baird DK.** Influence of heart rate and atrial transport on left ventricular volume and function: relation to hemodynamic changes produced by supraventricular arrhythmia. Am J Cardiol 1981;48:632–638.
24. **Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N.** A variant form of angina pectoris. Am J Med 1959;27:375–388.
25. **Maddahi J, Berman DS, Matsuoka DT, Waxman AD, Stankus KE, Forrester JS, Swan HJ.** A new technique for assessing right ventricular ejection fraction using rapid multiple gated equilibrium cardiac blood pool scintigraphy. Circulation 1979;60:581–589.
26. **Kostuk WJ, Chamberlain MJ, Sang HC.** Radionuclide angiocardiography, a noninvasive method for evaluating left ventricular ejection fraction and regional wall motion; comparison with contrast left ventricular angiography. Can Med Assoc J 1978;119:877–883.
27. **Jengo JA, Mena I, Blaufuss A, Criley JM.** Evaluation of left ventricular function (ejection fraction and segmental wall motion) by single pass radioisotope angiography. Circulation 1977;57:326–332.
28. **Abboud FM, Schmid PG, Heistad DD, Mark AL.** Regulation of peripheral and coronary circulation. In: Levine HJ, ed. Clinical Cardiovascular Physiology. New York: Grune & Stratton, 1976:143–257.
29. **Shepherd JT.** Role of the veins in the circulation. Circulation 1966;33: 484–491.
30. **Parker JO, Case RB.** Normal left ventricular function. Circulation 1979; 60:4–12.
31. **Slutsky R, Karliner J, Ricci D, Schuler G, Pfisterer M, Peterson K, Ashburn W.** Response of left ventricular volume to exercise in man assessed by radionuclide equilibrium angiography. Circulation 1979;60:565–571.
32. **Gorlin R, Cohen LS, Elliot WC, Klein MD, Lane FJ.** Effect of supine exercise on left ventricular volume and oxygen consumption in man. Circulation 1965;32:361–371.
33. **Clausen JP.** Circulatory adjustments to dynamic exercise and effect of physical training in normal subjects and patients with coronary artery disease. Prog Cardiovasc Dis 1976;18:459–495.
34. **Port S, Cobb FR, Coleman RE, Jones RH.** The effect of age on left ventricular function at rest and during exercise. N Engl J Med 1980;303: 1131–1137.
35. **Rozanski A, Maddahi J, Pantaleo N, Gutman J, Garcia E, Diamond G, Forrester J, Swan HJC, Berman D.** Assessment of left ventricular function during exercise in patients with normal coronary arteriograms: comparison to patients with a very low likelihood of coronary artery disease (abstr). Circulation 1981;64:Suppl IV:IV–262.
36. **Manyari DE, Melendez L, Driedger AA, Cradduck T, Purves P, Kostuk WJ.** Left ventricular volume changes during supine exercise in patients with and without coronary artery disease (abstr). J Nucl Med 1981;22:48.
37. **Weiss JL, Weisfeldt ML, Mason SJ, Garrison JB, Livengood SV, Fortuin NJ.** Evidence of Frank-Starling effect in man during severe semisupine exercise. Circulation 1979;59:655–661.
38. **Diamond EG, Benchimol A.** Correlation of intracardiac pressure and precordial movement in ischemic heart disease. Br Heart J 1963;25:389–392.
39. **Malmborg RO.** A clinical and hemodynamic analysis of factors limiting the cardiac performance in patients with coronary heart disease. Acta Med Scand [Suppl] 1965; 426:1–34.
40. **Parker JO, DiGiogi S, West RO.** A hemodynamic study of acute coronary insufficiency precipitated by exercise. Am J Cardiol 1966;17:470–483.
41. **McCallister B, Yipintsoi T, Hallerman F.** Left ventricular performance during mild supine leg exercise in coronary artery disease. Circulation 1968;37: 922–931.
42. **Weiner L, Dwyer E, Cox W.** Left ventricular hemodynamics in exercise induced angina pectoris. Circulation 1968;38:240–249.

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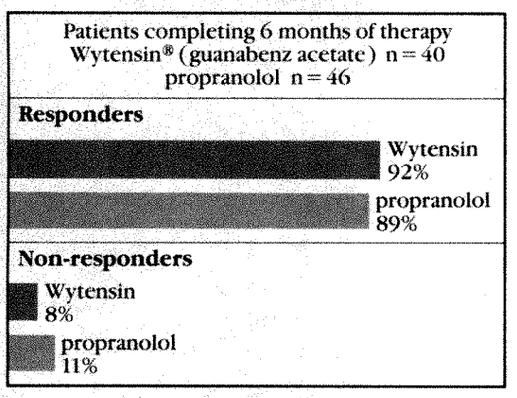
- no potassium depletion
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- no acid-base disturbances
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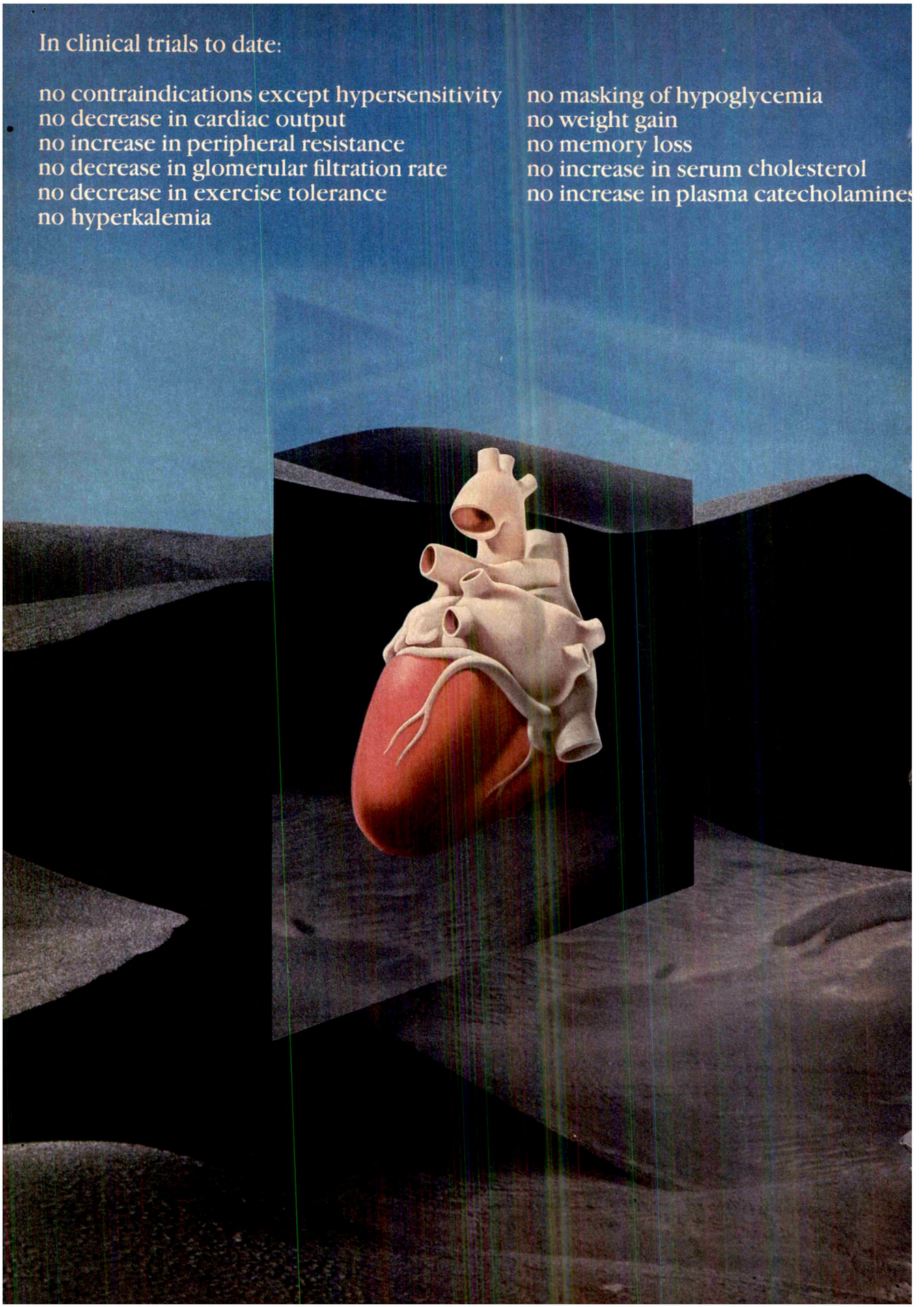
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Initial monotherapy in hypertension

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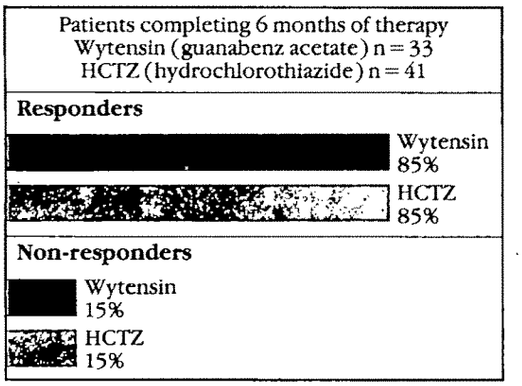
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no decrease in cardiac output
no increase in peripheral resistance
no decrease in glomerular filtration rate
no decrease in exercise tolerance
no hyperkalemia
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no weight gain
no memory loss
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| calcium | — | ↑ |
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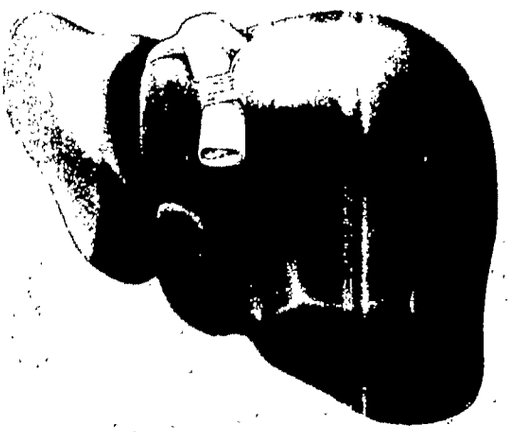
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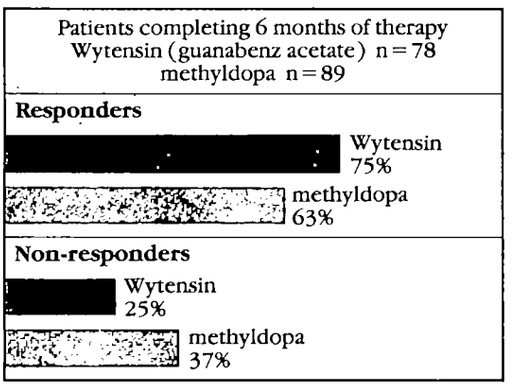
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|---|---|
| no sodium retention | no immunological disturbances |
| no weight gain | no liver damage |
| no decrease in GFR | no hemolytic anemia |



Wyeth

# Another dimension of management beyond the scope of methyldopa

**Highly effective in double-blind, multicenter studies**




**Important homeostatic advantages**

| | Wytensin | methyldopa |
|---|---|---|
| sodium excretion | ▬ | ⬇ |
| plasma volume | ▬ | ⬆ |
| weight | ⬇ | ⬆ |
| glomerular filtration rate | ▬ | ⬇ |

**Wytensin® does not produce sodium retention or volume expansion.**[3]
Methyldopa causes sodium retention and volume expansion with consequent development of drug tolerance. In contrast, drug tolerance has not developed with Wytensin probably because it does not induce retention of sodium and body fluid.

**Wytensin® is virtually free of serious adverse reactions.**
Unlike methyldopa, Wytensin does not produce immunological blood or liver toxicity or produce a positive Coombs' test. Wytensin also lacks the relatively high incidence of sexual dysfunction or mental depression seen with methyldopa.

**Wytensin® side effects are often transient or avoidable.**
Patients may experience drowsiness and dry mouth early during Wytensin therapy, but these effects are mostly mild, especially when the initial dosage is 4 mg b.i.d., with the second dose administered **h.s.**

New

**WyTensin®**

(guanabenz acetate)

4 mg b.i.d.

Initial monotherapy in hypertension

See important information on last page.

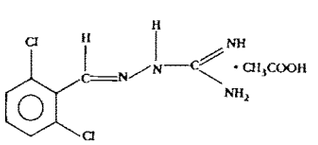
Initial monotherapy in hypertension

# New Wytensin (guanabenz acetate) 4 mg b.i.d.

More than 1,400 patients evaluated
No sodium retention
No electrolyte or metabolic risk factors
A favorable therapeutic index
Convenient, compliance-enhancing b.i.d. dosage
No contraindications except hypersensitivity

**Description**

Wytensin (guanabenz acetate), an antihypertensive agent for oral administration, is an aminoguanidine derivative, 2,6-dichlorobenzylideneaminoguanidine acetate, and its structural formula is:



It is an odorless, white to off-white, crystalline substance, sparingly soluble in water and soluble in alcohol, with a molecular weight of 291.14. Each tablet of Wytensin is equivalent to 4 mg or 8 mg of free guanabenz base.

Wytensin is available as 4 or 8 mg tablets for oral administration.

**Clinical Pharmacology**

Wytensin is an orally active central alpha-2 adrenergic agonist. Its antihypertensive action appears to be mediated via stimulation of central alpha adrenergic receptors, resulting in a decrease of sympathetic outflow from the brain at the bulbar level to the peripheral circulatory system.

PHARMACOKINETICS

In human studies, about 75% of an orally administered dose of Wytensin is absorbed and metabolized with less than 1% of unchanged drug recovered from the urine. Peak plasma concentrations of unchanged drug occur between two and five hours after a single oral dose. The average half-life for Wytensin is about 6 hours. The site or sites of metabolism of Wytensin and the consequences of renal or hepatic insufficiency on excretion of Wytensin or its metabolites have not been determined. The effect of meals on the absorption of Wytensin has not been studied.

PHARMACODYNAMICS

The onset of the antihypertensive action of Wytensin begins within 60 minutes after a single oral dose and reaches a peak effect within two to four hours. The effect of an acute single dose is reduced appreciably six to eight hours after administration, and blood pressure approaches baseline values within 12 hours of administration.

The acute antihypertensive effect of Wytensin occurs without major changes in peripheral resistance, but its chronic effect appears to be a decrease in peripheral resistance. A decrease in blood pressure is seen in both the supine and standing positions without alterations of normal postural mechanisms, so that postural hypotension has not been observed. Wytensin decreases pulse rate by about 5 beats per minute. Cardiac output and left ventricular ejection fraction are unchanged during long-term therapy.

With effective control of blood pressure in hypertensive patients, Wytensin has not demonstrated any significant effect on glomerular filtration rate, renal blood flow, renal sodium or potassium excretion, renal concentrating ability, body fluid volume, or body weight. In clinical trials of six to thirty months, hypertensive patients whose blood pressure was controlled with Wytensin lost one to four pounds of body weight. The mechanism of this weight loss has not been established. Tolerance to the antihypertensive effect of Wytensin has not been observed.

During long-term administration of Wytensin, there is a small decrease in serum cholesterol and total triglycerides without any change in the high-density lipoprotein fraction. Plasma norepinephrine, serum dopamine beta-hydroxylase, and plasma renin activity are decreased during chronic administration of Wytensin. No changes in serum electrolytes, uric acid, blood-urea nitrogen, calcium, or glucose have been observed.

Wytensin and hydrochlorothiazide have been shown to have at least partially additive effects in patients not responding adequately to either drug alone.

**Indications and Usage**

Wytensin is indicated in the treatment of hypertension. It may be employed alone or in combination with a thiazide diuretic.

**Contraindication**

Wytensin is contraindicated in patients with a known sensitivity to the drug.

**Precautions**

1. Sedation: Wytensin causes sedation or drowsiness in a large fraction of patients. When Wytensin is used with centrally active depressants, such as phenothiazines, barbiturates, and benzodiazepines, the potential for additive sedative effects should be considered.

2. Patients with vascular insufficiency: Wytensin, like other antihypertensive agents, should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or severe hepatic or renal failure.

3. Rebound: Sudden cessation of therapy with central alpha agonists like Wytensin may rarely result in "overshoot" hypertension and more commonly produces an increase in serum catecholamines and subjective symptomatology.

INFORMATION FOR PATIENTS

Patients who receive Wytensin should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

LABORATORY TESTS

In clinical trials, no clinically significant laboratory test abnormalities were identified during either acute or chronic therapy with Wytensin. Tests carried out included CBC, urinalysis, electrolytes, SGOT, bilirubin, alkaline phosphatase, uric acid, BUN, creatinine, glucose, calcium, phosphorus, total protein, and Coombs' test. During long-term administration of Wytensin, there was a small decrease in serum cholesterol and total triglycerides without any change in the high-density lipoprotein fraction. In rare instances an occasional non-progressive increase in liver enzymes has been observed. However, no clinical evidence of hepatic disease has been found.

DRUG INTERACTIONS

Wytensin has not been demonstrated to cause any drug interactions when administered with other drugs, such as digitalis, diuretics, analgesics, anxiolytics, and antiinflammatory or antiinfective agents, in clinical trials. However, the potential for increased sedation when Wytensin is administered concomitantly with CNS depressant drugs should be noted.

DRUG/LABORATORY TEST INTERACTIONS

No laboratory test abnormalities were identified with the use of Wytensin.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No evidence of carcinogenic potential emerged in rats during a two-year oral study with Wytensin at doses up to 9.5 mg/kg/day, i.e., about 10 times the maximum recommended human dose. In the Salmonella microsome mutagenicity (Ames) test system, Wytensin at 200-500 mcg per plate or at 30-50 mcg/ml in suspension gave dose-related increases in the number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes. No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Schizosaccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those which were lethal to the cells in culture. In another eukaryotic system, *Saccharomyces cerevisiae*, Wytensin produced no activity in an assay measuring induction of repairable DNA damage. Reproductive studies showed a decreased pregnancy rate in rats administered high oral doses (9.6 mg/kg) of Wytensin, suggesting an impairment of fertility. The fertility of treated males (9.6 mg/kg) may also have been affected, as suggested by the decreased pregnancy rate of their mates, even though the females received Wytensin only during the last third of pregnancy.

PREGNANCY

Pregnancy Category C

WYTENSIN MAY HAVE ADVERSE EFFECTS ON THE FETUS WHEN ADMINISTERED TO PREGNANT WOMEN. A teratology study in mice has indicated a possible increase in skeletal abnormalities when Wytensin is given orally at doses of 3 to 6 times the maximum recommended human dose of 1.0 mg/kg. These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits. However, increased fetal loss has been observed after oral Wytensin administration to pregnant rats (14 mg/kg) and rabbits (20 mg/kg). Reproductive studies of Wytensin in rats have shown slightly decreased live-birth indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6.4 and 9.6 mg/kg. There are no adequate, well-controlled studies in pregnant women. Wytensin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Because no information is available on the excretion of Wytensin in human milk, it should not be administered to nursing mothers.

PEDIATRIC USE

The safety and effectiveness of Wytensin in children less than 12 years of age have not been demonstrated. Therefore, its use in this age group cannot be recommended at this time.

**Adverse Reactions**

The incidence of adverse effects has been ascertained from controlled clinical studies conducted in the United States and is based on data from 859 patients who received Wytensin for up to 3 years. There is some evidence that the side effects are dose-related.

The following table shows the incidence of adverse effects occurring in at least 5% of patients in a study comparing Wytensin to placebo, at a starting dose of 8 mg b.i.d.

| Adverse Effect | Placebo (%) n = 102 | Wytensin (%) n = 109 |
|---|---|---|
| Dry mouth | 7 | 28 |
| Drowsiness or sedation | 12 | 39 |
| Dizziness | 7 | 17 |
| Weakness | 7 | 10 |
| Headache | 6 | 5 |

In other controlled clinical trials at the starting dose of 16 mg/day in 476 patients, the incidence of dry mouth was slightly higher (38%) and that of dizziness was slightly lower (12%), but the incidence of the most frequent adverse effects was similar to the placebo-controlled trial. Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time. In more recent studies using an initial dose of 8 mg/day in 274 patients, the incidence of drowsiness or sedation was lower, about 20%.

Other adverse effects were reported during clinical trials with Wytensin but are not clearly distinguishable from placebo effects and occurred with a frequency of 3% or less:

Cardiovascular—chest pain, edema, arrhythmias, palpitations.
Gastrointestinal—nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort.
Central nervous system—anxiety, ataxia, depression, sleep disturbances.
ENT disorders—nasal congestion.
Eye disorders—blurring of vision.
Musculoskeletal—aches in extremities, muscle aches.
Respiratory—dyspnea.
Dermatologic—rash, pruritus.
Urogenital—urinary frequency, disturbances of sexual function.
Other—gynecomastia, taste disorders.

**Drug Abuse and Dependence**

No reported dependence or abuse has been associated with the administration of Wytensin.

**Overdosage**

Accidental ingestion of Wytensin caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two children aged one and three years. Gastric lavage and administration of pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both patients.

Since experience with accidental overdosage is limited, the suggested treatment is mainly supportive while the drug is being eliminated from the body and until the patient is no longer symptomatic. Vital signs and fluid balance should be carefully monitored. An adequate airway should be maintained and, if indicated, assisted respiration instituted. There are no data available on the dialyzability of Wytensin.

**Dosage and Administration**

Dosage with Wytensin should be individualized. A starting dose of 4 mg twice a day is recommended, whether Wytensin is used alone or with a thiazide diuretic. Dosage may be increased in increments of 4 to 8 mg per day every one to two weeks, depending on the patient's response. The maximum dose studied to date has been 32 mg twice daily, but doses as high as this are rarely needed.

**How Supplied**

Wytensin® (guanabenz acetate) Tablets, Wyeth®, are available in the following dosage strengths:

4 mg, NDC 0008-0073, white, round tablet marked "WYETH" and "73", in bottles of 100.

8 mg, NDC 0008-0074, white, round, scored tablet marked "WYETH" and "74", in bottles of 100.

**Keep bottles of Wytensin Tablets tightly closed.**
**Dispense in tight containers.**
**Protect from light.**

Issued August 17, 1982


**References:**

1. Walker BR *et al.*: Comparative antihypertensive effects of guanabenz and methyldopa. *Clin Ther* 4:275, 1981.
2. Walker BR *et al.*: Guanabenz and methyldopa on hypertension and cardiac performance. *Clin Pharmacol Ther* 22:868, 1977.
3. Bosanac P *et al.*: Renal effects of guanabenz: a new antihypertensive. *J Clin Pharm* 16:531, 1976.


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Philadelphia, Pa 19101


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# Radionuclide Analysis of Peak Filling Rate, Filling Fraction, And Time to Peak Filling Rate

## Response to Supine Bicycle Exercise in Normal Subjects And Patients With Coronary Disease

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**Using gated equilibrium radionuclide angiography, variables of diastolic filling were analyzed at rest and during supine bicycle exercise in normal subjects (Group 1, n = 18), coronary patients with normal resting ejection fractions (Group 2, n = 26), and coronary patients with reduced resting ejection fractions (Group 3, n = 8). Indexes analyzed were peak filling rate and filling fraction during the first third of diastole. At rest, the peak filling rate was significantly lower in coronary patients than in normal subjects (3.18 ± 0.82 end-diastolic volume [EDV]/s in Group 1 versus 2.41 ± 0.66 EDV/s in Group 2, p <0.005; and 1.34 ± 0.26 EDV/s in Group 3, p <0.001 versus Group 1). These differences persisted at peak exercise. Coronary patients also had significantly lower filling fractions at rest and during exercise than did normal control subjects. The time from end-systole to peak filling rate was longer at rest in patients in Group 2 (203 ± 52 ms) than in subjects in Group 1 (172 ± 50 ms, p <0.025). This remained true when the time to peak filling was normalized by the R-R interval. Although the exercise time to peak filling was longer in coronary patients in both Groups 2 and 3 than in Group 1, these differences were not apparent when the interval was normalized by the R-R interval. Thus, abnormalities in peak filling rate and filling fraction exist in patients with coronary disease both at rest and during exercise, but large overlaps exist between normal and coronary patients. Caution is advised in comparing the timing of events during diastole because apparent group differences may be related in part to rest or exercise heart rate.**

Traditional analysis of left ventricular diastolic performance requires invasive pressure monitoring and cineangiographic techniques.[1,2] These approaches have occasionally uncovered abnormal diastolic performance in coronary patients that has not always been associated with impaired systolic performance. Abnormalities have occurred in patients studied at rest who have coronary disease even when acute ischemia or previous myocardial infarction was not found.[3,4] In addition, these disturbances can also be induced by acute ischemia[5–9] and other forms of stress.[10]

Noninvasive characterization of diastolic performance was recently performed with both gated equilibrium radionuclide ventriculography[11] and first-pass radionuclide ventriculography.[12] Others have evaluated diastolic radionuclide data at rest and during exercise[13] in normal and coronary patients and found abnormalities in left ventricular filling in patients with coronary disease. The purpose of this study was to reexamine a number of noninvasive variables of diastolic function at rest and during exercise in patients with coronary heart disease that have been suggested as being reliable and subtle markers of cardiac dysfunction.

From the Division of Cardiology and Department of Radiology, Veterans Administration Medical Center, San Diego, California. This study was supported in part by the Research Service of the Veterans Administration Medical Center, San Diego, California. Dr. Mancini was supported by the Canadian Heart Foundation, Ottawa, Canada. Dr. Higgins is a recipient of U.S. Public Health Service Research Career Development Award Grant 1K04HL00201 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received January 4, 1982; revised manuscript received July 29, 1982, accepted July 30, 1982.

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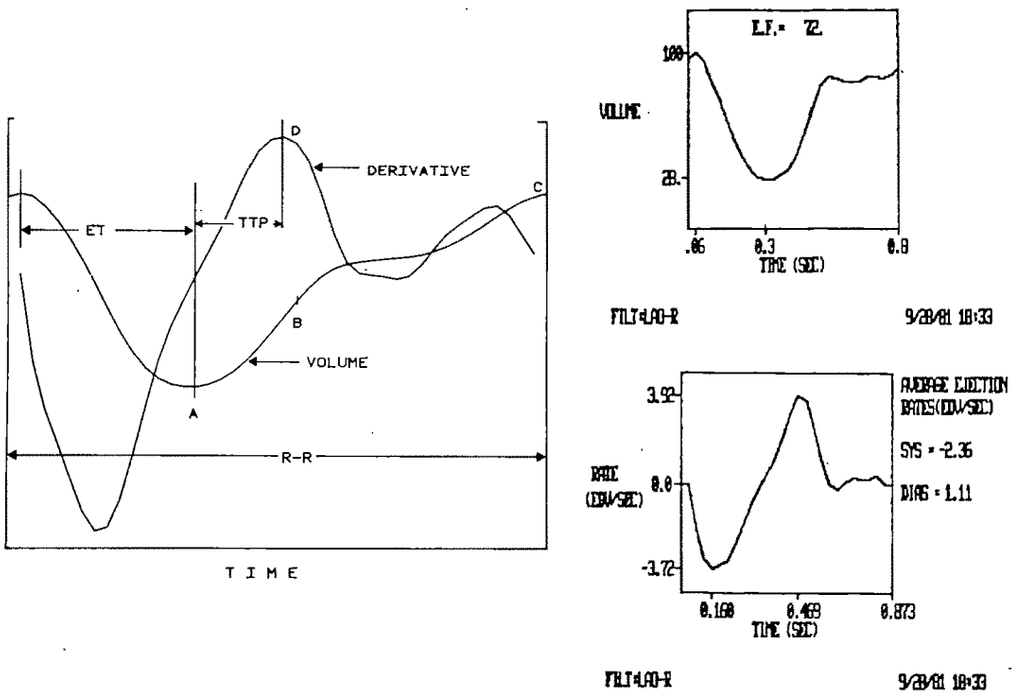



**FIGURE 1. Left,** volume curve and first derivative curve. Time is given along the abscissa. ET = ejection time; TTP = time to peak filling rate. The time interval between points A and B constitutes one third of diastole (one third of the time between points A and C). The difference between counts at A and B divided by the counts at B expressed as a percentage defines the filling fraction. The peak filling rate is taken from the derivative curve at point D and expressed as end-diastolic volumes/second. **Right,** A typical volume and first-derivative curve. The data are derived from the filtered images, but the curves are not themselves smoothed.

Using gated equilibrium radionuclide angiography at rest and with symptom-limited supine bicycle exercise in normal subjects and patients with coronary disease, we performed the following study to (1) determine the peak left ventricular filling rate and filling fraction during the first third of diastole, (2) determine the behavior of these indexes with exercise, and (3) investigate the timing of the peak left ventricular filling rate both in absolute terms and in relation to the R-R interval and ejection time.

This study confirms and extends recent studies[11–13] using radionuclide techniques to evaluate abnormalities of diastolic filling in coronary patients. However, we attempt to demonstrate the potential methodologic limitations of this technique which often arise from the effects of changes in heart rate and the timing of atrial systole. Furthermore, an appreciation of the drawbacks in the use of these variables in assessing individual patients is provided.

## Methods

**Patient population:** Group 1 consisted of 18 normal control volunteers (aged 43 ± 4 years), 13 male and 5 female, without symptoms or signs of systemic disease. No subject was taking medications and all had normal resting radionuclide left ventricular ejection fractions, electrocardiograms, and physical examinations.

Group 2 consisted of 26 patients with coronary disease (aged 48 ± 6 years) with normal radionuclide left ventricular ejection fractions at rest (≥45%). Ten of them had had previous myocardial infarction as evidenced by a history of chest pain, an elevated serum creatinine kinase level, and characteristic electrocardiographic changes at least 6 months previously. No patient had evidence of valvular heart disease. Eleven were taking beta-blocking medications at the time of the study.

Group 3 consisted of 8 patients with coronary disease (aged 47 ± 6 years) with a depressed radionuclide left ventricular ejection fraction at rest (<45%). Four had had myocardial infarction at least 6 months earlier. One patient had no clinical history of infarction but had Q waves in the lateral limb leads. Two patients were taking beta-blocking medications and 1 was on chronic digitalis glycoside therapy. No patient had evidence of valvular heart disease.

**Equilibrium radionuclide angiography:** All studies were performed with a portable scintillation camera (Picker Dyna-Mo), with the gamma detector placed in the 45° left anterior oblique position with a 10 to 15° caudal tilt. A general purpose collimator was used in all studies, and the photopeak of the camera was set at 140 keV with a 20% window.

For analysis of left ventricular function, the data were reformatted with the aid of an electrocardiographic gate, allowing the production of composite 32-frame cardiac cycles. The scan frames were frequency filtered, using both spatial (5 × 5 point) and temporal (7 point) filters. Cardiac cycles that fell outside a ±10% range of the R-R interval were excluded. Using threshold and second derivative techniques, a variable left ventricular region-of-interest was obtained for the 32 frames of the composite cardiac cycle. These regions were applied to the filtered data to produce ventricular volume curves. Background was assigned lateral to the left ventricle at end-systole.[14,15] All data were analyzed using a general nuclear medicine computer (MDS, A², Ann Arbor, Michigan).

The following variables were analyzed (Fig. 1). Left ventricular ejection time was defined as the time between the

early apex (end-diastole) of the time-activity (volume) curve and its nadir (end-systole). End-diastole was defined by the volume curve. The first derivative of the volume curve provides frame by frame ejection and filling rates. The early peak negative deflection of this first derivative curve was defined as peak ejection. The late positive peak was defined as peak filling rate (EDV/s). The time to peak filling rate was defined as the time from end-systole on the volume curve to the time of the late peak of the first derivative curve. The filling fraction was obtained by dividing the time from end-systole to the end of the R-R interval into 3 equal intervals; the time for the first third of diastole could then be determined. Filling fraction was then defined as the difference between the counts at the end of the first third of diastole and at end-systole divided by the counts at the end of the first third of diastole and expressed as a percentage.

At rest, the duration of all frames was ≤0.03 second (mean 0.024 ± 0.003), and with exercise all frame durations were ≤0.02 second (mean 0.013 ± 0.002).[16]

The "weighted forward backward breakup volume curve" used in this study has become a standard commercial algorithm used by many laboratories to evaluate cardiac function. Methods for merging the forward and backward derived curves and the importance of a number of weighting techniques were investigated in our laboratory by studying 5 dogs undergoing atrial pacing and repeated left ventriculography and by performing frame-by-frame analyses at several paced rates. Ejection fraction as well as peak ejection and filling rates were derived from either QRS-gated forward, reverse, or composite curves generated by both linear and exponential weighting of the forward and reverse breakup curves. These values were compared with results obtained from the mean heart rate-volume curves. Linear weighting interpolation for deriving the composite curve provided a reasonable approximation of the mean heart rate-volume curve. However, the correlation of filling rates and later diastolic volume curve events could more accurately be characterized by the forward-reverse breakup technique than by the forward curve alone.[17] In the present study, for analysis of forward breakup, the radionuclide volume curves were gated with respect to the onset of the QRS interval and averaged with a symmetrical weight distribution forward in time after the ±10% R-R interval exclusion. Beats were weighted in proportion to the mean heart rate beat, with the mean heart rate beats receiving the greatest weight. The reverse breakup curve was obtained by aligning the tail end of the curves (backward in time) with the same weights. The forward and reverse generated curves were then combined to generate the composite volume curve. The composite curves were produced by assuming that the initial portion of the forward curve and the terminal portion of the reverse curve were accurate and that the remaining intermediate portion of the curves could be obtained by linear weighting of the forward and reverse curves. The ejection fraction, filling fraction, peak filling rate, and time from

**TABLE I Ejection Fraction (EF) and Diastolic Filling Indexes at Rest (R) and During Exercise (E) in Normal Subjects and Patients With Coronary Artery Disease (CAD)**

| | | Normal Subjects (Group 1, n = 18) | Patients With CAD and Normal Rest LVEF (Group 2, n = 26) | Patients With CAD and Subnormal Rest LVEF (Group 3, n = 8) |
|---|---|---|---|---|
| EF (%) | R | 65 ± 6‖ | 59 ± 9* | 38 ± 5†,‡ |
| | E | 75 ± 7‖ | 57 ± 14† | 37 ± 8†,‡ |
| PFR | R | 3.13 ± 0.82 | 2.41 ± 0.66§ | 1.34 ± 0.26†,‡ |
| EDV/s | E | 6.40 ± 1.78‖ | 4.77 ± 2.00‖,¶ | 3.20 ± 1.30*,†,‡,# |
| FF (%) | R | 46 ± 13 | 36 ± 12¶ | 13 ± 5†,‡ |
| | E | 39 ± 17 | 20 ± 15†,‖ | 14 ± 10§ |

* p <0.025 (versus Group 1); † p <0.001 (versus Group 1); ‡ p <0.001 (versus Group 2); § p <0.005 (versus Group 1); ‖ p <0.001 (R versus E); ¶ p <0.01 (versus Group 1); # p <0.005 (R versus E).
Values are mean ±1 standard deviation. FF = filling fraction; LV = left ventricular; PFR = peak filling rate.

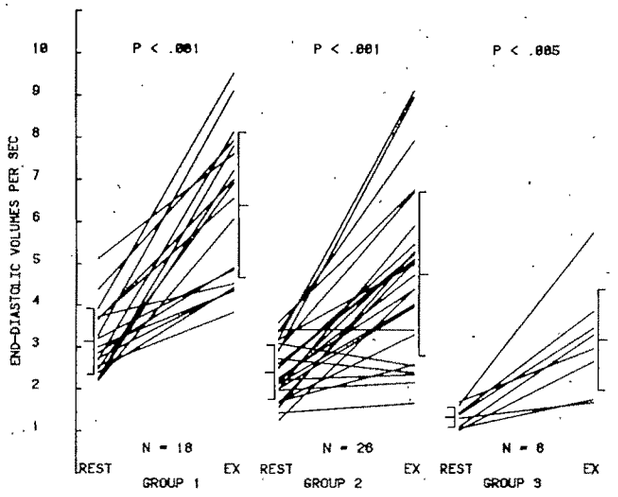



**FIGURE 2.** The response of peak diastolic filling rate to exercise (EX) in normal subjects (Group 1) and patients with coronary disease with normal (Group 2) and decreased rest left ventricular ejection fraction (Group 3). P values refer to comparisons of rest and exercise values within each group. Mean values ±1 standard deviation are shown by the **bars.**

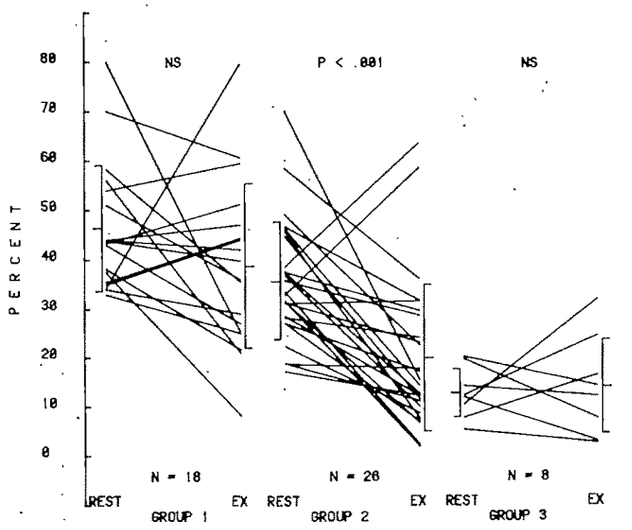



**FIGURE 3.** The response of the filling fraction to exercise (EX) in normal subjects (Group 1) and patients with coronary artery disease with normal (Group 2) and decreased rest ejection fraction (Group 3). P values refer to comparisons of rest and exercise values within each group. Mean values ±1 standard deviation are shown by the **bars.** NS = not significant.

end-systole to peak filling rate were determined from the merged, composite (that is, interpolated) volume-time curve.

In a subgroup of 26 patients, variability in the measurement of the indexes of interest between 2 observers was as follows: peak filling rate, ±8% (range −0.06 to +0.46 EDV/s); filling fraction, ±9% (range −8 to +8 filling fraction percentage units); and time from end-systole to peak filling rate, ±4% (range −20 to +10 ms).

**Clinical protocol:** The patients' own red cells were labelled ex vivo with 20 to 25 mCi of technetium-99m using the method of Smith and Richards.[18] The details of the exercise protocol were previously reported.[19,20] After equilibrium was reached, electrocardiographically gated scintillation data were collected for 5 minutes at rest. Graded supine exercise was performed and additional data collections were made at maximal exercise (usually 3 minutes in duration). Exercise was discontinued if the patient complained of shortness of breath, fatigue, or chest discomfort but was not limited by S-T segment depression. None of the normal subjects complained of chest pain or developed S-T segment depression. In the coronary patients with a normal left ventricular ejection fraction at rest, 14 of the 26 had an abnormal S-T segment response to exercise (≥1 mm S-T depression in 1 or more of lateral chest leads $V_3$ to $V_6$). Ten of them also had chest pain and in 2 of them the S-T response consisted of S-T elevations at peak exercise. In the coronary patients with a low left ventricular ejection fraction, 3 of the 8 had chest pain at peak exercise, in 2 of whom S-T segment depressions developed ≥1 mm, whereas 1 had S-T elevation.

All patients gave informed consent to this protocol which was approved by the University of California, San Diego Human Subjects Committee.

**Statistics:** Data are given as the group mean ±1 standard deviation. Comparisons were performed by the appropriate paired or unpaired Student's *t* test. Correlations were tested by linear regression analysis.

## Results

**Ejection fraction and diastolic filling indexes at rest and during exercise (Table I, Fig. 2 and 3):** Table I summarizes the results of ejection fraction, peak filling rate, and filling fraction in the 3 groups. The ejection fraction increased significantly with exercise in the normal subjects did not change in either group of coronary patients.

At rest, the peak filling rate was highest in the normal group (Group 1) and lowest in coronary patients with a depressed resting ejection fraction (Group 3) (3.13 ± 0.82 versus 1.34 ± 0.26 EDV/s, $p < 0.001$). In addition, coronary patients with a normal resting ejection fraction had lower peak filling rates at rest than did normal subjects ($p < 0.005$). With exercise, all 3 groups showed significant increases in peak filling rates (Fig. 2), but once again coronary patients had significantly lower values compared with the normal group. Coronary patients in Group 3 who had the lowest exercise ejection fractions also attained the lowest exercise peak filling rates. The magnitude of changes was greatest in Group 1 (+3.26 ± 1.70 EDV/s) compared with Group 2 (+2.36 ± 1.75 EDV/s, $p < 0.05$ versus Group 1) and Group 3 (+1.86 ± 1.10 EDV/s, $p < 0.001$ versus Group 1).

The filling fraction showed a similar trend at rest, that is, normal subjects had the highest filling fractions and coronary patients with low resting ejection fractions had the lowest filling fractions. Group 2 patients with normal resting ejection fraction had filling fractions of intermediate magnitude between Group 1 and Group 3. In contrast to peak filling rate, the filling fraction showed no significant change with exercise in the normal subjects or in coronary patients with subnormal ejection fractions at rest (Group 3). Furthermore, Group 2 patients showed a significant decrease in filling fraction with exercise (Fig. 3). The exercise filling fraction was lower in both groups of coronary patients than in normal subjects.

**TABLE II Timing Variables at Rest (R) and During Exercise (E) in Normal Subjects and Patients With CAD**

| | | Normal Subjects (Group 1, n = 18) | Patients With CAD and Normal Rest LVEF (Group 2, n = 26) | Patients With CAD and Subnormal Rest LVEF (Group 3, n = 8) |
|---|---|---|---|---|
| RR (ms) | R | 903 ± 130 | 880 ± 120 | 880 ± 100 |
| | E | 386 ± 57* | 470 ± 90*,† | 550 ± 120*,‡,§ |
| ET (ms) | R | 264 ± 33 | 260 ± 50 | 280 ± 80 |
| | E | 164 ± 31* | 190 ± 50* | 214 ± 42†,‖ |
| TTP (ms) | R | 172 ± 36 | 203 ± 51¶ | 176 ± 54 |
| | E | 98 ± 34* | 130 ± 50*,¶ | 151 ± 49† |
| TTP/R-R (%) | R | 19 ± 4 | 24 ± 7¶ | 21 ± 8 |
| | E | 26 ± 9‖ | 28 ± 10‖ | 28 ± 10 |
| TTP/ET (%) | R | 70 ± 27 | 82 ± 31 | 70 ± 35 |
| | E | 64 ± 31 | 74 ± 34 | 75 ± 29 |

* $p < 0.001$ (R versus E); † $p < 0.005$ (versus Group 1); ‡ $p < 0.001$ (versus Group 1); § $p < 0.05$ (versus Group 2); ‖ $p < 0.05$ (R versus E); ¶ $p < 0.025$ (versus Group 1).

Values are mean ±1 standard deviation. EF = ejection fraction; ET = ejection time; TTP = time from end-systole to peak filling rate.

**Analysis of timing variables (Table II, Fig. 4 and 5):** Table II summarizes the results of timing variables at rest and with exercise in all 3 groups. The R-R interval and ejection time were not different at rest among the groups, and in all 3 groups these intervals shortened significantly with exercise. During exercise the R-R interval was shortest in normal subjects, longest in Group 3 patients, and intermediate in Group 2 patients. The exercise ejection time was similar in Group 1 and 2 but was longer in Group 3 (214 ± 42 ms versus 164 ± 31 ms in normal subjects, $p < 0.005$).

Group 2 patients had a longer rest time to peak filling rate (203 ± 51 ms) than did normal subjects (172 ± 50 ms, $p < 0.025$), and this difference persisted when it was expressed as a function of the R-R interval but not when expressed as a function of the ejection time. However, Group 3 patients had a resting time to peak filling rate that was similar to that of the normal group, and normalization by R-R interval or ejection time did not help distinguish them from normal subjects.

With exercise the time to peak filling rate decreased significantly in Groups 1 and 2, but this change was not apparent when the interval was expressed as a function of the ejection time. The exercise time to peak filling rate tended to account for a greater proportion of the R-R interval in all 3 groups and statistical significance was achieved in Groups 1 and 2 (19 ± 4% at rest versus 26 ± 9% with exercise, $p < 0.05$ for Group 1; 24 ± 7% at

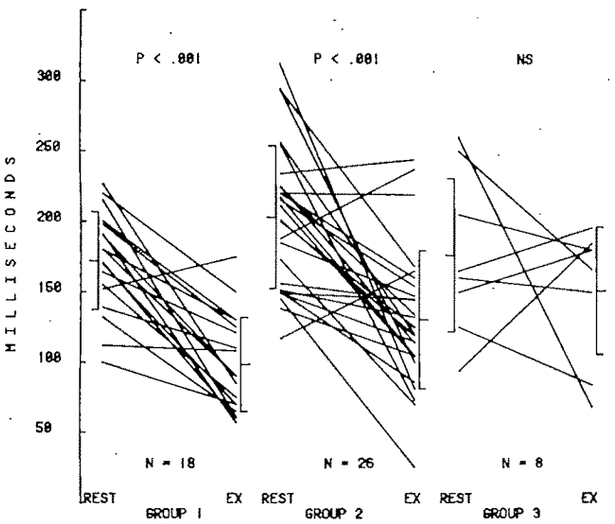



**FIGURE 4.** The time from end-systole to peak filling rate and its response to exercise (EX) in normal subjects (Group 1) and patients with coronary artery disease with normal (Group 2) and decreased rest left ventricular ejection fraction (Group 3). P values refer to comparison of rest and exercise values within each group. Mean ±1 standard deviation is shown by the **bars**.

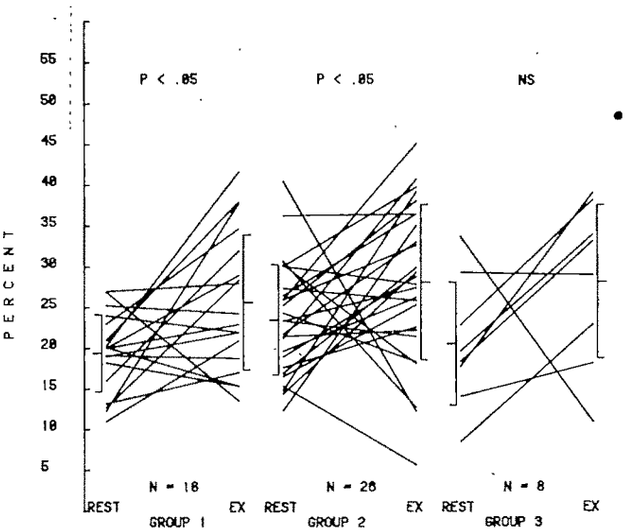



**FIGURE 5.** The time from end-systole to peak filling rate expressed as a percentage of the R-R interval and its response to exercise (EX) in normal subjects (Group 1) and patients with coronary artery disease with normal (Group 2) and decreased rest ejection fraction (Group 3). P values refer to comparisons of rest and exercise values within each group. Mean values ±1 standard deviation are shown by the **bars**.

**TABLE III Diastolic Filling Indexes in Normal Subjects and Coronary Patients at Rest (R) and During Exercise (E): Subclassification of Coronary Patients With Normal Rest Left Ventricular Ejection Fraction**

| | Peak Diastolic Filling Rate (EDV/s) | | Filling Fraction (%) | |
|---|---|---|---|---|
| | Rest | Exercise | Rest | Exercise |
| Normal subjects (n = 18) | 3.13 ± 0.82 | 6.40 ± 1.78* | 46 ± 13 | 39 ± 17 |
| Coronary patients with normal LV rest ejection fraction (n = 26) | | | | |
| On beta-blocking drugs (n = 11) | 2.40 ± 0.74‡ | 5.04 ± 1.78*,¶ | 33 ± 10† | 28 ± 18 |
| Off beta-blocking drugs (n = 15) | 2.42 ± 0.58† | 4.57 ± 2.06*,† | 38 ± 13 | 15 ± 10*,§,‖ |
| Previous infarction (n = 10) | 2.61 ± 0.59¶ | 4.66 ± 2.01¶,** | 33 ± 11‡ | 28 ± 19 |
| No previous infarction (n = 16) | 2.29 ± 0.66‡‡ | 4.84 ± 1.92*,‡ | 38 ± 12¶ | 15 ± 9§,‖,†† |
| Positive EKG response to exercise (n = 14) | 2.41 ± 0.64‡ | 4.61 ± 2.21‡,†† | 37 ± 13¶ | 18 ± 14††,‡‡ |
| Negative EKG response to exercise (n = 12) | 2.42 ± 0.66‡ | 4.95 ± 1.60*,¶ | 34 ± 10‡ | 22 ± 16‡,§§ |
| Abnormal ejection fraction response to exercise (n = 17) | 2.41 ± 0.63† | 4.14 ± 1.44*,§ | 34 ± 11† | 20 ± 13††,‡‡ |
| Normal ejection fraction response to exercise (n = 9) | 2.41 ± 0.69¶ | 5.96 ± 2.23*,¶¶ | 39 ± 14 | 20 ± 18‡,‖‖ |

*p <0.001 (R versus E); † p <0.01 (versus normal subjects);‡ p <0.025 (versus normal subjects); § p <0.001 (versus normal subjects); ‖ p <0.05 (versus presence of abnormal clinical feature in subclassification); ¶ p <0.05 (versus normal subjects); ** p <0.01 (R versus E); †† p <0.005 (R versus E); ‡‡ p <0.005 (versus normal subjects); §§ p <0.025 (R versus E); ‖‖ p <0.05 (R versus E); ¶¶ p <0.025 (versus presence of abnormal clinical feature in subclassification).

Values are mean ±1 standard deviation.

**TABLE IV Time From End-Systole to Peak Diastolic Filling Rate (TTP) in Normal Subjects and Coronary Patients at Rest (R) and Exercise (E): Subclassification of Coronary Patients With Normal Left Ventricular Ejection Fraction (EF)**

| | TTP (ms) | | TTP/R-R (%) | |
|---|---|---|---|---|
| | Rest | Exercise | Rest | Exercise |
| Normal subjects (n = 18) | 172 ± 36 | 98 ± 34* | 19 ± 4 | 26 ± 9† |
| Coronary patients with normal LV rest EF (n = 26) | | | | |
| On beta-blocking drugs (n = 11) | 218 ± 55‡ | 119 ± 49* | 26 ± 8‡ | 25 ± 11 |
| Off beta-blocking drugs (n = 15) | 192 ± 44 | 139 ± 48‡,§ | 22 ± 5‖ | 30 ± 9¶ |
| Previous infarction (n = 10) | 206 ± 64 | 120 ± 32§,‖ | 25 ± 9‖ | 27 ± 9 |
| No previous infarction (n = 16) | 201 ± 40‖ | 137 ± 56‡,** | 23 ± 5†† | 29 ± 10¶ |
| Positive ECG response to exercise (n = 14) | 216 ± 46†† | 141 ± 49**,†† | 25 ± 7†† | 31 ± 9 |
| Negative ECG response to exercise (n = 17) | 188 ± 52 | 118 ± 47§ | 22 ± 7 | 25 ± 10 |
| Abnormal EF response to exercise (n = 17) | 208 ± 49‡ | 137 ± 52‡,** | 24 ± 8‡ | 29 ± 9 |
| Normal EF response to exercise (n = 9) | 200 ± 46 | 117 ± 41** | 22 ± 5 | 27 ± 12 |

* p <0.001 (R versus E); † p <0.05 (R versus E); ‡ p <0.025 (versus normal subjects); § p <0.01 (R versus E); ‖ p <0.05 (versus normal subjects); ¶ p <0.025 (R versus E); ** p <0.005 (R versus E); †† p <0.01 (versus normal subjects).

Values are mean ±1 standard deviation. ECG = electrocardiographic.

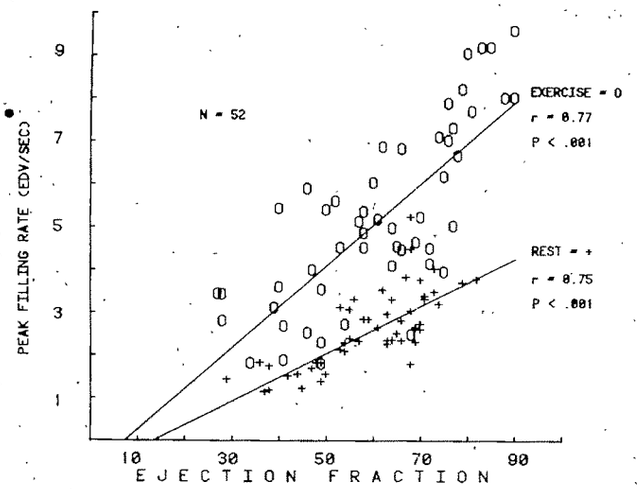



**FIGURE 6.** Correlation of ejection fraction and peak filling rate at rest and exercise for the entire study population.

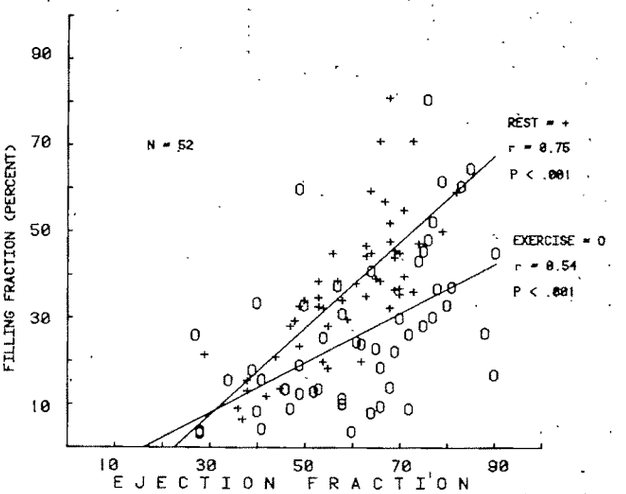



**FIGURE 7.** Correlation of ejection fraction and filling fraction at rest and exercise for the entire study population.

rest versus 28 ± 10% with exercise, $p < 0.05$ for Group 2).

The time to peak filling rate was longer with exercise in both coronary groups when compared with normal subjects, but this difference was lost when normalization by R-R interval and ejection time was undertaken.

**Subclassification of coronary patients with normal rest left ventricular ejection fraction (Group 2):** To further define the timing of diastolic events and the factors that might affect them, patients in Group 2 were analyzed with respect to intake of beta-blocking medication (n = 11), presence of previous myocardial infarction (n = 10), occurrence of an ischemic electrocardiographic response to exercise (n = 14), and occurrence of an abnormal ejection fraction response to exercise (n = 17). The ejection fraction response to exercise was considered abnormal when the exercise ejection fraction was <55% or failed to increase by 5% from a normal resting value.

The rest and exercise filling indexes and timing variables are summarized in Tables III and IV, respectively. Results in normal subjects are provided for ease of comparison. In general, the subgroups behaved as did the entire group with few exceptions. Of importance was that (1) coronary patients with a normal ejection fraction response to exercise attained a mean peak filling rate that was not statistically different from the values of the normal subjects, and (2) patients ingesting beta-blocking drugs had a longer resting time to peak filling rate than did normal subjects even when this interval was normalized by the R-R interval.

**Relation of filling rates to ejection fraction:** The rest and exercise peak filling rates are shown as a function of the corresponding rest and exercise ejection fraction for all patients in Figure 6. There was a significant correlation between these 2 variables both at rest ($r = 0.75$, $p < 0.001$) and at peak exercise ($r = 0.77$, $p < 0.001$). For the population as a whole, the filling fraction and ejection fraction showed a significant correlation at rest ($r = 0.75$, $p < 0.001$), and this correlation, although significant, was only fair at peak exercise ($r = 0.54$, $p < 0.001$) (Fig. 7).

**Sensitivity and specificity of diastolic variables in detecting coronary artery disease:** From our normal population we defined normal diastolic indexes in 2 ways, by using (1) 2 standard deviations from the group mean, or (2) the most extreme normal value as our cutoff criterion. The sensitivities (the number of true-positive tests divided by the number of patients with coronary artery disease) for detecting coronary disease in patients with a normal resting ejection fraction (Group 2, n = 26) are shown in Table V. Using these criteria, the specificity (number of true-negative tests

**TABLE V Sensitivity of Diastolic Variables for the Detection of Coronary Artery Disease in Patients With Normal Rest Left Ventricular Ejection Fraction (Group 2, n = 26)**

| | | Test Criteria* | Sensitivity | Test Criteria† | Sensitivity |
|---|---|---|---|---|---|
| PFR (EDV/s) | R | <1.49 | 8% (2) | <2.20 | 42% (11) |
| | E | <2.84 | 23% (6) | <3.84 | 31% (8) |
| FF (%) | R | <20 | 12% (3) | <33 | 46% (12) |
| | E | <4 | 8% (2) | <8 | 15% (4) |
| TTP (ms) | R | >244 | 19% (5) | >227 | 23% (6) |
| | E | >166 | 15% (4) | >175 | 12% (3) |
| TTP/R-R (%) | R | <27 | 23% (6) | <27 | 23% (6) |
| | E | <44 | 4% (1) | <42 | 4% (1) |
| PFR and/or prolonged TTP | R | (Defined | 23% (6) | (Defined | 54% (14) |
| | E | above) | 31% (8) | above) | 35% (9) |
| Low PFR and/or prolonged TTP/R-R | R | (Defined | 27% (7) | (Defined | 50% (13) |
| | E | above) | 23% (6) | above) | 31% (8) |

* Defined by using ±2 standard deviations from mean value of normal group. † Defined by using the extreme value from the normal group. E = exercise; FF = filling fraction; PFR = peak filling rate; R = rest; TTP = time to peak filling rate; TTP/R-R = time to peak filling rate normalized by the R-R interval. Numbers in parentheses indicate number of patients.

divided by the number of subjects without coronary disease) and predictive accuracy (the number of true-positive tests divided by the total number of positive tests) were each 100%.

## Discussion

Traditional analysis of isovolumic relaxation and diastolic behavior requires invasive angiocardiographic techniques to relate changes in pressure to changes in volume. This interrelation is governed not only by properties intrinsic to the ventricular muscle, such as elastic and viscous properties, but also by extrinsic factors which include the pericardium, atrial systole, heart rate, arterial pressure, and ventricular interaction.[2,21–24] Also, the pressure-volume relation in diastole is curvilinear such that the ventricle is relatively compliant at low volumes but becomes progressively less so as volumes increase.

Patients with coronary disease may manifest both acute and chronic alterations in the diastolic pressure-volume relation. In some patients, diastolic pressure is elevated despite normal left ventricular volumes[3,25] and this elevation may be due to increased wall stiffness because of fibrosis. Transient changes in the diastolic pressure-volume relation can be induced by acute ischemia.[5,6,8–10] Mechanisms that may explain these changes are numerous and include incomplete or impaired relaxation, altered diastolic "tone," tension prolongation during recovery from hypoxia, and perhaps also ischemic contracture of myofibrils.[24] Others have demonstrated changes in viscous properties induced by ischemia.[21]

Radionuclide angiography provides merely a gross approximation of diastolic function because only relative volumes are determined and expressed as a function of end-diastolic counts. These volumes cannot be related to intraventricular pressure without resorting to invasive techniques. In addition, it is well known that mere changes in ventricular volume without ischemia can increase chamber stiffness without implying a change in muscle stiffness.[1] Furthermore, the mechanisms involved in abnormalities of timing of events during various phases of the cardiac cycle cannot specifically be delineated without knowing the timing of valvular opening and closing. This knowledge cannot be provided by analysis of a radionuclide time-activity curve alone. Hence, it should be appreciated that the time from end-systole to peak filling rate contains both isovolumic relaxation as well as early diastolic filling. Anomalies in this interval may be difficult to interpret not only because of the combination of these 2 distinct phases of the cardiac cycle, but also because changes in diastolic filling may be affected by aberrations in myocardial relaxation.[2,24,26,27] Nevertheless, these methods provide an attractive qualitative approach to an analysis of diastolic function which circumvents the invasive angiocardiographic techniques and can readily be applied to large patient populations.

Relatively little data presently exist on the radionuclide assessment of diastolic function at rest and with exercise. Our determination of peak left ventricular filling rates using gated equilibrium radionuclide angiography at rest is in close agreement with those of Bonow et al[11] and Reduto et al,[13] the latter group having used first-pass techniques during upright exercise as well. In addition, the values are comparable to those calculated by Hammermeister and Warbasse,[4] using angiographic techniques. In contrast, Kemper et al[12] report markedly lower values at rest, the reason for which is not readily apparent from their report.

Clear differences in the peak filling rate were present at rest, the normal group having the highest values and the coronary group with low resting ejection fractions having the lowest values. This finding agrees with those of other investigators.[11,13] However, despite this general trend, substantial overlap exists between normal and coronary patients except when left ventricular dysfunction is already profound and readily apparent (Fig. 2). Thus, the usefulness of this isolated measurement at rest as a marker of coronary disease in any individual patient is limited (Table V). Only 11 of the 26 (42%) coronary patients with a normal ejection fraction at rest had a peak filling rate lower than the lowest control value. In contrast, 76% of the coronary patients with a normal resting ejection fraction reported on by Bonow et al[11] had a low peak filling rate. One reason for this difference may be the number of patients examined, our groups being smaller. However, the problem of overlap in these groups is still apparent.

The peak filling rate at rest in the coronary patients was lower than that in the normal subjects even when systolic function at rest was normal. The explanation for this observation in coronary patients without evidence of infarction or acute ischemia is not readily apparent. As suggested,[11] it may be due to (1) clinically inapparent ischemia, too mild to cause angina, electrocardiographic changes, or abnormalities of systolic function, (2) previous periods of ischemia which may produce subtle, irreversible changes in left ventricular relaxation without altering systolic function, or (3) previous periods of ischemia which may produce very slowly reversible changes in diastolic filling that are more long-lived than changes in systolic performance. Little direct evidence for these hypotheses is presently available. When global ejection fraction is taken as the measure of systolic function, peak filling rate appears to be more sensitive to the presence of coronary disease (that is, 42% of coronary patients with a normal rest ejection fraction had a low peak filling rate). However, when a systolic variable employing differentiation is assessed, such as peak ejection rate, it has also been abnormal in coronary patients at rest without infarction, acute ischemia, or abnormal ejection fraction when compared with that of normal individuals.[16,28] This observation agrees with the work of Hammermeister and Warbasse[4] who also noted that in the absence of valvular disease, peak rate of volume change was similar in both systole and diastole and both were lower in coronary patients when compared with normal subjects. Therefore, comparison of the sensitivity of ejection fraction and peak diastolic filling rate as a marker of coronary disease may in some respects be inappropriate. It should also be readily apparent that such abnormalities are not likely to be specific for the detection of

coronary disease, because patients with constrictive pericarditis, some forms of cardiomyopathy, and even mitral stenosis may manifest abnormalities of diastolic filling at rest.

The response of peak filling rate to exercise is shown in Figure 2. The rates increased significantly from the value at rest in all 3 groups; however, both the increases and the absolute rates attained were lower in coronary patients. This behavior was also noted by Reduto et al.[13] There was no discernible effect on this behavior with respect to the presence or absence of propranolol, previous myocardial infarction, or a positive electrocardiographic response to exercise. However, patients with a normal ejection fraction response to exercise attained peak filling rates that were similar to those in normal patients.

It is important to emphasize that a fundamental difference exists between rest and exercise in what is measured as peak filling rate. Although at rest the contribution of atrial systole is usually apparent and can readily be excluded, the same is not true for exercise when the contribution of atrial systole may be a major determinant of the measured peak filling rates because of the much shorter R-R interval. This limitation of the methodology is not easily circumvented. Nevertheless, all patients remained in sinus rhythm during exercise, and the behavior of peak filling rates with exercise still provides information about differences in the way volume is handled in the different groups, despite the complicating feature of atrial systole.

The filling fraction as measured during the first third of diastole was proposed by Reduto et al[13] as an index of diastolic function. They found that, on the whole, coronary patients had a lower filling fraction at rest and during exercise when compared with that of normal subjects. However, despite this, they found that substantial overlap existed between these groups. Filling fraction did not change significantly from rest to exercise in their normal subjects and in the coronary patients with a normal ejection fraction response to exercise. In contrast, their patients with an abnormal ejection fraction response showed a decrease in filling fraction with exercise. Our data agree with this both in magnitude and in the directional changes (Table I, Fig. 3). However, when considering our coronary patients with a normal resting ejection fraction, we found that virtually all subgroups had a decreased filling fraction during exercise, including patients with a normal ejection fraction response to exercise and absent electrocardiographic responses (Table III). This finding suggests that the response of the filling fraction to exercise may provide useful clinical information in the detection of coronary disease when other methods have failed. However, it should be emphasized that this decrease in filling fraction occurred very frequently in normal subjects (Fig. 3). This behavior in normal patients was also noted by Reduto et al,[13] who thought it might represent a normal physiologic response due to incomplete left ventricular relaxation associated with rapid heart rates. This finding has been documented in dogs undergoing atrial pacing by Weisfeldt et al[26] and Mitchell et al.[27] Alternatively, untrained normal subjects have increased ventricular volumes with exercise,[29] which may result in an increased chamber stiffness in the absence of ischemia.

Measurement of the filling fraction during the first third of diastole has the advantage over the peak filling rate of potentially excluding the effect of atrial systole during exercise at rapid heart rates. However, because the filling fraction is arbitrarily measured during the first third of diastole, it is difficult to reckon with the meaning of changes in this variable. With exercise, diastole in total is shortening, with most of the shortening occurring during slow filling, as is isovolumic relaxation. The period encompassed by the filling fraction measurement may therefore be very different from rest to exercise, that is, at rest the filling fraction might extend into slow filling, whereas during exercise it might end sometime during rapid filling.

Further characterization of diastolic behavior is provided by an analysis of the time of occurrence of peak filling rate. At rest the time from end-systole to the occurrence of peak filling is longer in coronary patients than in normal subjects[11,12,16] and this is true even in many patients without evidence of previous infarction or acute ischemia. Bonow et al[11] showed that this interval by itself did not appear to be useful as a predictor of coronary disease, but when combined with subnormal peak filling rate at rest, the sensitivity for detection of coronary disease was increased from 85 to 91%. Kemper et al[12] also found that this isolated interval was not a useful predictor of coronary disease. Neither of these groups corrected this interval for the duration of the R-R interval. Although the normal and coronary patients reported on by Bonow et al[11] had a similar resting heart rate, in the usual clinical situation in which an individual's timing interval is to be evaluated, a meaningful interpretation can only be provided if the effects of heart rate can be excluded, especially because many patients undergo diagnostic tests while ingesting beta-blocking medications. It appears to us that normalization of the interval by the R-R interval is a reasonable approach to this problem. As in other studies,[11,12] we found that the time to peak filling was longer in coronary patients with a normal ejection fraction than in our control subjects, and this relation held true when it was normalized by the R-R interval. Furthermore, patients ingesting propranolol had an abnormal interval even when normalized by R-R interval. At rest, however, this normalized interval identified only 23% of coronary patients with a normal resting ejection fraction (Table V).

With exercise, the time to peak filling appeared longer in coronary patients with a normal resting ejection fraction than in the control group ($p < 0.025$); however, those differences disappeared when the interval was normalized by the R-R interval. That is to say, although our normal patients had the shortest time to peak filling, they also had the shortest R-R interval with exercise. The coronary patients had both a longer time to peak filling and a longer R-R interval. Thus, when the interval is expressed as a percentage of the R-R interval,

the apparent differences between groups is minimized. Therefore, although real differences evidently exist in the timing of diastolic events, caution is advised in the interpretation of this interval in an individual patient if the effects of the underlying heart rate are not first taken into account.

## References


1. **Covell JW, Ross J Jr.** Nature and significance of alterations in myocardial compliance. Am J Cardiol 1973;32:455–499.
2. **Grossman W, McLaurin LP.** Diastolic properties of the left ventricle. Ann Intern Med 1976;84:316–326.
3. **Bristow JD, Van Zee BE, Judkins MP.** Systolic and diastolic abnormalities of the left ventricle in coronary artery disease: studies in patients with little or no enlargement of ventricular volume. Circulation 1970;42:219–228.
4. **Hammermeister KE, Warbasse JR.** The rate of change of left ventricular volume in man. II. Diastolic events in health and disease. Circulation 1974;49:739–747.
5. **Tebbe U, Hoffmeister N, Sauer G, Neuhaus KL, Kreuzer H.** Changes in left ventricular diastolic function in coronary artery disease with and without angina pectoris assessed from exercise ventriculography. Clin Cardiol 1980;3:19–25.
6. **McLaurin LP, Rolett EL, Grossman W.** Impaired left ventricular relaxation during pacing-induced ischemia. Am J Cardiol 1973;32:751–757.
7. **Ross J Jr, Gault JH, Mason DT, Linhart JW, Braunwald E.** Left ventricular performance during muscular exercise in patients with and without cardiac dysfunction. Circulation 1966;34:597–608.
8. **Barry WH, Brooker JZ, Alderman EL, Harrison DC.** Changes in diastolic stiffness and tone of the left ventricle during angina pectoris. Circulation 1974;49:255–263.
9. **Mann T, Brodie BR, Grossman W, McLaurin LP.** Effect of angina on the left ventricular diastolic pressure-volume relationship. Circulation 1977;55: 761–766.
10. **Flessas AP, Connelly GP, Handa S, Tilney CR, Kloster CK, Rimmer RH Jr, Keeple JF, Klein MD, Ryan TJ.** Effects of isometric exercise on the end-diastolic pressure, volumes, and function of the left ventricle in man. Circulation 1976;53:839–847.
11. **Bonow RO, Bacharach SL, Green MV, Kent KM, Rosing DR, Lipson LC, Leon MB, Epstein SE.** Impaired left ventricular diastolic filling in patients with coronary artery disease: assessment with radionuclide angiography. Circulation 1981;64:315–323.
12. **Kemper AJ, Polack J, Blanco JA, Parisi AF, Tow DE.** Resting left ventricular early diastolic filling in normal subjects and patients having coronary artery disease (abstr). J Nucl Med 1981;22:84.
13. **Reduto LA, Wickemeyer WJ, Young JB, Del Ventura LA, Reid JW, Glaeser DH, Quinones MA, Miller RR.** Left ventricular diastolic performance at rest and during exercise in patients with coronary artery disease: assessment with first-pass radionuclide angiography. Circulation 1981;63:1228–1237.
14. **Slutsky R, Karliner JS, Battler A, Pfisterer M, Swanson S, Ashburn W.** Reproducibility of ejection fraction and ventricular volume by gated radionuclide angiography after myocardial infarction. Radiology 1979;132: 155–159.
15. **Slutsky R, Pfisterer M, Verba J, Battler A, Ashburn W.** Equilibrium radionuclide angiography: influence of different background and left ventricular assignments on ejection fraction results. Radiology 1980;135:725–730.
16. **Bacharach SL, Green MV, Borer JS, Hyde JE, Farkas SP, Johnston GS.** Left-ventricular peak ejection rate, filling rate, and ejection fraction: frame rate requirements at rest and exercise. J Nucl Med 1970;20:189–193.
17. **Bhargava V, Slutsky R, LeWinter M.** Contrast angiographic validation of forward reverse break-up techniques for estimation of radionuclide volume curves (abstr). Circulation 1981;64:Suppl IV:IV-74.
18. **Smith TD, Richards P.** A simple kit for the preparation of 99m Tc-labelled red blood cells. J Nucl Med 1976;17:126–132.
19. **Slutsky R, Karliner JS, Ricci D, Pfisterer M, Schuler G, Peterson K, Ashburn W.** Response of left ventricular volume to exercise in man with radionuclide equilibrium angiography. Circulation 1979;60:565–571.
20. **Slutsky R, Karliner JS, Gerber K, Battler A, Froelicher V, Gregoratos G, Peterson K, Ashburn W.** Peak systolic blood pressure/end-systolic volume: assessment at rest and during exercise in normal subjects and patients with coronary heart disease. Am J Cardiol 1980;45:813–820.
21. **Templeton GH, Wildenthal K, Willerson JT, Mitchell JH.** Influence of acute myocardial depression on left ventricular stiffness and its elastic and viscous components. J Clin Invest 1975;56:278–285.
22. **Janicki JS, Weber KT.** Factors influencing the diastolic pressure volume relation of cardiac ventricles. Fed Proc 1980;39:133–140.
23. **Ross J Jr.** Acute displacement of the diastolic pressure-volume curve of the left ventricle: role of the pericardium and the right ventricle. Circulation 1979;59:32–37.
24. **Grossman W, Barry WH.** Diastolic pressure-volume relations in the diseased heart. Fed Proc 1980;39:148–155.
25. **Diamond G, Forrester JS.** Effect of coronary artery disease and acute myocardial infarction on left ventricular compliance in man. Circulation 1972;45:11–19.
26. **Weisfeldt ML, Frederiksen JW, Yin FCP, Weiss JL.** Evidence of incomplete left ventricular relaxation in the dog: prediction from the time constant for isovolumic pressure fall. J Clin Invest 1978;62:1296–1302.
27. **Mitchell JH, Linden RJ, Sarnoff SJ.** Influence of cardiac sympathetic and vagal nerve stimulation on the relation between left ventricular diastolic pressure and myocardial segment length. Circ Res 1960;8:1100–1107.
28. **Slutsky RA, Mancini GBJ, Gerber K, Carey PH, Ashburn WL, Higgins CB.** Radionuclide analysis of ejection time, peak ejection rate, and time to peak ejection rate. Response to supine bicycle exercise in normal subjects and patients with coronary heart disease. Am Heart J, in press.
29. **Bar-Shlomo B-Z, Druck MN, Morch JE, Jablonsky G, Hilton D, Feigin DH, McLaughlin PR.** Left ventricular function in trained and untrained healthy subjects. Circulation 1982;65:484–488.

# Determinants of Variable Exercise Performance Among Patients With Severe Left Ventricular Dysfunction

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**The relation between bicycle exercise performance and determinants of central and peripheral cardiovascular function was assessed in 17 patients with class II to III heart failure and in 9 normal subjects. Proportional changes in oxygen consumption ($VO_2$) from rest (R) to maximal exercise (Ex), or Mets, were used as an objective measure of the exercise capacity or functional reserve of the cardiovascular system. Left ventricular ejection fraction (EF) and proportional changes in end-diastolic volume, stroke volume, and cardiac output were determined from appropriate count data by equilibrium radionuclide angiography. Proportional changes in arteriovenous oxygen difference ($A\text{-}VO_2$) were derived from the equation $Ex/_R\ A\text{-}VO_2 = Ex/_R\ VO_2 \div Ex/_R\ CO$, where CO = count output.**

**Each subject exercised to an anaerobic end-point. Maximal $VO_2$ was significantly lower in patients than in normal subjects. Because $Ex/_R\ A\text{-}VO_2$ was comparable in normal subjects and patients, the lower exercise performance in patients resulted from a reduced count output response. The reduced CO response in patients resulted from failure of the ejection fraction to increase or from an attenuated heart rate response, or both.**

**Exercise performance was variable in both groups. Multivariable analysis in the patient group identified changes in heart rate, count output, and $A\text{-}VO_2$ with exercise as important predictors of Mets, but found no relation between Mets and changes in ejection fraction or stroke counts during exercise. Similarly, multiple regression analyses between Mets and determinants of cardiovascular function demonstrated significant correlations with $Ex/_R$ heart rate, $Ex/_R$ count output, and $Ex/_R\ A\text{-}VO_2$ in both groups. In patients, EF at rest ranged from 0.09 to 0.36, but it did not correlate with Mets, nor did changes in ejection fraction, stroke counts, or end-diastolic counts during exercise. The variable exercise performance among patients with severe left ventricular dysfunction was determined predominantly by a variable heart rate and $A\text{-}VO_2$ response and not by rest or exercise indexes of left ventricular function.**

Patients with ventricular dysfunction demonstrate a generally reduced but highly variable exercise capacity. Despite severe ventricular dysfunction, certain patients may even have normal exercise tolerance.[1] The parameters that determine this variable ability to exercise have not been delineated. Recent studies[1–4] show that measurements of left ventricular function at rest have little or no correlation with exercise capacity in patients with heart failure. No previous study has related central and peripheral components of cardiovascular function during exercise with objective measurements of exercise capacity in patients with a wide range of ventricular dysfunction.

The purpose of the present study was to relate indexes of left ventricular and peripheral cardiovascular function at rest and during exercise with maximal exercise capacity during upright bicycle ergometry. Left ventricular function was measured noninvasively with radionuclide angiography, and maximal exercise capacity was assessed by determining maximal oxygen consumption and achievement of anaerobic end-points of exercise.

## Methods

**Study groups:** The study was performed in 17 patients aged 27 to 68 years with New York Heart Association functional class II to III heart failure and in 9 subjects aged 31 to 55 years without cardiovascular disease. Clinical characteristics are summarized in Table I. All patients were male. Twelve patients had coronary artery disease with documented previous myocardial infarction. Four patients had idiopathic dilated cardiomyopathy. One patient had heart failure after successful aortic and mitral valve replacement and no clinically apparent valvular insufficiency. In all cases, cardiac failure had been clinically stable for at least 2 months. All patients were receiving digoxin and diuretics at the time of the study; none was receiving beta-adrenergic blocking drugs or vasodilator drugs other than occasional sublingual nitroglycerin. Patients were excluded from the study if they had angina pectoris that limited exercise, physical or radiographic

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**TABLE I Clinical Characteristics**

| | Normal Subjects | Patients With Cardiac Failure |
|---|---|---|
| Number | 9 | 17 |
| Age (yr)* | 52 ± 6 | 54 ± 8 |
| Sex | 8M, 1F | All male |
| Weight (kg)* | 75.2 ± 6.0 | 77.1 ± 8.3 |
| NYHA functional class | I | 2 patients,* class II<br>15 patients,* class III |

* Mean ± standard deviation. NYHA = New York Heart Association.

signs of obstructive lung disease, or intermittent claudication.

The control group consisted of 6 normal volunteers who had no symptoms or signs of cardiovascular disease, 1 subject who had no signs or symptoms of cardiovascular disease but was referred for evaluation of exercise intolerance, and 2 subjects referred for evaluation of chest pain who had normal cardiac catheterization findings. Written informed consent was obtained from each subject.

**Exercise test protocol:** The exercise test was performed in the postabsorptive state. Administration of digoxin and diuretics was continued. Exercise was performed in the upright position with the subject sitting on an isokinetic bicycle ergometer (Fitron). The electrocardiogram was monitored continuously. The standard limb leads and leads $V_5$ and $V_6$ were recorded initially and after each minute of exercise. Arterial blood pressure was measured by cuff manometry at rest and during each minute of exercise. Exercise began at 150 kpm/min (50 W); the work load was increased by 150 kpm every 3 minutes. The exercise rate was constant at 60 rpm. Exercise was continued until limited by excessive fatigue or shortness of breath, or both.

**Respiratory gas analysis and calculation of anaerobic threshold:** The concentration of expired oxygen was analyzed continuously with a Beckman OM-14 oxygen analyzer; carbon dioxide was analyzed with a Beckman LB-2 analyzer. Minute ventilation was measured with a Pneumoscan spirometer. Instruments were calibrated at the beginning of each study and before every measurement. Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured before exercise and during the third minute of each exercise stage. Appropriate corrections were made for barometric pressure and temperature of the expired gases. Maximal $\dot{V}O_2$ was calculated for each subject, and for descriptive purposes was expressed as a multiple of resting oxygen consumption, defined as Mets. Anaerobic end-points of exercise were confirmed from the ratio of $\dot{V}CO_2/\dot{V}O_2$ and from the ratio of minute ventilation/$\dot{V}O_2$ using criteria described by Wasserman and co-workers.[5,6]

**Radionuclide angiography:** Multigated radionuclide angiograms were recorded by labelling red blood cells in vivo with 30 mCi of technetium-99m. Radionuclide angiograms were acquired using a Searle L.E.M. mobile scintillation camera with a high sensitivity collimator and hardware zoom, and an R-wave triggered gate interfaced to a Medical Data Systems $A^2$ computer. Studies were acquired in the histogram mode, in a 64 × 64 matrix of 24 frames each containing 125,000 counts. The acquisition time was approximately 1.5 to 2 minutes for each study. Serial radionuclide angiograms were recorded before exercise and during the second and third minutes of each exercise stage.

The multigated radionuclide studies were analyzed without data processing. The left ventricular ejection fraction was calculated using a varying region of interest technique. Regions were assigned using an operator-assisted semiautomated edge-detection program. Analysis of counts in each region allowed the construction of time activity curves and the determination of ejection fraction. End-diastole (ED) and end-systole (ES) were determined from the peaks and troughs of the time activity curve, respectively. The ejection fraction (EF) was calculated from the following formula: EF = (ED counts-background) − (ES counts-background)/(ED counts-background). Relative stroke count (SC) changes from rest to exercise were derived from the background and time-corrected end-diastolic count rate (EDCR), thus: $Ex/_R$ SC = $Ex/_R$ EDCR × $Ex/_R$ EF. The end-diastolic count rate was in each case back-corrected to the time of the resting study to allow for isotope decay. The formula used was EDCRo = EDCRt × $e^{\lambda t}$, where EDCRo = the back-corrected value, EDCRt = the value recorded at time t, and $\lambda = 0.693$/isotope half-life. Relative count output changes as indexes of cardiac output changes from rest to exercise were calculated from the following formula: $Ex/_R$ CO = $Ex/_R$ SC × $Ex/_R$ HR, where HR = heart rate in beats/min.

Arteriovenous oxygen difference, or the difference between arterial and mixed venous oxygen content, was not measured directly in the study group. Relative changes in arteriovenous oxygen difference (A-$VO_2$) were derived from the equation $\dot{V}O_2$ = CO × A-$VO_2$, so that: $Ex/_R$ A-$VO_2$ = $Ex/_R$ $\dot{V}O_2$ × $R/_{Ex}$ CO. In the following sections the change in A-$VO_2$ will refer to this derived value.

The foregoing methods were validated in a group of 6 patients, 4 of whom were involved in the present study, who performed staged exercise in a manner identical to that described herein. The resting ejection fraction in this group ranged from 0.10 to 0.42 (mean 0.26). Arteriovenous oxygen difference was measured directly by sampling from a cannula in the brachial artery and a Swan-Ganz catheter in the pulmonary artery. Measurements were made at the beginning of the third minute of each exercise stage and thus coincident with the oxygen consumption and radionuclide measurements. Cardiac output was calculated at rest and during each exercise stage by the Fick method. Stroke volume was obtained by dividing cardiac output by heart rate.

Noninvasive and invasive measurements were compared by regression analysis and by comparing individual data as a function of progressive work load.

**Statistical analysis:** Group data of patients and normal subjects were compared using Student's *t* test. The relative importance of several cardiovascular variables as determinants of exercise capacity was assessed in the 17 patients by stepwise multivariable analysis. In addition, exercise performance as expressed by Mets was related to cardiovascular variables by multiple regression analyses. All group data were expressed as mean ± standard deviation.

## Results

**Validation studies:** Data in Figures 1 and 2 demonstrate the validity of the noninvasive measurements made in the present study. Proportional changes in stroke counts, count outputs, and derived A-$VO_2$ correspond well with direct measurements of stroke volume ($r = 0.67$), cardiac output ($r = 0.89$), and arteriovenous oxygen difference ($r = 0.78$) (Fig. 1). Figure 2 illustrates individual and mean data describing proportional changes in cardiovascular variables derived by noninvasive and direct measurements during progressive exercise; mean data were essentially the same.

Duplicate resting radionuclide studies were recorded in 11 of the 17 study patients. The mean ejection fraction of the group was 0.22 ± 0.06; the mean difference between the 2 ejection fraction measurements was 0.05

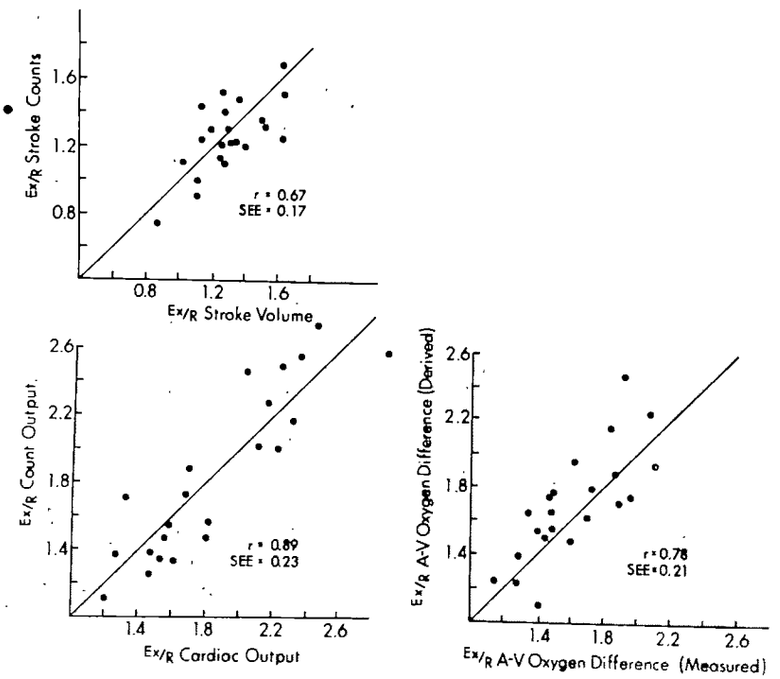



**FIGURE 1.** Validation of methods. The relation is shown between proportional ($Ex/_R$) changes in stroke volume, cardiac output, and arteriovenous oxygen differences (**horizontal axis**) and corresponding noninvasive estimates (**vertical axis**). The values represent data from various exercise stages in 6 patients. The line of identity is shown. SEE = standard error of the estimate.

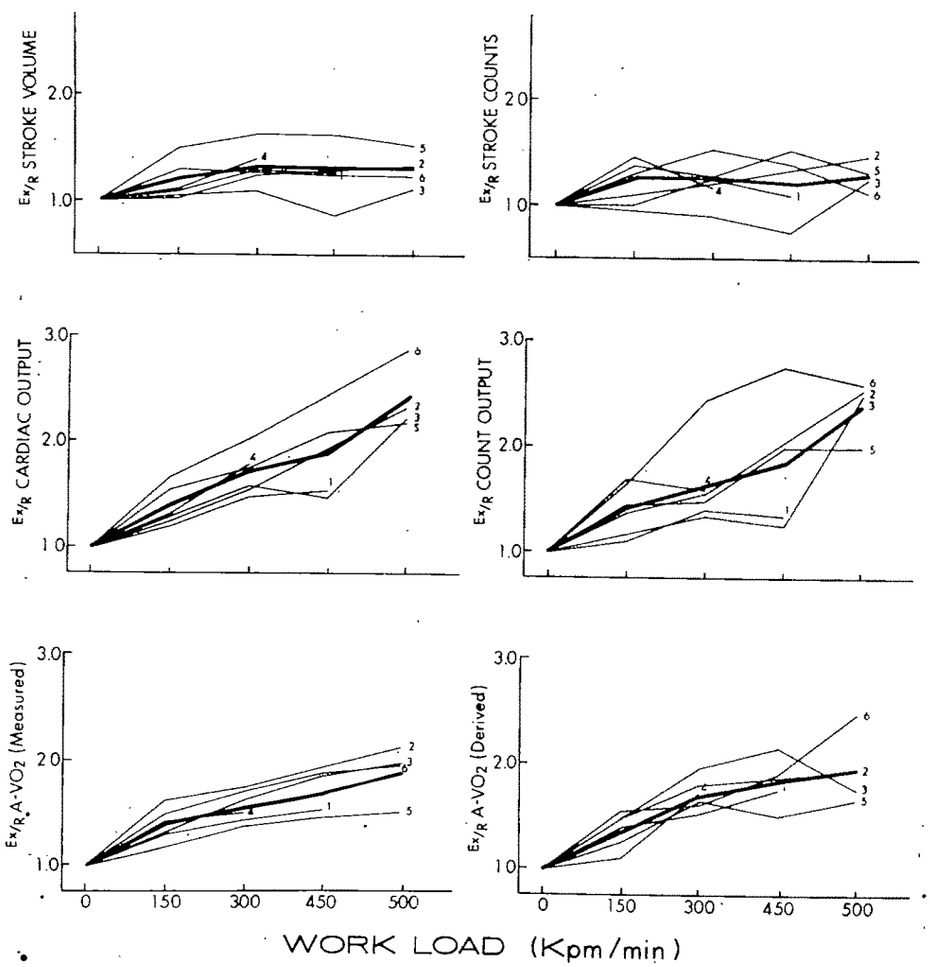



**FIGURE 2.** Validation of methods. Comparison between proportional ($Ex/_R$) changes in stroke volume, cardiac output, and arteriovenous oxygen differences (**left panels**) and the corresponding noninvasive estimates (**right panels**). Individual data from 6 patients are expressed as a function of work load. Mean data (**heavy lines**) are almost identical for invasive and noninvasive measurements.

**TABLE II Gas Exchange and Cardiovascular Performance in 9 Normal Subjects and 17 Patients With Cardiac Failure**

| | Rest | | | Maximal Exercise | | |
|---|---|---|---|---|---|---|
| | Normal Subjects | Patients | p | Normal Subjects | Patients | p |
| Work load | ... | ... | ... | 761 ± 170 | 476 ± 140 | <0.001 |
| $\dot{V}O_2$ | 4.5 ± 1.3 | 4.0 ± 1.1 | NS | 23.5 ± 7.6 | 14.8 ± 4.3 | <0.01 |
| Mets | ... | ... | ... | 5.5 ± 1.6 | 3.9 ± 1.2 | 0.01 |
| RQ | 0.80 ± 1.10 | 0.85 ± 0.05 | NS | 1.12 ± 0.08 | 1.16 ± 0.12 | NS |
| HR (beats/min) | 79 ± 21 | 75 ± 22 | NS | 158 ± 17 | 132 ± 17 | 0.001 |
| SBP (mm Hg) | 131 ± 12 | 133 ± 22 | NS | 201 ± 25 | 176 ± 38 | NS |
| EF | 0.60 ± 0.06 | 0.23 ± 0.07 | <0.0001 | 0.76 ± 0.08 | 0.23 ± 0.07 | <0.0001 |
| Max $Ex/_R$ EDC | ... | ... | ... | 0.99 ± 0.20 | 1.11 ± 0.14 | NS |
| Max $Ex/_R$ SC | ... | ... | ... | 1.27 ± 0.24 | 1.12 ± 0.22 | NS |
| Max $Ex/_R$ CO | ... | ... | ... | 2.58 ± 0.54 | 1.87 ± 0.48 | <0.01 |
| Max $Ex/_R$ A-$VO_2$ | ... | ... | ... | 2.09 ± 0.39 | 2.04 ± 0.52 | NS |

Values are mean ± standard deviation. NS = not significant; RQ = respiratory quotient; SBP = systolic blood pressure.

± 0.001. The mean difference in end-diastolic counts was 4.7 ± 2.7%.

**Left ventricular function at rest:** In patients there was a wide range of left ventricular dysfunction; the ejection fraction range was 0.09 to 0.36 (mean 0.23). The ejection fraction was at least 0.50 in all normal subjects (range 0.50 to 0.68; mean 0.60) (Table II).

**Exercise performance:** Exercise performance as expressed by maximal work load, $\dot{V}O_2$, or Mets was significantly reduced in patients compared with normal subjects (Table II). Among the 9 normal subjects, the 2 lowest values for Mets, 2.8 and 3.5, were seen in the patients investigated for chest pain. Neither took regular physical exercise. The highest value, 8.3, was seen in a subject who engaged in long-distance cycling. The relation between oxygen consumption ($\dot{V}O_2$) and work load is shown in Figure 3. Although at comparable work loads $\dot{V}O_2$ was similar in the patients and normal subjects, maximal $\dot{V}O_2$ was reduced greatly in the patients.

Each subject exercised in excess of the anaerobic end-point (Fig. 4). The respiratory quotient ($\dot{V}CO_2/\dot{V}O_2$) exceeded 1.0 in each subject at maximal exercise. The ventilatory equivalent (minute ventilation/$\dot{V}O_2$) initially decreased, then increased slowly before abruptly rising at the maximal work load in each subject. The respiratory quotients and ventilatory equivalents at maximal exercise were comparable in

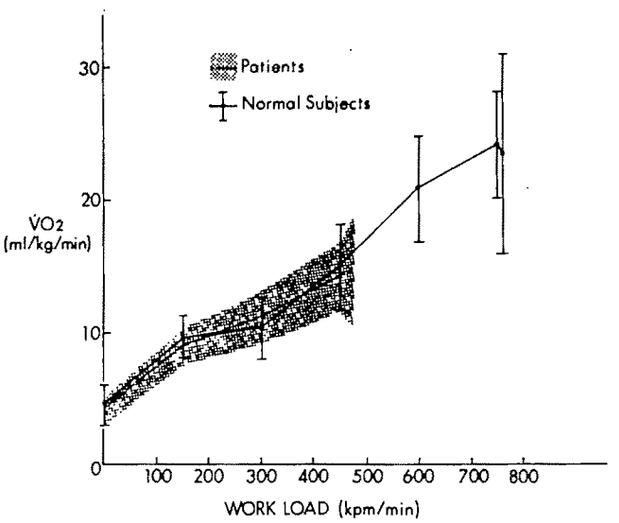



**FIGURE 3.** Relation between oxygen consumption ($\dot{V}O_2$) and work load with upright bicycle exercise in 9 normal subjects and 17 patients with left ventricular failure. Values represented are mean ± standard deviation.

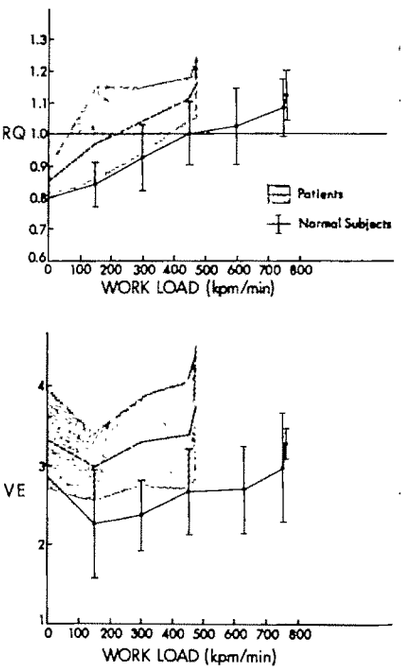



**FIGURE 4.** Changes in respiratory quotient (RQ) and ventilatory equivalent (VE) with progressive increases in work load during bicycle exercise in 9 normal subjects and 17 patients with left ventricular failure. Respiratory quotient represents the ratio of carbon dioxide production to oxygen consumption. Ventilatory equivalent expresses the ratio of minute ventilation to oxygen consumption. Comparable anaerobic end-points of exercise are seen in each group.

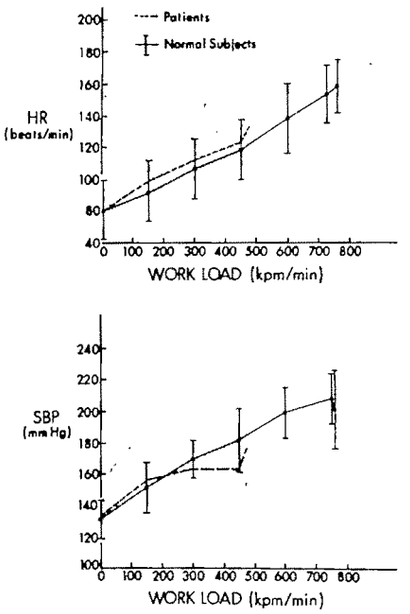



**FIGURE 5.** Changes in heart rate (HR) and systolic blood pressure (SBP) with increasing work load during upright bicycle exercise in 9 normal subjects and 17 patients with left ventricular failure. At comparable work loads, heart rate and systolic blood pressure were similar for each group. Normal subjects achieved higher work loads at a higher heart rate and systolic blood pressure than patients.

patients and normal subjects, indicating that comparable anaerobic end-points of exercise were achieved.

**Cardiovascular response to exercise:** Changes in heart rate, systolic blood pressure, and radionuclide indexes of cardiac function between rest and maximal exercise in all subjects are summarized in Table II. Responses to progressive exercise are illustrated in Figures 5 to 7. Heart rate responses during maximal exercise were lower in patients than in normal subjects ($p = 0.001$). A small difference in systolic blood pressure ($p > 0.05$) between the groups was also seen. The disparity between ejection fraction in patients and normal subjects was marked at maximal exercise ($p < 0.0001$). Patients has a significantly lower exercise/rest count output at maximal exercise than normal subjects ($p < 0.01$). The small differences in exercise/rest stroke counts and exercise/rest end-diastolic counts did not reach statistical significance, but the progressive data shown in Figure 6 suggest that patients had a diminished stroke count response despite a greater increase in end-diastolic counts during exercise. Changes in A-$VO_2$ from rest to maximal exercise were comparable in both groups.

**Determinants of maximal exercise performance:** The determinants of oxygen consumption can be expressed in the following equations: (1) $\dot{V}O_2$ = cardiac output·A-V oxygen difference; (2) Cardiac output =

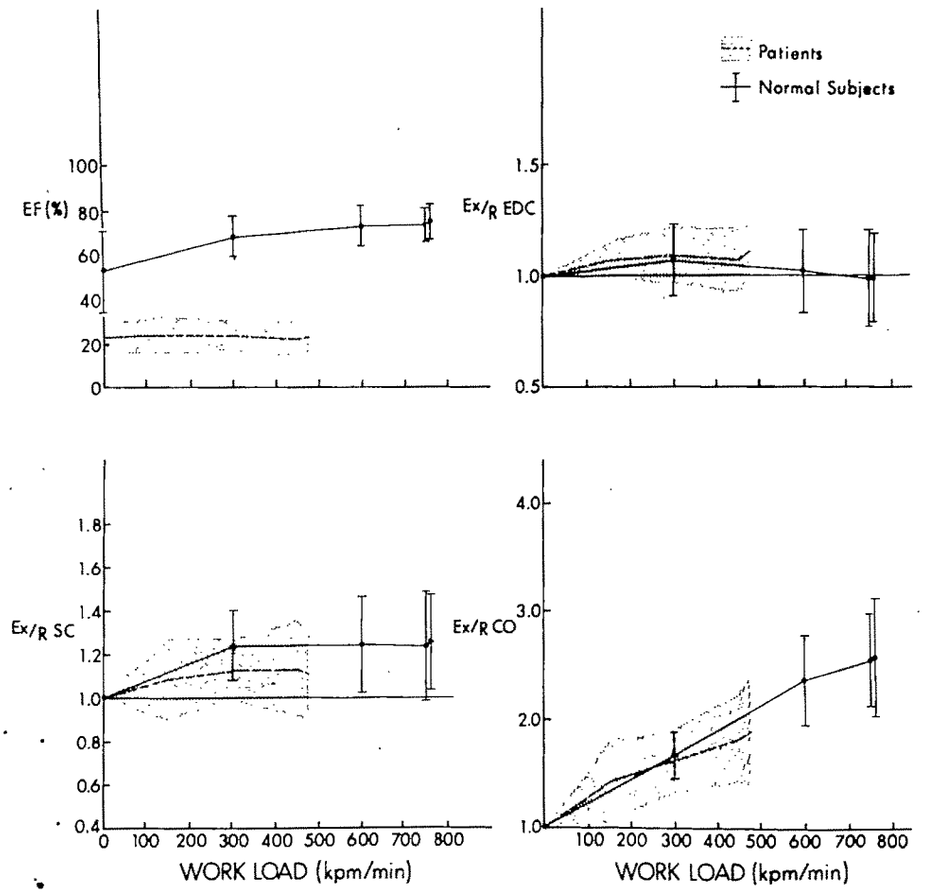



**FIGURE 6.** Changes in ejection fraction (EF), end-diastolic counts (EDC), stroke counts (SC), and count output (CO) with progressive upright bicycle exercise in 9 normal subjects and 17 patients with left ventricular failure. All values are represented as proportional changes from rest to exercise.

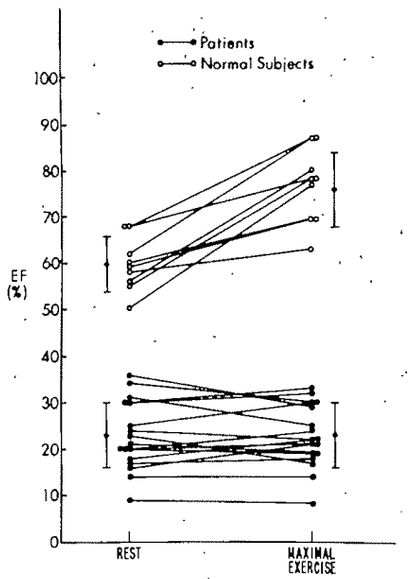



**FIGURE 7.** Changes in ejection fraction (EF) from rest to maximal upright bicycle exercise in 9 normal subjects (**open circles**) and 17 patients with left ventricular failure (**closed circles**). Mean values ± standard deviation are shown for group data.

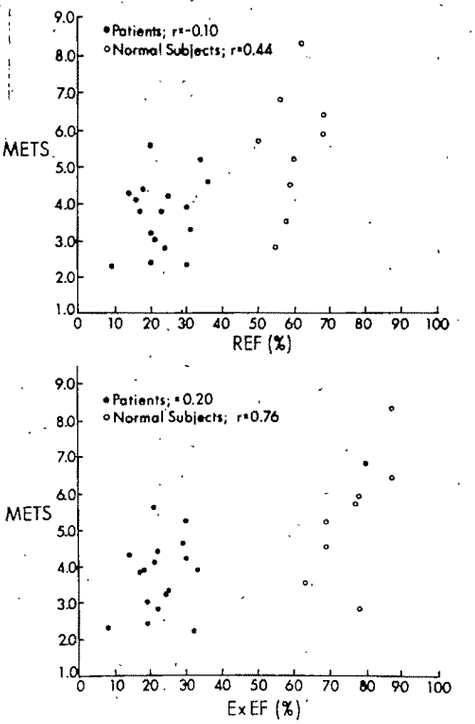



**FIGURE 8.** Relation between proportional change in oxygen consumption from rest to maximal exercise (Mets), and resting ejection fraction (REF, **upper panel**) and exercise ejection fraction (ExEF, **lower panel**). Correlations are seen for normal subjects (**open circles**), but not for patients with left ventricular failure (**closed circles**).

stroke volume (SV)·HR; (3) SV = end-diastolic volume (EDV)·EF; so that, (4) $\dot{V}O_2$ = EDV·EF·HR·A-$VO_2$. Maximal work performance in study patients and normal subjects was expressed as a multiple of resting oxygen consumption, that is, Mets = $MaxEx/_R$ $\dot{V}O_2$ = $MaxEx/_R$ EDC·$MaxEx/_R$ EF·$MaxEx/_R$ HR·$MaxEx/_R$ A-$VO_2$. Relations between Mets achieved and various factors that might influence exercise performance were examined in both study groups by univariate analysis; individual data are plotted in Figures 8 to 12. No correlation existed between age and Mets achieved in the study patients (r = 0.04) or the normal subjects (r = 0.20).

Despite the wide range of ejection fraction at rest and the variable response of the ejection fraction during exercise in patients, there was essentially no relation between either measurement and exercise performance as measured by Mets (Fig. 8) (r = −0.10 for rest and 0.20 for exercise ejection fraction). In normal subjects, resting ejection fraction was weakly related to Mets (r = 0.44, p >0.05). The relation between exercise ejection fraction and Mets was stronger (r = 0.76, p = 0.02). When the relation between Mets and proportional increases in ejection fraction from rest to maximal exercise was examined, a weak correlation could be demonstrated for normal subjects (r = 0.32, p >0.05), but not for patients (r = 0.10) (Fig. 9). In normal subjects, weak negative correlations were seen between exercise/rest stroke counts and Mets (r = −0.37, p >0.05) and between exercise/rest end-diastolic counts and Mets (r = −0.28, p >0.05) (Fig. 10); no correlation was seen in patients (r = 0.03 and 0.08, respectively). A positive correlation was observed between exercise/rest count output at maximal exercise and Mets in normal subjects (r = 0.65, p = 0.06) and in patients (r = 0.51, p = 0.03) (Fig. 11). Similar positive correlations were observed between $Ex/_R$ A-$VO_2$ and Mets in normal subjects (r = 0.83, p = 0.005) and in patients (r = 0.63, p = 0.01). Of the various determinants of cardiac output considered in patients, the strongest positive correlation with Mets was observed for exercise/rest heart rate (r = 0.57, p =

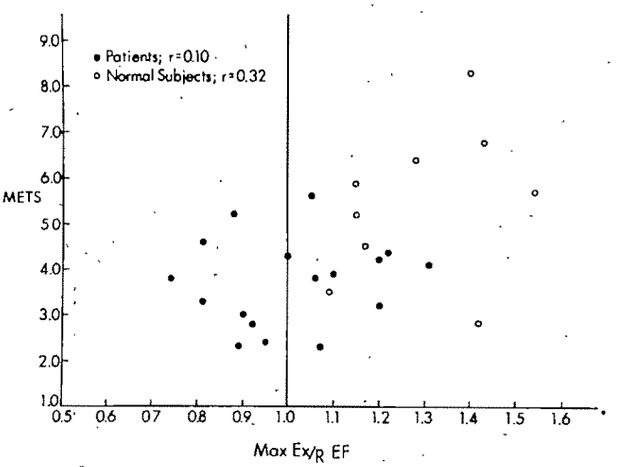



**FIGURE 9.** Relation between proportional change in oxygen consumption from rest to maximal exercise (Mets) and proportional change in ejection fraction (Max $Ex/_R$ EF) for normal subjects (**open circles**) and patients with left ventricular failure (**closed circles**).

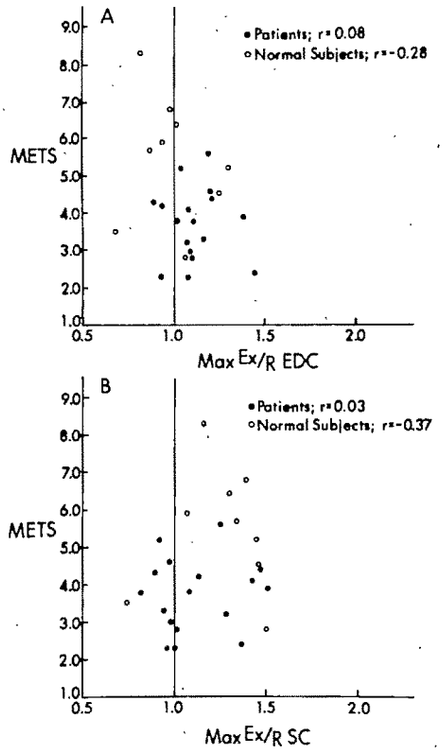



**FIGURE 10.** Relation between proportional change in oxygen consumption from rest to maximal exercise (Mets) and proportional changes in end-diastolic counts (Max $Ex/_R$ EDC, **upper panel**) and stroke counts (Max $Ex/_R$ SC, **lower panel**). Weak negative correlations are seen for normal subjects (**open circles**) but not for patients with left ventricular failure (**closed circles**).

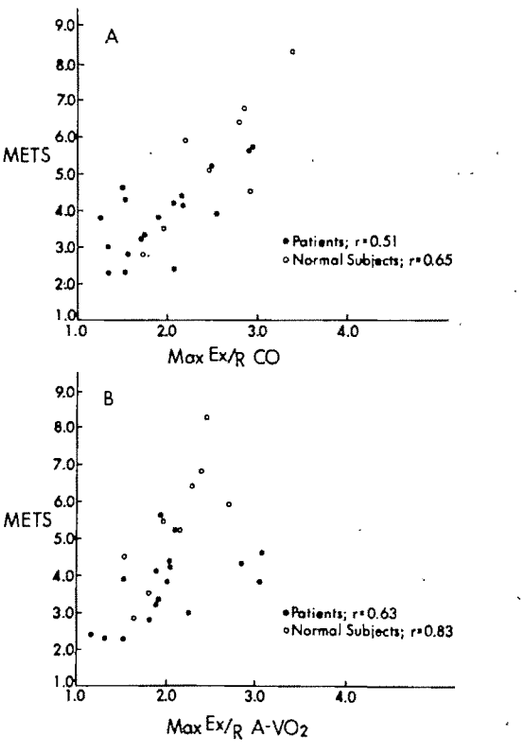



**FIGURE 11.** Relation between proportional change in oxygen consumption from rest to maximal exercise (Mets) and proportional changes in count output (Max $Ex/_R$ CO, **upper panel**) and arteriovenous oxygen difference (Max $Ex/_R$ A-$VO_2$, **lower panel**). Positive correlations are seen for normal subjects (**open circles**) and for patients with left ventricular failure (**closed circles**).

0.015) (Fig. 12). A positive correlation also was observed between Mets and heart rate in the normal subjects ($r = 0.50$), although this correlation was not significant for the small group.

Multivariable analysis of the determinants of Mets was carried out in 3 stages in the patients but not in the smaller group of normal subjects. The first stage combined $Ex/_R$ CO and $Ex/_R$ A-$VO_2$, the second combined $Ex/_R$ HR, $Ex/_R$ SC, and $Ex/_R$ A-$VO_2$, and the third included $Ex/_R$ HR, $Ex/_R$ EF, $Ex/_R$ EDC, and $Ex/_R$ A-$VO_2$ as possible determinants of Mets achieved during maximal exercise. This analysis demonstrated an approximately equal contribution to Mets achieved from $Ex/_R$ CO and $Ex/_R$ A-$VO_2$. It also confirmed the importance of $Ex/_R$ HR, but not $Ex/_R$ EF or $Ex/_R$ SC, as a determinant of Mets.

Two patients achieved normal or near-normal exercise performance as defined by a maximal value for Mets >5.0. The mechanism by which this was achieved can be seen from individual data in Figures 8 to 12. Although both patients had markedly abnormal ejection fractions at rest and during exercise, a normal or near-normal cardiovascular response to exercise was associated with a normal exercise/rest count output in each case. The patient who achieved the highest Mets (5.6) maintained a normal exercise/rest count output through normal stroke count and heart rate responses; the increase in stroke counts was achieved through an increase in end-diastolic counts, because EF did not change significantly. The patient who achieved the second highest value (5.2 Mets) did not increase stroke counts normally, but achieved a normal count output response through a compensatory increase in heart rate.

The mechanisms of achieving an adequate exercise performance in patients is further illustrated by the data from 5 patients who reached values of Mets between 4.0 and 5.0. Three of these patients doubled their count output by increasing ejection fraction and heart rate during exercise. The remaining 2 patients demonstrated a poor count output response but markedly increased arteriovenous oxygen difference.

## Discussion

Previous studies have demonstrated that patients with ventricular dysfunction have a highly variable exercise capacity.[1-3] However, the parameters that determine this variable exercise capacity have not been defined. Recent work by Benge,[1] Franciosa,[2,3] Port,[4] Conn,[7] and their co-workers has shown that resting left ventricular function correlates poorly with exercise performance. The present study was performed to correlate indexes of central and peripheral cardiovascular function measured at rest and during exercise with maximal upright bicycle exercise performance.

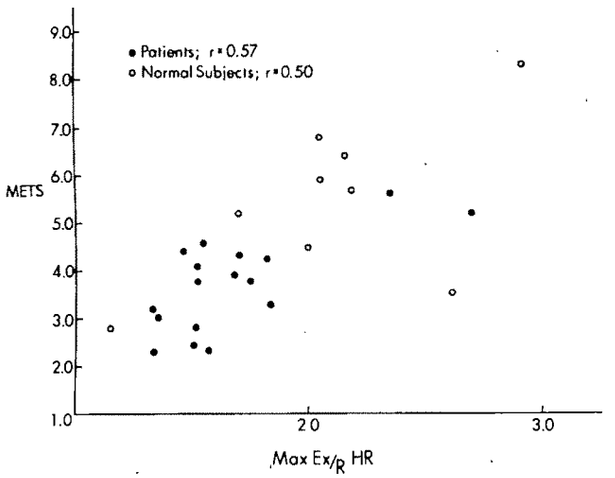



**FIGURE 12.** Relation between proportional change in oxygen consumption from rest to maximal exercise (Mets) and proportional change in heart rate (Max $Ex/_R$ HR) for normal subjects (**open circles**) and patients with left ventricular failure (**closed circles**). Correlations are seen for both groups.

**Methodology:** Oxygen consumption during maximal dynamic exercise involving at least 50% of total muscle mass is a measure of the functional capacity or reserve of the cardiovascular system.[8,9] Failure of the $\dot{V}O_2$ to rise with increasing work loads[8,10] has been used as objective evidence that maximal oxygen delivery and extraction have been achieved; however, such a plateau in the relation between $\dot{V}O_2$ and work load frequently is not attained in patients with cardiac dysfunction.[11,12] The ventilatory responses to metabolic acidosis are alternative indexes that maximal or near maximal oxygen consumption has been achieved.[5,6] Anaerobic endpoints of exercise can be calculated from measurements of ventilation, oxygen consumption, and carbon dioxide production, as described by Wasserman and McIlroy.[5] Subjects in the present study all achieved maximal or near-maximal exercise performance as defined by exercise to or above an anaerobic threshold.

For the purpose of analysis, exercise performance was expressed as a proportional change in oxygen consumption from rest to exercise, defined as Mets, rather than an absolute maximal $\dot{V}O_2$ measurement. Proportional changes in multiple variables of central and peripheral cardiovascular function from rest to exercise were thus related to Mets.

The measurement of ejection fraction by equilibrium radionuclide angiography is well established.[13–15] Several investigators[16,17] estimated left ventricular volumes by relating background-corrected counts in the left ventricular region at end-diastole to ventricular volume as determined by cardiac catheterization. Because variable tissue attenuation of radioactivity within the ventricular chambers may influence such measurements, we chose to use relative changes in left ventricular counts as a measurement of volume changes between rest and exercise. These measurements are independent of variable tissue attenuation but are dependent on the precision of measuring background-corrected end-diastolic counts. Duplicate measurements in the present study demonstrated a high degree of reproducibility for the estimations. The validation of this approach for examining changes in ventricular volume, cardiac output, and A-$VO_2$ during exercise is supported by studies in which noninvasive and direct measurements were made simultaneously in patients with left ventricular dysfunction.

**Determinants of maximal exercise performance:** *Normal subjects:* Cardiac output in normal subjects increases linearly with oxygen consumption, the increase varying 3- to 5-fold between rest and maximal exercise.[8,9,12,18–22] Heart rate appears to be the major contributor to the linear increase in cardiac output because increases in stroke volume reach a plateau at submaximal work loads.[8,19,20] The maximal change in stroke volume during exercise is a function of muscle mass and body position. Thus, Mitchell et al[9] reported an approximate doubling in stroke volume during maximal treadmill exercise, whereas Clausen et al[19,23] observed a 30% increase in the stroke volume during maximal leg exercise on a bicycle ergometer. Only slight increases in stroke volume may occur during maximal arm exercise.[19] Studies reporting no change or a minimal increase in end-diastolic volume during exercise[22,24] suggest that increases in stroke volume during exercise result from increases in ejection fraction.

Arteriovenous oxygen difference may increase as much as 3-fold in normal young subjects during maximal treadmill exercise; Mitchell et al[20] noted an increase in A-$VO_2$ which averaged 2.2 in normal young subjects at maximal treadmill exercise. The effect of physical training on the ability to widen A-$VO_2$ appears small: Clausen[23] reported that physical training increased maximal oxygen consumption by 17 to 18% in normal middle-aged volunteers; approximately 50% of the increase was attributed to a widening of the A-$VO_2$.

Data from our group of normal subjects are consistent with the preceding observations. Analysis of group data demonstrated increases in heart rate, systolic blood pressure, count output, and A-$VO_2$ with increasing work load. Statistical analysis demonstrated correlations between proportional change in heart rate, count output and A-$VO_2$ from rest to exercise, and the proportional change in oxygen consumption (Mets). The correlation between Mets achieved and the A-$VO_2$ response indicates that variable oxygen extraction was a determinant of the variable exercise performance. This is consistent with the expected variability in physical conditioning among these subjects.

*Patients:* As observed by Franciosa et al[2] and Epstein et al,[12] maximal oxygen consumption was markedly lower in our patients than in normal subjects. There was considerable variability between individual patients; although each patient exercised to an anaerobic endpoint, the proportional change in oxygen consumption at maximal exercise varied from 2.2 to 5.5 Mets. There was also considerable overlap of maximal oxygen consumption between normal subjects and patients with reduced ventricular function. The overall reduction in maximal oxygen consumption in patients resulted from a reduced maximal count output, because proportional

changes in A-$VO_2$ were comparable in normal subjects and patients. Reduced count output in turn appeared to result from a lower maximal heart rate and smaller increases in stroke counts during exercise; mean stroke counts increased 27% in normal subjects compared with 12% in patients. These findings are similar to those of Epstein et al,[12] who measured cardiac output, stroke volume, oxygen consumption, and A-$VO_2$ by cardiac catheterization during treadmill exercise in normal subjects and patients with functional class II to III heart failure. Compared with normal subjects, patients demonstrated lower maximal oxygen consumption, cardiac index, stroke volume, and heart rate. Despite a lower pulmonary arterial saturation at maximal exercise in patients than in normal subjects, maximal A-$VO_2$ and the proportional change in A-$VO_2$ from rest to exercise were similar in the 2 groups.

The present study provides additional information regarding the relation between indexes of central and peripheral cardiovascular function and the variable exercise capacity seen in patients with left ventricular dysfunction. Regression analyses demonstrated positive correlations between proportional changes in count output, A-$VO_2$, and heart rate and proportional changes in oxygen consumption. Multivariable analysis confirmed these findings and suggested approximately equal influences from count output and A-$VO_2$. The patients demonstrated a wide range of resting ventricular dysfunction. As observed by others,[1–4,7] there was essentially no correlation between resting ejection fraction and maximal oxygen consumption. Previous studies have not determined whether changes in ejection fraction during exercise contribute to the variable maximal exercise consumption. In the present study, neither the ejection fraction during exercise nor the proportional change in ejection fraction correlated with maximal oxygen consumption. There was no correlation between changes in either stroke counts or end-diastolic counts and maximal oxygen consumption.

As in normal subjects, the major cardiac determinant of variable exercise performance in patients was heart rate. Previous investigators have noted an attenuated heart rate response to exercise in certain patients with left ventricular failure[12,25] and have suggested that impaired autonomic function is responsible. This finding is supported by experimental data[26] and is consistent with our finding of reduced blood pressure response to exercise in these patients. The attenuated heart rate response in our patients was not age related, nor was it secondary to inadequate exercise performance because comparable anaerobic end-points were achieved in all patients.

The results of the present study confirm that patients with severe left ventricular dysfunction usually have a lower exercise capacity than normal subjects. Such patients have a low resting ejection fraction and a diminished ejection fraction response to exercise; many also have an inadequate chronotropic response to exercise. However, occasionally normal or near-normal exercise performance may be achieved by maintaining a normal cardiac output response through compensatory increases in end-diastolic volume or heart rate. The highly variable exercise performance among these patients is related predominantly to the variability in heart rate and A-$VO_2$ responses during exercise rather than to differences in the ejection fraction at rest or exercise or changes in stroke volume during exercise.

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## References

1. **Benge W, Litchfield RL, Marcus ML.** Exercise capacity in patients with severe left ventricular dysfunction. Circulation 1980;61:955–959.
2. **Franciosa JA, Ziesche S, Wilen M.** Functional capacity of patients with chronic left ventricular failure. Am J Med 1979;67:460–466.
3. **Franciosa JA, Park M, Levine B.** Lack of correlation between exercise capacity and indices of resting left ventricular performance in heart failure. Am J Cardiol 1981;47:33–39.
4. **Port S, McEwan P, Cobb FR, Jones RH.** Influence of resting left ventricular function on the left ventricular response to exercise in patients with coronary artery disease. Circulation 1981;63:856–863.
5. **Wasserman K, McIlroy MB.** Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. Am J Cardiol 1964;14:844–852.
6. **Wasserman K, Whipp BJ.** Exercise physiology in health and disease. Am Rev Resp Dis 1975;112:219–249.
7. **Conn EH, Williams RS, Wallace AG.** Exercise responses before and after physical conditioning in patients with severely depressed left ventricular function. Am J Cardiol 1982;49:296–300.
8. **Rowell LB.** Human cardiovascular adjustments to exercise and thermal stress. Physiol Rev 1974;54:75–159.
9. **Mitchell JH, Sproule BJ, Chapman CB.** The physiological meaning of the maximal oxygen intake test. J Clin Invest 1958;37:538–541.
10. **Taylor HL, Buskirk E, Henschel A.** Maximal oxygen intake as an objective measure of cardio-respiratory performance. J Appl Physiol 1955;8:73–80.
11. **Chapman CB, Mitchell JH, Sproule BJ, Polter D, Williams B.** The maximal oxygen intake test in patients with predominant mitral stenosis: a preoperative and postoperative study. Circulation 1960;22:4–13.
12. **Epstein SE, Beiser GD, Stampfer M, Robinson B, Braunwald E.** Characterization of the circulatory response to maximal upright exercise in normal subjects and patients with heart disease. Circulation 1967;35:1049–1062.
13. **Green MV, Brody WR, Douglas MA, Redwood DR, Bailey JJ, Johnston GS.** Count rate measurement of left ventricular ejection fraction from gated scintigraphic images (abstr). J Nucl Med 1976;17:557.
14. **Burow RD, Strauss HW, Singleton R, Pond M, Rehn T, Bailey IK, Griffith LC, Nickoloff E, Pitt B.** Analysis of left ventricular function for multiple gated acquisition cardiac blood pool imaging: comparison to contrast angiography. Circulation 1977;56:1024–1028.
15. **Swain JL, Morris KG, Bruno FP, Cobb FR.** Comparison of multigated radionuclide angiography with ultrasonic sonomicrometry over a wide range of ventricular function in the conscious dog. Am J Cardiol 1980;46:976–982.
16. **Slutsky R, Karliner J, Ricci D, Kaiser R, Pfisterer M, Gordon D, Peterson K, Ashburn W.** Left ventricular volumes by gated equilibrium radionuclide angiography: a new method. Circulation 1979;60:556–564.
17. **Dehmer GJ, Lewis SE, Hillis LD, Tweig D, Falkoff M, Parkey RW, Willerson JT.** Nongeometric determination of left ventricular volumes from equilibrium blood pool scans. Am J Cardiol 1980;45:293–300.
18. **Hossack KF, Bruce RA, Green B, Kusumi F, DeRouen TA, Trimble S.** Maximal cardiac output during upright exercise: approximate normal standards and variations with coronary heart disease. Am J Cardiol 1980;46:204–212.
19. **Clausen JP.** Circulatory adjustments to dynamic exercise and effects of physical training in normal subjects and patients with coronary artery disease. Prog Cardiovasc Dis 1976;18:459–495.
20. **Mitchell JH, Blomqvist G.** Maximal oxygen uptake. New Engl J Med 1971;284:1018–1022.
21. **Thadani U, Parker JO.** Hemodynamics at rest and during supine and sitting bicycle exercise in normal subjects. Am J Cardiol 1978;41:52–59.
22. **Rerych SK, Scholz PM, Newman GE, Sabiston DC, Jones RH.** Cardiac function at rest and during exercise in normals and patients with coronary heart disease: evaluation of radionuclide angiocardiography. Ann Surg 1978;187:449–464.
23. **Clausen JP, Klausen K, Rasmussen B, Trap-Jensen J.** Central and peripheral circulatory changes after training of the arms or legs. Am J Physiol 1973;225:675–682.
24. **Slutsky R, Karliner J, Ricci D, Schuler G, Pfisterer M, Peterson K, Ashburn W.** Response of left ventricular volume to exercise in man assessed by radionuclide equilibrium angiography. Circulation 1979;60:565–571.
25. **Goldstein RE, Beiser GD, Stampfer M, Epstein SE.** Impairment of autonomically mediated heart rate control in patients with cardiac dysfunction. Circ Res 1975;36:571–578.
26. **Spann JF Jr, Childsey CA, Braunwald E.** Reduction of cardiac stores of norepinephrine in experimental heart failure. Science 1964;145:1439–1441.

# Determinants of Ventricular Tachycardia in Patients With Coronary Artery Disease and Ventricular Aneurysm

## Clinical, Hemodynamic, and Angiographic Factors

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**Many patients with coronary artery disease (CAD) in whom ventricular tachycardia (VT) develops have transmural scars or frank aneurysms. However, only a minority of patients with ventricular aneurysms go on to develop VT. To determine which factors are associated with the development of VT in patients with aneurysms, we retrospectively reviewed the records of 154 patients with CAD and segments of akinesia or dyskinesia, or both, on left ventriculography. Of the 154 patients, 85 had 24-hour Holter monitoring or 48 consecutive hours of continuous electrocardiographic monitoring in an intensive care unit within 6 months of catheterization. VT occurring at least 10 days after myocardial infarction (MI) or in the chronic phase was recorded in 19 patients (Group I); the remaining 66 patients did not have VT (Group II). The clinical, hemodynamic, and angiographic characteristics of these 2 groups showed no significant difference with respect to age, time from first transmural MI to catheterization, congestive heart failure (CHF), ejection fraction, or presence of dyskinesia. Patients with VT had significantly larger aneurysms and a higher prevalence of septal akinesia or dyskinesia. However, stepwise discriminant analysis revealed septal akinesia or dyskinesia to be the only independently significant variable distinguishing the 2 groups. Thus, septal involvement appears to be a major determinant of VT in patients with CAD and ventricular aneurysm.**

Previous studies in patients with CAD and VT indicate that tachycardia often arises in the setting of multivessel disease and ventricular aneurysm.[1–5] However, VT develops in only a minority of patients with ventricular aneurysms.[7–9] The factors responsible for the development of this tachycardia in the presence of ventricular aneurysm have not been determined.

This study retrospectively reviews the clinical, hemodynamic, and angiographic characteristics of 85 patients with ventricular aneurysm secondary to CAD. In 19 of the 85 patients ventricular tachycardia developed during Holter or intensive care unit monitoring. Characteristics of the patients with VT were compared with those of patients without evidence of this arrhythmia.

### Methods

The records of 708 patients who underwent coronary arteriography and biplane left ventriculography at Mount Sinai Hospital in 1979 were retrospectively reviewed. Catheterization was accomplished by the Sones or Judkins technique and included selective coronary arteriography, right and left anterior oblique left ventriculography, measurement of left ventricular end-diastolic pressure, and calculation of the ejection fraction of the left ventricle in the right anterior oblique plane. Patients without a left anterior oblique plane ventriculogram were excluded from this study. CAD was diagnosed when at least 1 major coronary artery had a stenotic lesion causing ≥50% reduction in luminal diameter. Ventricular aneurysm was diagnosed when either right anterior oblique or left anterior oblique left ventriculography, or both, demonstrated a segment of akinesia or dyskinesia involving ≥10% of the total diastolic perimeter.[10] Because most aneurysms did not bulge from the residual myocardial segments in diastole, the silhouettes of the left ventricle in systole and diastole were superimposed so as to allow approximation of the length of the aneurysmal segment in diastole. Once obtained, this length was expressed as a percentage of the total diastolic perimeter in a manner similar to that described by Field et al.[11] Five possible locations of aneurysmal segments were identified: anterior, apical, and inferior from the right anterior oblique view and septal or posterolateral from the left anterior oblique plane. In addition, aneurysmal segments were described as either retaining or having lost their trabeculations.

A ventricular aneurysm was found in 154 patients with CAD. The complete inpatient chart, the catheterization report, and the attending physician's office chart of these 154 patients were reviewed. Within 6 months of catheterization,

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**TABLE I Clinical Characteristics**

| | Group I (VT) | Group II (No VT) | p |
|---|---|---|---|
| Age (yr) | 53 ± 11 | 58 ± 11 | <0.05* |
| Males (%) | 79 | 80 | NS |
| Previous MIs (n) | 1.2 ± 0.4 | 1.4 ± 0.7 | NS |
| Days between first MI and catheterization | 1,515 ± 321 | 1,743 ± 413 | NS |
| CHF (%) | 32 | 27 | NS |
| Cardiomegaly (chest X-ray) (%) | 47 | 30 | NS |
| Q waves on ECG (%) | 100 | 92 | NS |
| Diabetes mellitus (%) | 16 | 21 | NS |
| Hypertension (%) | 21 | 38 | NS |
| Hyperlipidemia (%) | 21 | 17 | NS |
| Smoking (%) | 53 | 47 | NS |
| Active angina (%) | 32 | 82 | <0.0001† |

* Difference does not remain significant after stepwise discriminant analysis. † Difference remains significant after stepwise discriminant analysis. ECG = electrocardiogram; NS = not significant.

**TABLE II Hemodynamic and Coronary Arteriographic Characteristics**

| | Group I (VT) | Group II (No VT) | p |
|---|---|---|---|
| LVEDP (mm Hg) | 19 ± 7 | 21 ± 8 | NS |
| RAO ejection fraction (%) | 43 ± 15 | 49 ± 18 | NS |
| LMCA (mean % narrowing) | 8 ± 18 | 17 ± 32 | NS |
| RCA (%) | 79 ± 32 | 85 ± 28 | NS |
| Circumflex (%) | 44 ± 39 | 69 ± 32 | <0.006* |
| LAD (%) | 81 ± 31 | 83 ± 26 | NS |
| LAD stenosis before first septal (%) | 47 | 41 | NS |
| Vessels with ≥50% stenosis (n) | 1.9 ± 0.5 | 2.3 ± 0.7 | 0.03† |

* Difference remains significant after stepwise discriminant analysis. † Difference does not remain significant after stepwise discriminant analysis. LAD = left anterior descending artery; LMCA = left main coronary artery; LVEDP = left ventricular end-diastolic pressure; NS = not significant; RAO = right anterior oblique; RCA = right coronary artery.

85 patients had either 24-hour Holter monitoring (26 patients) or continuous electrocardiographic monitoring in an intensive care unit for at least 48 consecutive hours (59 patients). This study is based on the characteristics of these 85 patients.

VT (3 or more consecutive ventricular ectopic beats) occurred in 19 patients at least 10 days after MI or in the chronic phase of ischemic heart disease (Group I). Sixty-six patients had no ventricular arrhythmias or ventricular arrhythmias other than VT such as isolated premature contractions or bigeminy (Group II). Patients with VT during the acute phase of MI or during an episode of transient MI, digoxin toxicity, or significant electrolyte or metabolic derangement were excluded from the analysis.

Clinical, hemodynamic, and angiographic characteristics were recorded in each of the 85 patients. The clinical variables recorded were age, sex, history of diabetes mellitus, hyperlipidemia, hypertension, cigarette smoking, presence of active angina, number of previous MIs, time from first MI to catheterization (an indirect estimate of the age of the aneurysm), presence of clinical signs and/or symptoms of CHF, cardiomegaly by chest X-ray, and presence of pathologic Q waves on the electrocardiogram. The hemodynamic variable recorded for each patient was left ventricular end-diastolic pressure. The angiographic variables studied were the percentage of stenosis and location of obstructions in each major coronary artery. Patients with disease of the left anterior descending artery were further classified as having the stenosis before or after the first septal perforator. In addition, the total number of vessels with ≥50% stenosis was recorded for each patient. Data derived from left ventriculography included calculation of ejection fraction and identification of any akinetic and dyskinetic segments, percentage of perimeter involved, location of aneurysmal segments, and presence or absence of trabeculation in the endocardial surface of the aneurysm.

Of the 19 patients in Group I, 2 were receiving digoxin alone, 6 digoxin and a diuretic, and 11 an antiarrhythmic drug (quinidine in 7, pronestyl in 3, and Norpace in 1). In Group II, 3 patients were receiving digoxin alone, 4 a diuretic agent alone, and 20 digoxin and a diuretic drug. The small number of patients within each of these subgroups precluded meaningful comparisons.

**Statistical methods:** The characteristics of the patients with VT were compared with those of patients without VT. The 2 groups of patients were compared for all continuous and discrete variables using $t$ and chi-square tests, respectively. A p value ≥0.05 was considered not significant. A stepwise discriminant analysis was performed to determine which variable best discriminated between the 2 groups.

The data analyzed were derived from the subset of 85 patients who met the qualifying criteria on the basis of biplane angiography, electrocardiographic monitoring, and so forth. Inferences based on these data are made with some reservation. In addition, given our sample size, the power of our method to detect as significant a difference of 20% between the 2 groups, was about 65%, that is, the beta error was approximately 35% at an alpha of 5%.

## Results

**General population:** In Group I, VT occurred in the late hospital phase of an acute MI in 5 patients and in the chronic phase in 14 patients. Recurrent sustained VT was documented in 3 patients, recurrent nonsustained VT in 9, and an isolated episode of nonsustained VT in 7. Three patients in Group I had an episode of ventricular fibrillation in addition VT.

In Group II, 2 patients had frequent ventricular premature contractions (≥15/h) with rare couplets, 5 had frequent ventricular premature contractions with occasional runs of bigeminy or trigeminy, and 54 had infrequent multiform or uniform ventricular premature contractions, or both. Five patients had no ventricular arrhythmia.

**Clinical characteristics:** The clinical characteristics of the 2 groups of patients are compared in Table I. There was no significant difference between Groups I and II with respect to sex, number of previous MIs, time between the first MI and cardiac catheterization, presence of CHF, cardiomegaly on chest X-ray, or the presence of Q waves on the electrocardiogram. In addition, there was no significant difference between the 2 groups with respect to a history of diabetes mellitus, hypertension, hyperlipidemia, or smoking. However, patients in Group I were significantly younger than those in Group II, although this difference did not remain significant after stepwise discriminant analysis. Patients with VT had a significantly lower prevalence of active angina at the time of study.

**TABLE III Characteristics of the Aneurysmal Segments Identified by Left Ventriculography**

| | Group I (VT) | Group II (No VT) | p |
|---|---|---|---|
| Size of aneurysm (mean % of perimeter) | 40 ± 12 | 32 ± 14 | <0.02* |
| Akinesia (%) | 100 | 95 | NS |
| Dyskinesia (%) | 47 | 28 | NS |
| Septal akinesia or dyskinesia (%) | 89 | 42 | <0.002† |
| Anterior akinesia or dyskinesia (%) | 53 | 32 | NS |
| Apical akinesia or dyskinesia (%) | 79 | 64 | NS |
| Inferior akinesia or dyskinesia (%) | 47 | 67 | NS |
| Posterolateral akinesia or dyskinesia (%) | 5 | 3 | NS |
| Trabeculations preserved (%) | 0 | 8 | NS |

* Difference does not remain significant after stepwise discriminant analysis. † Difference remains significant after stepwise discriminant analysis.

**Hemodynamics and coronary arteriography:** The hemodynamic and coronary arteriographic characteristics of the 2 groups are shown in Table II. There was no significant difference between Groups I and II with respect to left ventricular end-diastolic pressure or right anterior oblique ejection fraction. The mean left ventricular end-diastolic pressure was elevated in both groups, and the mean ejection fraction was slightly depressed in both.

Coronary arteriography revealed that patients in Group I had a significantly smaller number of vessels with ≥50% stenosis (1.9 ± 0.5 versus 2.3 ± 0.7, p = 0.03). This difference was observed because patients in Group I had a significantly lower mean percentage of narrowing of the circumflex artery than did patients in Group II (44 ± 39% versus 69 ± 32%, p <0.006). No significant difference between the 2 groups was detected with reference to the other coronary arteries. The frequency with which significant stenosis of the left anterior descending artery occurred before the first septal perforator did not differ significantly in the 2 groups.

**Left ventriculography:** The characteristics of the aneurysmal segments in both groups as identified from the left ventriculogram are shown in Table III. The mean size of the aneurysms, measured as a percentage of the diastolic perimeter, was significantly larger in patients in Group I than in Group II (40 ± 12% versus 32 ± 14%, p <0.02); however, this difference did not remain significant after stepwise discriminant analysis. A higher percentage of patients in Group I had dyskinetic segments; however, this difference did not reach statistical significance. Akinesia or dyskinesia occurred with a significantly higher frequency in the septal region in Group I patients (89 versus 44%, p <0.002). No significant differences were detected with respect to the other 4 locations. Eighty of the 85 patients had aneurysmal segments without normal endocardial trabeculation; the 5 patients with preserved endocardial trabeculation were all in Group II.

Stepwise discriminant analysis revealed that septal involvement was the most important variable differentiating Group I from Group II. The second most important factor was the difference in the degree of circumflex disease.

## Discussion

VT in the setting of CAD and ventricular aneurysm was first described in 1934.[12,13] Since then, a close association between malignant ventricular arrhythmias and ventricular aneurysm has been well established.[1–9,14–16] Despite these observations, however, only a minority of patients with ventricular aneurysm appear to develop VT.[7–9] Factors that predispose certain patients with aneurysms to VT are yet to be identified.

Previous work by our group showed that certain electrophysiologic abnormalities differentiated patients with aneurysm and VT from those with aneurysms without VT.[17] In the present study we examined clinical, hemodynamic, and angiographic characteristics to identify additional variables that might predispose a patient with aneurysm to VT. None of the clinical or hemodynamic characteristics we evaluated were able to distinguish between patients with and those without VT. Patients with VT had a lower incidence of active angina and less severe CAD secondary to less severe disease in the circumflex artery.

Septal akinesia or dyskinesia was the most important angiographic variable differentiating between the 2 groups of patients. Septal involvement correctly identified 89% of the patients with VT, whereas 58% of the patients without VT did not have septal involvement.

In a review of 109 patients with ventricular aneurysm secondary to CAD, Rochemaure et al[8] found that 8 of 39 patients (21%) with large aneurysms (>6 cm in diameter at autopsy) had VT. In contrast, only 1 of 48 patients (2%) with a medium or small aneurysm developed VT. Mourdjinis et al[9] observed that 6 of 10 patients with "large" aneurysms developed malignant ventricular arrhythmias, whereas none of the 29 patients with "minor" aneurysms developed malignant arrhythmias. In agreement with the findings of these investigators, our patients who had VT tended to have larger aneurysms than did patients without tachycardia. However, the size of the aneurysm did not distinguish between the 2 groups once septal involvement was taken into account in the multivariate analysis. Although septal akinesia or dyskinesia frequently occurs in the presence of a large aneurysm, 3 patients had large aneurysms that did not involve the septum and none appeared to have VT.

The importance of the location of aneurysmal segments was apparent in a previous study by Wiener et al.[17] All of their patients with ventricular aneurysms and VT had fragmented activity along the septal border zone of their aneurysm. In contrast, fragmented activity along the septal border was rarely observed in their patients with aneurysms who did not have VT. Horowitz et al[18] identified the septum as the source of sustained VT in almost half of their 29 patients operated on for this arrhythmia. Our finding of a significantly higher incidence of septal akinesia or dyskinesia in patients with clinically identified VT is consistent with these mapping studies. Septal involvement may be important in the development of ventricular arrhythmia because of the high density of Purkinje fibers in the ventricular septum. Alternatively, because the septum usually receives a dual blood supply, some

muscle or Purkinje fibers rendered ischemic by occlusion of 1 coronary artery may be maintained by flow from the other coronary artery and become a focus of electrical instability.

Septal involvement occurs frequently in patients with CAD and ventricular aneurysm. Of our original cohort of 154 patients with aneurysms, 40% had septal scars. Indeed, 42% of our patients without VT had septal involvement. Some of these patients may have had VT that we were unable to detect. Patients were monitored at different times in the course of their disease, in addition, we relied on 48 hours of intensive care unit monitoring as a substitute for Holter monitoring. Lastly, we now appreciate that 24-hour Holter monitoring might be insufficient to detect malignant ventricular arrhythmias.[19,20]

Two patients with an angiographically normal septum had VT. The correlation between angiographic and pathologic evidence of septal scarring is not well established. Patients with a small scar in the septal region may appear to have normal septal wall motion on angiography. In addition, superimposition of the shadow of an apical aneurysm may obscure the septum. Therefore, factors in addition to septal involvement must be involved in the genesis of VT.

Other than septal involvement, the only variable differentiating between patients with and those without VT was the degree of circumflex disease. Why patients with VT generally have less severe circumflex disease than do patients without VT is not apparent. This may be a chance observation secondary to sampling error. Therefore, our group of patients with VT, 89% of whom have septal scars, may be biased with respect to severe circumflex disease.

Recently, Bulkley et al[21] suggested that endocardial disease may be an important variable differentiating patients with aneurysms in whom VT develops from those in whom it does not.[18] Specifically, VT developed in 10 of 13 patients with endocardial fibroelastasis and little or no mural thrombus, whereas VT developed in only 2 of 10 patients with mural thrombus. Our study did not review pathologic data.

**Clinical implications:** Analysis of the clinical, hemodynamic, and angiographic characteristics of 85 patients with ventricular aneurysm suggests that septal involvement is a major determinant of VT. Prospective studies in patients with myocardial scars are needed to correlate angiographic observations with the development of ventricular arrhythmias. Angiographic data from this study together with the electrophysiologic observations of Wiener et al[17] suggest that surgical intervention for refractory ventricular arrhythmias should include intraoperative assessment of the ventricular septum.

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## References

1. **Bouvrain Y, Slama R, Motte G, Waynberger M, Crevelier A.** Les tachycardies ventricularies: étiologie et évolution à propos de 161 malades. Arch Mal Coeur 1968;61:909–920.
2. **Sharma SD, Ballantyne F, Goldstein S.** The relationship of ventricular asynergy in coronary heart disease to ventricular premature beats. Chest 1974;66:358–362.
3. **Weaver W, Lorch G, Alvarez H, Cobb L.** Angiographic findings and prognostic indications in patients resuscitated from sudden cardiac death. Circulation 1976;54:895–900.
4. **Calvert S, Lown B, Gorlin R.** Ventricular premature beats and anatomically defined coronary heart disease. Am J Cardiol 1977;39:627–634.
5. **Schulze RA, Humphries JO, Griffith LSC, Ducci H, Achuff S, Baird MG, Mellits SCD, Pitt B.** Left ventricular and coronary angiographic anatomy: relationship to ventricular irritability in the late hospital phase of acute myocardial infarction. Circulation 1977;55:839–843.
6. **Spielman SR, Greenspan AM, Horowitz LN, Kastor JA, Josephson ME.** Anatomic substrates of recurrent sustained ventricular tachycardia (abstr). Clin Res 1979;27:569.
7. **Dubnow MH, Burchell HB, Titus JL.** Post infarction ventricular aneurysm: a clinico-morphologic and electrocardiographic study of 80 cases. Am Heart J 1965;70:753–760.
8. **Rochemaure J, Himbert J, Lenegre J.** Evolution des aneurismes ventriculaires aprés infarctus du myocarde. Arch Mal Coeur 1966;59:1649–1664.
9. **Mourdjinis A, Olsen F, Raphael MJ, Mounsey JPD.** Clinical diagnosis and prognosis of ventricular aneurysm. Br Heart J 1968;30:497–513.
10. **Gorlin R, Klein MD, Sullivan JM.** Prospective correlative study of ventricular aneurysm: mechanistic concept and clinical recognition. Am J Med 1967;42:512–531.
11. **Field B, Russel R, Dowling J, Rackley C.** Regional left ventricular performance in the year following myocardial infarction. Circulation 1972;46:679–689.
12. **Scherf D, Erlsbacher O.** Zur symptomatologie des partiellen herzaneurysmas. Med Klin 1934;30:1687–1689.
13. **Parade GW.** Aneurysmatische elongation des herzens. Med Klin 1934;30:1357–1359.
14. **Wasserman E, Yules J.** Cardiac aneurysm with ventricular tachycardia: case report and review of the literature. Ann Intern Med 1953;39:948–956.
15. **Ricks WB, Winkle RA, Shumway NE, Harrison DC.** Surgical management of life threatening ventricular arrhythmias in patients with coronary artery disease. Circulation 1977;56:38–42.
16. **Robertson JF, Cain ME, Horowitz LN, Spielman SR, Greenspan AM, Waxman HL, Josephson ME.** Anatomic and electrophysiologic correlates of ventricular tachycardia requiring left ventricular stimulation. Am J Cardiol 1981;48:263–268.
17. **Wiener I, Mindich B, Pitchon R.** Determinants of ventricular tachycardia in patients with ventricular aneurysms: results of intraoperative epicardial and endocardial mapping. Circulation 1982;66:856–861.
18. **Horowitz LN, Harken AH, Kastor JA, Josephson ME.** Ventricular resection guided by epicardial and endocardial mapping for treatment of recurrent ventricular tachycardia. N Engl J Med 1980;302:499–503.
19. **Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Dunkman WB.** Limitations of routine long term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 1978;58:408–414.
20. **Morganroth J, Michelson EL.** Inadequacy of limited Holter monitoring to detect complex ventricular arrhythmias (abstr). Circulation 1979;60:Suppl II:II-255.
21. **Bulkley BH, Platia EV, Stone GW, Hochman JS.** Ventricular aneurysms and endocardial pathology: relationships to malignant arrhythmias (abstr). Circulation 1981;64:Suppl IV:IV-306.

# Relation of Exercise to the Recurrence Rate of Myocardial Infarction in Men

## Ontario Exercise-Heart Collaborative Study

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**The Ontario Exercise-Heart Collaborative Study was a multicenter randomized clinical trial of high intensity exercise for the prevention of recurrent myocardial infarction in men. The 4-year recurrence rate among 379 patients on a program of high intensity exercise did not differ significantly from that among 354 control patients on a program of light exercise, despite the greater reduction in heart rate in the former group. The relative odds of recurrence in the high intensity group were 1.09, with 95% confidence limits of 0.61 and 1.96.**

Recent epidemiologic studies[1,2] have shown that physical activity is associated with a reduced incidence of coronary disease, although the association was not strong.[3] However, these studies are used to some extent as the rationale for exercise in the prevention of recurrence in patients who have had myocardial infarction. A retrospective analysis suggested that this approach might have value,[4] but in prospective studies carried out in Sweden[5] and the United States[6] the results have been equivocal, although a group in Finland[7] reported a significantly lower incidence of early sudden death in a group with a multifactorial approach which included an exercise prescription.

The Ontario Exercise-Heart Collaborative Study[8] was designed as a randomized clinical trial to determine whether a program of high intensity exercise was associated with a lower rate of reinfarction than a program of light exercise, insufficient to produce a training effect on the cardiovascular system, but which controlled for a possible group therapy effect seen by various investigators after myocardial infarction.[9,10]

The design of the study has been described in detail elsewhere.[8] Its objective was to test the hypothesis that over a 4-year period a 50% reduction in the recurrence of infarction could be achieved by a high intensity exercise program. Such a reduction would be of a definite clinical significance, and a study to test this hypothesis was shown to be feasible in an uncontrolled study carried out by Rechnitzer et al.[4] Although a smaller degree of reduction in the recurrence rate might be of clinical importance, the number of subjects required to demonstrate a positive effect would be inordinately large.[11]

The best baseline rate of recurrence available at the beginning of the trial was that of 22% reported by Weinblatt et al[12] from the HIP study in New York. Therefore, sample size calculations were based on detecting a 50% reduction in recurrence (from 22 to 11%), with a Type I error of 0.05, Type II error of 0.10, and an anticipated dropout rate of 35%.

The trial began in 1972 as a 4-center collaborative clinical trial, but was enlarged in 1974 to include 3 additional centers because the observed dropout rate exceeded that on which the power calculation of the original design was based. The former are referred to as the "major" centers and the latter as the "satellite" centers.

Participating Centers (all in Ontario, Canada): McMaster University, Hamilton; Queen's University, Kingston; University of Ottawa, Ottawa; University of Toronto and Toronto Rehabilitation Center, Toronto; University of Waterloo, Waterloo; University of Western Ontario, London; and University of Windsor, Windsor. This project was supported by Research Grant PR263 from the Ontario Ministry of Health, Toronto, Ontario, Canada. Manuscript received January 26, 1982; revised manuscript received July 2, 1982, accepted July 2, 1982.

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## Methods

A total of 733 male subjects participated in the study, 706 patients having had a myocardial infarction between 2 and 12 months and 27 patients between 13 and 17 months before entry. The subjects ranged in age from 26 to 56 years.

All subjects had at least 2 of the following diagnostic criteria: typical chest discomfort, a significant increase in cardiac enzyme levels (serum glutamic oxalacetic transaminase, creatine phosphokinase), or electrocardiographic changes compatible with a transmural or subendocardial infarction. Additional eligibility criteria were the following: (1) absence of cardiac failure; (2) absence of diabetes or controlled diabetes, not insulin-dependent; (3) diastolic blood pressure ≤110 mm Hg, but possibly receiving antihypertensive medication; (4) absence of any orthopedic disability that would limit progressive physical activity; (5) absence of significant airway obstruction in spirometric measurements ($FeV_1/VC \geq 60\%$); (6) consent of the family physician and a signed informed consent by each subject for entrance into the study.

The subjects were placed on high intensity exercise (HIE) or low intensity exercise (LIE) by stratified random allocation. The stratifying variables were (1) presence or absence of hypertension, defined as 3 readings >160 systolic or 90 diastolic, or both; (2) blue collar versus white collar employment; (3) presence or absence of angina; (4) Type A versus Type B behavioral pattern as measured by the standardized interview technique of Rosenman.[13]

**TABLE I Characteristics at Entry of Subjects in Both HIE and LIE Groups**

| | | Characteristics at Entry of Subjects in Both Groups | | Characteristics at Entry of Subjects Who Later Dropped Out | |
|---|---|---|---|---|---|
| | Total | HIE | LIE | HIE | LIE |
| Randomized population | 761 | 390 | 371 | ... | ... |
| Exclusions* | 28 | 11 | 17 | ... | ... |
| Valid study group | 733 | 379 | 354 | 174 | 159 |
| Age at entry (yr) | | | | | |
| Median | 47.5 | 47.3 | 47.7 | 46.4 | 47.3 |
| Range | 25.9–55.7 | 25.9–55.3 | 26.1–55.7 | 25.9–55.3 | 26.1–55.7 |
| Interval from infarction to entry (mo) | | | | | |
| Median | 6.2 | 6.2 | 6.2 | 6.7 | 6.2 |
| Range | 2–17 | 2–17 | 2–15 | 2–17 | 2–15 |
| Number of infarctions previous to study infarction (%)† | | | | | |
| 0 | 91.1 | 91.6 | 90.7 | 89.7 | 87.4 |
| 1 | 7.0 | 6.6 | 7.3 | 8.0 | 11.3 |
| 2 | 0.4 | 0.5 | 0.3 | 0.6 | 0.6 |
| 3 | 0.4 | 0.3 | 0.6 | 0.6 | 0.6 |
| Unknown | 1.1 | 1.1 | 1.1 | 1.1 | 0.0 |
| Length of hospitalization for index infarction (days) | | | | | |
| Subjects (n) | 711 | 367 | 344 | 170 | 154 |
| Median | 18.8 | 18.0 | 19.6 | 17.2 | 19.1 |
| Not hospitalized (%)† | 3.0 | 3.2 | 2.8 | 2.3 | 3.1 |
| Stratification risk factors (%)† | | | | | |
| Angina | | | | | |
| Present | 31.2 | 30.6 | 31.9 | 32.2 | 33.7 |
| Absent | 68.8 | 69.4 | 68.1 | 67.8 | 67.3 |
| Hypertension | | | | | |
| Present | 16.2 | 17.7 | 14.7 | 19.5 | 15.7 |
| Absent | 83.3 | 82.3 | 85.3 | 80.5 | 84.3 |
| Occupation | | | | | |
| Blue collar | 41.6 | 42.2 | 41.0 | 46.6 | 46.5 |
| White collar | 58.4 | 57.8 | 59.0 | 53.4 | 53.5 |
| Personality | | | | | |
| Type A | 70.5 | 69.9 | 71.2 | 74.1 | 77.4 |
| Type B | 29.5 | 30.1 | 28.8 | 25.9 | 22.6 |
| Smoking habit (%)† | | | | | |
| Smoker | 33.5 | 34.6 | 36.4 | 44.3 | 49.7 |
| Exsmoker | 55.5 | 55.4 | 55.6 | 48.3 | 45.9 |
| Nonsmoker | 8.6 | 9.5 | 7.6 | 6.3 | 3.8 |
| Unknown | 0.4 | 0.5 | 0.3 | 1.1 | 0.6 |
| Cholesterol (mg/100 ml)‡ | | | | | |
| Number of subjects | 427 | 228 | 199 | 98 | 75 |
| Median | 216 | 217 | 216 | 218 | 218 |
| Range | 112–316 | 120–316 | 112–315 | 132–316 | 125–315 |
| Triglycerides (mg/100 ml)‡ | | | | | |
| Subjects (n) | 427 | 228 | 199 | 98 | 75 |
| Median | 151 | 150 | 151 | 156 | 166 |
| Range | 50–642 | 50–597 | 50–642 | 58–597 | 50–642 |
| Ventricular premature beats (%) | | | | | |
| None | 59.8 | 59.6 | 59.9 | ... | ... |
| Occasional | 28.0 | 26.1 | 29.9 | ... | ... |
| Frequent (≥5/min) | 9.9 | 11.9 | 7.9 | ... | ... |
| Missing data | 2.4 | 2.4 | 2.3 | ... | ... |
| Subjects on propranolol (%) | 10.7 | 10.4 | 11.0 | ... | ... |

* Incorrectly diagnosed, baseline data only. † Totals are not always 100% because of rounding errors. ‡ Based on the 427 subjects who had complete lipid determinations.

Medical examination at entry included measurement of height, weight, and skinfold thickness; electrocardiography; hemoglobin, fasting plasma glucose, cholesterol, and triglyceride determinations; and a chest X-ray if one had not been taken at the time of discharge from hospital. Table I shows that the baseline characteristics had very similar distributions in the HIE and LIE groups.

**Exercise test protocols:** The exercise test protocols have been described in detail elsewhere.[8] The Stage 1 test, a progressive incremental load test carried out on a cycle ergometer, was used to determine the exercise prescription. A Stage II test, a steady state exercise test carried out on a cycle ergometer, was also used at the major centers to determine cardiac output and other physiologic responses to exercise.[14] The tests were repeated at 6 months, at 12 months, and at 12-month intervals thereafter. Quality control data on the exercise measurements were collected regularly and the measured values were found to be reproducible.[15]

For each individual, a regression equation relating heart rate to oxygen uptake (4 major centers) or approximated oxygen uptake (3 satellite centers) was calculated by the least-squares method. The heart rate and oxygen uptake of 1.25 liters·min$^{-1}$ or 82 W (approximately 1.25 liters·min$^{-1}$) were derived from this equation ($HR_{1.25}$). In the HIE and LIE groups, 10 and 11% of the patients, respectively, were receiving beta-blocking drugs. Subjects in the HIE program on beta-blocking drugs were tested twice, once 48 hours after medication was stopped to determine the training response and once on medication to calculate the exercise prescription. Subjects in the LIE program were tested after medication was stopped.

**Training regimens:** The HIE subjects (n = 379) met regularly for a program of endurance training. They carried out an exercise prescription based on the subject's graded exercise test results.[16] The exercise prescription was calculated to give a walking or jogging pace requiring between 65 and 85% of the subject's estimated maximal oxygen uptake. After an introductory period of 8 weeks, the subjects were asked to supplement the supervised sessions (twice weekly in 6 centers, once weekly in 1 center) by carrying out the same exercise prescription on their own for a total of at least 4 times per week. Pulse counts were taken by the subjects during both the supervised and the unsupervised sessions to ensure reaching the prescribed exercise heart rate. Exercise tests were repeated after 8 weeks for review of the exercise prescription; thereafter, exercise tests were carried out every 6 months or more frequently if clinically indicated.

The LIE subjects (n = 354) met at least once a week for relaxation and supervised recreational activities such as volleyball, bowling, or swimming. The activities were structured to produce minimal training; at least 3 pulse counts were taken during each session to ensure that the patient's exercise intensity was not associated with a heart rate greater than observed at 50% of the estimated maximal oxygen uptake. The supervised sessions in both the HIE and the LIE groups lasted approximately 1 hour.

All supervised sessions included the attendance of a physician and the immediate availability of cardiopulmonary resuscitation equipment; exercise leaders were trained in cardiopulmonary resuscitation, and rapid communication with ambulance services was established.

Meetings of the supervisory personnel were held regularly to discuss the regimens of the 2 groups; in addition, 1 of the supervisory personnel visited each participating center annually to ensure that the class format for both the HIE and the LIE groups was uniform. Both HIE and LIE participants at all centers were encouraged to stop smoking and control obesity. If a subject's serum lipid level was abnormal, he was informed and advised to see his family physician. A standard letter to the physician reported cholesterol and triglyceride values and included suggestions for appropriate dietary control.

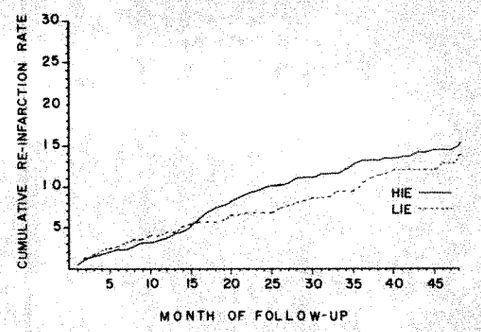



**FIGURE 1.** Cumulative dropout rates by month in HIE and LIE subjects over the 4-year intervention period.

There was no obvious contamination of the 2 groups. Although in some instances the instructors were common to both groups, the HIE and LIE groups met on separate occasions and took little interest in each other's activities. All subjects were asked to fill out an activity questionnaire at yearly intervals. Samplings of these questionnaires showed that the proportion of LIE subjects who were engaging in regular, vigorous exercise was less than 5%.

**Follow-up study:** Each follow-up assessment included an interim clinical history, a 12-lead resting electrocardiogram, and an exercise test. Of the 733 eligible subjects who entered the study, the potential follow-up period was 4 years in 450 subjects, 3 to 4 years in 225 subjects, and 2 to 3 years in 58 subjects. The mean follow-up period for all subjects was 3.3 years.

Patients who failed to appear for 3 consecutive activity sessions were contacted by telephone and encouraged to attend. If a patient did not attend a single session for 8 weeks, he was normally considered a dropout and was notified. Thirty-two subjects with coronary bypass and 3 who died from noncoronary disease were not classified as dropouts, because these reasons had no bearing on the subject's willingness to continue in the study.

The overall dropout rate was 45.4% (45.9% in the HIE and 44.9% in the LIE group). The characteristics on entry of the subjects who subsequently dropped out were similar to those of the groups to which they were originally allocated (Table I). The cumulative life table presentation (Fig. 1) demonstrates that most of the subjects who dropped out did so in the first year of the study. At the conclusion of the study, dropouts were traced to ascertain whether reinfarction had occurred. Reported recurrences were verified from medical records using the study criteria for infarction. Of the original 733 patients entered into the study, 92.4% were successfully traced.

## Results

The number of fatal and nonfatal reinfarctions in the HIE group were 15 and 39, respectively, and in the LIE group, 13 and 33. Thus, the proportion of fatal reinfarctions in the 2 groups (27.8% in the HIE and 28.3% in the LIE group) was very similar. Because the number of fatal reinfarctions was small, they were combined with nonfatal reinfarctions in the analyses of outcome. The overall reinfarction rates in the HIE and LIE groups were 14.2 and 13.0%, respectively.

**TABLE II Life Table Comparison of Reinfarction Experience in High and Low Intensity Exercise Groups, Including Dropouts in the Group to Which They Were Allocated**

| Follow-Up Year | Group | n | Reinfarctions* in Follow-Up Year (n) | Cumulative Results: Life Table Probability of Reinfarction Before End of Year | Cumulative Results: Relative Odds of Reinfarction in HIE/LIE Groups |
|---|---|---|---|---|---|
| 1 | HIE | 379 | 16 | 0.04 | 0.93 |
| | LIE | 354 | 16 | 0.05 | |
| 2 | HIE | 353 | 22 | 0.10 | 1.50 |
| | LIE | 330 | 8 | 0.07 | |
| 3 | HIE | 296 | 9 | 0.13 | 1.18 |
| | LIE | 283 | 14 | 0.11 | |
| 4 | HIE | 189 | 3 | 0.14 | 1.09† |
| | LIE | 187 | 6 | 0.14 | |

* Four reinfarctions in the HIE and 2 in the LIE group are not shown in this table because they occurred in the last fractional year of follow-up study for the subject involved.[17] To recapture this information, the analysis was redone using months rather than years as the follow-up interval. This analysis yielded virtually identical results. † 95% confidence limits, 0.61 to 1.96.

Table II gives the outcomes for the HIE and LIE groups calculated by a life table method.[17] The cumulative life table reinfarction rates are plotted in Figure 2. At each year of follow-up study, the outcome for LIE was, with 1 exception, slightly better than that for HIE. At the fourth year of follow-up study, the relative odds ratio of reinfarction in the HIE group was 1.09. The lower 95% confidence limit for this odds ratio is 0.61,[18] corresponding to a reduction of 39% in the risk of reinfarction.

The question arises as to whether the HIE group achieved the intended degree of cardiovascular training. The heart rate reduction at 1.25 liters·min$^{-1}$ at the end of 1 year was 5.2 ± 15.91 in the HIE group and 2.0 ± 14.73 in the LIE group. At the end of 4 years the heart rate reduction was 10.2 ± 13.39 in the HIE group and 4.0 ± 13.46 in the LIE group. Because the reduction was significantly greater in the HIE group than in the LIE group at 4 years ($p = 0.01$), it is reasonable to conclude that the exercise experience of the 2 groups was different.

In a trial with a high rate of dropouts, the full effect of an experimental intervention is bound to be diluted when the analysis retains dropouts in the group to which they were allocated. However, if an analysis were to exclude dropouts and the results were not more favorable for the intervention group, it would be reasonable to conclude that there was little treatment effect to be diluted. This, in fact, was what we found. When the life tables were recalculated to exclude subjects after the date of dropout, the relative odds for HIE/LIE were 1.24, with 95% confidence limits of 0.66 and 2.34. A third life table analysis, which compared the reinfarction experience in the 2 groups excluding dropouts entirely, resulted in a relative odds of 1.22. Although it would be improper to draw any conclusions about the treatment effect if these secondary analyses had shown an advantage of HIE, the absence of such an advantage reinforces the impression that a program of HIE had no specific effect in preventing reinfarction. Reinfarction rates among HIE droputs (11.5%) and LIE dropouts (12.6%) were very similar.

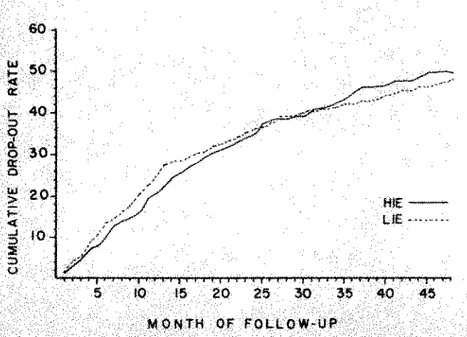



**FIGURE 2.** Cumulative reinfarction rates by month in HIE and LIE subjects over the 4-year intervention period.

Because this was a multicenter trial, 2 other observations are relevant. The first is that no significant differences existed in the overall rate of reinfarction among the 7 participating centers. The second is that in none of the centers was there a significant difference between the HIE and the LIE groups in the rate of reinfarction.

## Discussion

Exercise programs have become popular for rehabilitation after myocardial infarction,[19] but the justification in terms of a reduction in morbidity and mortality is still debated. Before the inception of this study, reports of exercise in cardiac rehabilitation were retrospective, nonrandomized, or lacked stratification for known risk factors.[4,20,21] The Ontario Exercise-Heart Collaborative Study was designed to circumvent some of these problems by prospectively investigating the effects of exercise training using a stratified randomized allocation to treatment groups.[8] When the trial was designed, the possibility of having an observed-only control group, in addition to an LIE group, was considered, but the available pool of subjects was insufficient to permit a 3-group trial Therefore, it was decided to have only a placebo control group on the grounds that the primary objective was to determine the specific ef-

fect of an HIE program designed to produce an improvement in cardiovascular fitness over and above any placebo effect associated with group membership.[9,10]

To determine whether an exercise training program would affect recurrence rates in postinfarction men, we decided that the subjects would have a reasonable chance of being trainable if the entry age were under 56 years. The randomization was stratified to control prognostic factors known to be important at the time the study began, that is, hypertension, angina, Type A behavioral pattern, and social class.

Although the dropout rates were high, they were nearly identical in the 2 groups; the relevant characteristics of dropouts were similar in the HIE and LIE groups (Table I), and the high follow-up rate of 92.4% allowed identification of the reinfarction status of the great majority of dropouts.

Previous clinical trials of the role of exercise in reducing the reinfarction rate in Sweden[5] and the United States[6] demonstrated no significant difference in reinfarction between exercise and control groups but suggested that there were considerable physiologic and psychologic benefits of the exercise regimen. A recent study carried out in Finland[7] indicated that the rate of sudden death may be reduced in a group receiving a multifactorial intervention program including exercise. Our results tend to confirm the observations made in Sweden[5] and the United States.[6] However, our study, by comparing 2 different levels of exercise intensity, extended these observations and suggests that LIE together with the social support of group membership previously reported as being beneficial[9,10] has an effect equivalent to that of an aggressive exercise prescription centered around jogging.

Why was the rate of reinfarction lower than expected, in advance of the trial, in both groups? Perhaps the medical criteria for entry, plus an element of self-selection, drew into the study patients with a more favorable prognosis. The close medical supervision and the social support entailed in such a program might have been considered contributory factors. However, the low recurrence rate in the control group of the American study[6] in which these features were minimal makes this unlikely.

Our results indicate that an HIE program compared with one designed to produce a minimal training effect does not reduce the risk of reinfarction. The lower 95% confidence limit for the relative odds ratio of high to low intensity exercise was 0.61, indicating that the hypothesized 50% reduction in the risk of reinfarction is highly unlikely. Two views may be taken of these results, depending on one's attitude toward the degree of benefit that would be worthwhile detecting. If a reduction of less than 50% in the risk of reinfarction is not considered to be worth the effort and expense of mounting an HIE program, we would be inclined to regard the results of this study as useful. However, if a lesser degree of benefit is deemed to be worth the cost of attainment, the present study must be considered inconclusive.

This study addresses the effect of exercise on the risk of reinfarction only. The potential long-term benefit of this type of intervention on the quality of life remains to be measured.

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## References

1. **Paffenbarger RS, Wing AL, Hyde RT.** Physical activity as an index of heart attack risk in college alumni. Am J Epidemiol 1978;108:161–175.
2. **Morris JN, Ekerlit MG, Pollard R, Chave SPW, Semmence AM.** Vigorous exercise in leisure time: protection against coronary heart disease. Lancet 1980;11:1207–1210.
3. **Froelicher VF.** Exercise and prevention of coronary atherosclerotic disease. Cardiovasc Clin 1978;9:13–23.
4. **Rechnitzer PA, Pickard HA, Paivio AU, Yuhasz MS, Cunningham DA.** Circulation 1972;24:853–857.
5. **Wilhelmsen L, Sanne H, Elmfeldt D, Grimby G, Tibblin G, Wedel H.** A controlled trial of physical training after myocardial infarction. Effects on risk factors, non-fatal reinfarction and death. Prev Med 1975;4:491–508.
6. **Shaw LW** for the project staff. Effects of a prescribed supervised exercise program on mortality and cardiovascular morbidity in patients after a myocardial infarction. Am J Cardiol 1981;48:39–46.
7. **Kallio V, Hamalainen H, Hakkila V, Luurila OJ.** Reduction in sudden death by a multifactorial intervention programme after acute myocardial infarction. Lancet 1979;11:1091–1094.
8. **Rechnitzer PA, Sangal S, Cunningham DA, Andrew GM, Buck CW, Jones NL, Kavanagh T, Parker JO, Shephard RJ, Yuhasz MS.** A controlled prospective study of the effect of endurance training on the recurrence rate of myocardial infarction. A description of the experimental design. Am J Epidemiol 1975;102:358–365.
9. **McPherson BD, Paivio AU, Yuhasz MS, Rechnitzer PA, Pickard HA, Lefcoe NM.** Psychological effect on an exercise program for post-infarct and normal adult men. J Sports Med Phys Fitness 1966;7:95–102.
10. **Rahe RH, Ward HW, Hayes V.** Brief group therapy in myocardial infarction rehabilitation; three to four year follow-up of a controlled trial. Psychosom Med 1979;41:229–242.
11. **Blackburn H.** Disadvantages of intensive exercise therapy after myocardial infarction. In: Ingelfinger F, Ebert RV, Finland M, Relman AS, eds. Controversy in Internal Medicine. New York: WB Saunders, 1974:162–172.
12. **Weinblatt ES, Shapiro S, Frank CW, Sager RV.** Prognosis of men after first myocardial infarction; mortality and first recurrence in relation to selected parameters. Am J Pub Health 1968;58:1329–1347.
13. **Rosenman RH.** The interviewer method of assessment of the coronary-prone behavior pattern. In: Dembroski TM, Weiss SM, Shields JL, Haynes SG, Feinleib M, eds. Coronary-Prone Behavior. New York: Springer Verlag, 1978:55–69.
14. **Jones NL, Campbell EKM, Edwards RHT, Robertson DG.** Clinical Exercise Testing. Philadelphia: WB Saunders 1975:50–55.
15. **Jones NL, Kane JW.** Quality control of exercise test measurements. Med Sci Sports Exerc 1979;11:368–372.
16. **Cunningham DA, Rechnitzer PA.** Exercise prescription and the post coronary patient. Arch Phys Med Rehab 1974;55:296–300.
17. **Mantel N.** Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163–170.
18. **Miettinen OS.** Estimability and estimation in case referent studies. Am J Epidemiol 1976;103:226–235.
19. American Heart Association Subcommittee on Rehabilitation. Standards for cardiovascular exercise treatment program. Circulation 1979;59: 108A–109A.
20. **Gottheiner V.** Long-range strenuous sports training for cardiac reconditioning and rehabilitation. Am J Cardiol 1968;22:426–435.
21. **Hellerstein HK.** Exercise therapy in coronary disease. Bull NY Acad Med 1968;44:1028–1047.

# Predictors of Dropout From Cardiac Exercise Rehabilitation

## Ontario Exercise-Heart Collaborative Study

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**The Ontario Exercise-Heart Collaborative Study was a multicenter randomized clinical trial of high intensity exercise for the prevention of recurrent myocardial infarction in 733 men. Of the 678 subjects who could have participated for at least 3 years, 315 (46.5%) dropped out. Stepwise multiple linear logistic regression analysis was carried out to examine the relation between subject characteristics and the probability of dropping out during the study. Analysis was performed on the entry group as a whole by considering those subjects who had reinfarction while complying with the program and also by excluding all subjects with reinfarctions. The consistent and statistically significant predictors of dropout in both analyses were *smoking* and a *blue collar occupation.* Angina was significantly associated with dropout only when reinfarctions were excluded. It may be important to consider these factors when investigating the potential for compliance-improving strategies in reducing dropout from exercise rehabilitation programs.**

Retrospective nonexperimental studies of physical conditioning have suggested that exercise may reduce the rate of recurrent myocardial infarction.[1] However, these studies may be flawed by membership bias and other design weaknesses[2]; prospective clinical trials in which patients were randomly allocated into exercising and control groups have shown little evidence of a lower recurrence of myocardial infarction in the exercising group than in the control group.[3–6] However, these randomized studies have been weakened by a high rate of dropout.[3–7]

The Ontario Exercise-Heart Collaborative Study (OEHCS) was an experimental study of the effect of physical conditioning on reinfarction, in which subjects were stratified by risk factors and then randomized into high and low intensity exercise groups.[8] As compliance with long-term exercise rehabilitation programs was suspected to be a potential problem, 1 objective was to investigate dropout from the 2 groups. If a potential dropout can be identified at entry, it may be feasible to initiate compliance-improving strategies. Interim observations on the characteristics of the potential dropout in the OEHCS have been reported[7]; the present analysis deals with observations made between 1972, when the study was initiated, and 1979, when the study was completed.

From the Ontario Exercise-Heart Collaborative Study, representing the following Ontario universities: McMaster University, Hamilton; Queen's University, Kingston; University of Toronto, Toronto; University of Western Ontario, London; Ottawa University, Ottawa; University of Waterloo, Waterloo; University of Windsor, Windsor. This work was supported in part by Grant PR 263 from the Ontario Ministry of Health, Toronto, Ontario, Canada. Manuscript received May 17, 1982; revised manuscript received August 3, 1982, accepted August 6, 1982.

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### Methods

**Subjects:** From initial screening procedures, described elsewhere by Rechnitzer et al,[6,8] 733 patients entered the study, of whom 678 were followed up for ≥3 years; 46 patients were lost to follow-up for reinfarction status (because of surgical intervention or because they could not be traced) and 14 patients had missing data related to study variables. The resulting 618 cases provide the basis for the logistic regression analyses reported below. Variables listed in Table I were analyzed for association with dropout; 3 of the variables had a substantial proportion of missing values (cholesterol 41%, triglycerides 41%, ponderal index [height/weight$^{1/3}$] 39%) and for these variables the mean value computed over all cases was substituted for missing values.[9] The appropriateness of this procedure is discussed later.

**Exercise regimens:** The training regimens are described elsewhere.[6,8] The high intensity exercise group carried out supervised endurance exercise at between 65 and 85% of estimated maximal oxygen uptake; subjects were asked to

**TABLE I Characteristics of Subjects at Entry**

| | A. Including Subjects With Reinfarction | | B. Excluding Subjects With Reinfarction | |
|---|---|---|---|---|
| | Dropouts (n = 270)* | Compliers (n = 348)* | Dropouts (n = 244)* | Compliers (n = 295)* |
| | Means (Standard Deviations) | | | |
| 1. Age (yr) | 45.5 (6.5)† | 46.7 (6.7) | 45.4 (6.5)† | 46.8 (5.8) |
| 2. Cholesterol (mg/100 ml) | 221 (35) | 216 (39) | 220 (36) | 215 (39) |
| 3. Triglycerides (mg/100ml) | 176 (97) | 160 (75) | 170 (86) | 160 (78) |
| 4. Ponderal index (height/ weight$^{1/3}$) | 41 (2) | 41 (2) | 41 (2) | 41 (2) |
| 5. Systolic pressure (mm Hg)‡ | 130 (16)† | 128 (15) | 130 (16)† | 128 (15) |
| 6. Diastolic pressure (mm Hg)‡ | 85 (10) | 84 (9) | 85 (10) | 84 (9) |
| | Percentages | | | |
| 7. Sport§ | | | | |
| Yes | 6 | 8 | 6 | 8 |
| No | 94 | 92 | 94 | 92 |
| 8. Jogging§ | | | | |
| Yes | 2 | 5 | 3 | 5 |
| No | 98 | 95 | 98 | 95 |
| 9. Angina | | | | |
| Yes | 33 | 26 | 34† | 23 |
| No | 67 | 74 | 66 | 77 |
| 10. Occupation | | | | |
| Blue collar | 46† | 35 | 44† | 34 |
| White collar | 54 | 65 | 56 | 66 |
| 11. Smoker | | | | |
| Yes | 47† | 26 | 45† | 23 |
| No | 53 | 74 | 55 | 77 |
| 12. Cough‖ | | | | |
| Yes | 22† | 12 | 22† | 11 |
| No | 78 | 88 | 78 | 90 |
| 13. Behavior¶ | | | | |
| A | 74 | 69 | 74 | 68 |
| B | 26 | 31 | 27 | 32 |
| 14. Prior MI | | | | |
| 0 | 9 | 6 | 8 | 5 |
| 1+ | 91 | 95 | 92 | 95 |

* The number of subjects given at the top of the column applies to all variables except 2, 3, and 4. For these variables the sample size for dropouts and compliers in analysis A is 122 and 195, respectively, and in analysis B is 112 and 165. † Differences between dropouts and compliers were significant; see Table II for detailed analysis. ‡ Resting. § >1 h/wk. ‖ Cough or sputum (sometimes or often). ¶ Rosenman/ Friedman Type A or B. MI = myocardial infarction.

supplement the twice weekly supervised sessions by carrying out homework on their own at least 4 other times/week. The light intensity exercise group met once a week for progressive relaxation and supervised recreation activities structured to produce minimal training. All supervised sessions were attended by a physician and cardiopulmonary resuscitation equipment was immediately available.

**Determination of dropout:** Individuals missing 8 consecutive supervised activity sessions were considered dropouts. Reasons for dropout were categorized as follows: transition (change of job or domicile), inconvenience (time of day or too busy), psychosocial factors (lack of motivation or interest), medical problems (such as increasing angina, arthritis, and alcoholism), miscellaneous, and unknown. Subjects who died from causes other than myocardial infarction or who had coronary bypass surgery were not considered dropouts. The classification of subjects who left the trial because of reinfarction is discussed later.

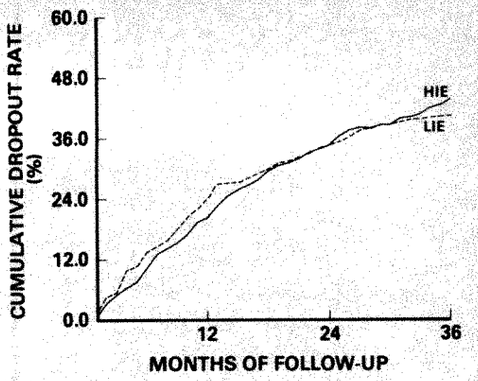



**FIGURE 1.** Month-by-month life-table cumulative dropout in the 678 subjects who were stratified and randomly allocated to the high intensity exercise group (HIE; n = 351) and to the low intensity exercise group (LIE; n = 327) and who were traced for reinfarction status at the end of the study.

**Statistical analysis:** Of the 618 subjects eligible for the multivariate analyses, 270 were classified as dropouts, of whom 26 subsequently had a reinfarction during the 3-year observation period. Among the 348 compliers, 53 left the trial due to a reinfarction during the 3-year period. In order to reduce the potential bias arising from factors related both to reinfarction and to dropout, 2 approaches were taken in the comparison of dropouts and compliers.

The first approach assumed that subjects whose reinfarction occurred while they were complying with the program were "forced" dropouts and were considered compliers. Thus in this analysis, the 270 dropouts were compared with the remaining 348 subjects, including among the latter those who had reinfarction while in the study.

The second approach assumed that subjects withdrawing because of reinfarction should not be considered compliers for, had the infarction not occurred, they might have subsequently dropped out. After considering the various types of association that could occur among predictor variables and the risk of reinfarction we concluded that the potential bias of the first analysis would be reduced most by excluding all reinfarctions. Therefore, in this analysis 244 dropouts were compared with 295 compliers.

For each of these 2 approaches, a stepwise multiple linear logistic regression[9] was performed with 3-year dropout status as the dependent variable, and the 14 risk factors listed in Table I as explanatory variables. The following comparisons were made: (A) dropouts versus compliers (ignoring reinfarction status among compliers), and (B) dropouts versus compliers (excluding all subjects with reinfarction). This type of analysis allows the effect of a given variable to be calculated independently of any other variable with which it may or may not be associated.

Likelihood ratio tests were used in each analysis to determine which variables were statistically significant ($p < 0.05$) independent predictors of dropout. Standardized coefficients and 95% confidence intervals for the adjusted relative odds of dropout were calculated for each of these variables.[9]

## Results

Descriptive statistics for the 14 variables used in the prediction of dropout are listed in Table I. There was no difference in dropout rate between the 2 exercise intensity groups (Fig. 1). There was a considerable

difference in dropout among the participating centers, ranging from 67.2 to 37.4%, with an overall dropout rate of 46.5% (n = 315).

Transition was given as the reason for dropout by 24.8%, psychosocial reasons by 39.7%, medical reasons by 15.9%, and inconvenience by 5.7%; miscellaneous reasons were given by 12.1%, and the reason for dropout was unknown for 1.9%.

**Multivariate analysis of 3-year dropout status:** *(A) Dropouts and compliers, ignoring reinfarction among compliers (n = 618):* Stepwise logistic regression showed that the proportion of smokers, blue collar workers, and subjects with cough and sputum was significantly greater in dropouts than compliers; dropouts were also significantly younger than compliers, and had higher resting systolic blood pressure (Table I, Fig. 2). Smokers were 2.46 times more likely to be dropouts than nonsmokers, blue collar workers 1.66 times as likely as white collar workers to be dropouts, and subjects with cough and sputum 1.60 times more likely to be dropouts than those without cough and sputum (Table II). The results for resting systolic blood pressure imply that an increase of 10 mm Hg is associated with an estimated relative odds for dropout of 1.13; similarly, an increase of 10 years in age is associated with a reduction in relative odds for dropout to 0.72 (Table II). These results assume an additive model in which the effect of a given variable on dropout status is the same for all values of the other variables. However, although this model might be appropriate as a first approximation, we also examined the interactions among the 5 main variables associated with dropout (smoking, blue collar occupation, presence of cough, younger age, and higher systolic blood pressure). When the 10 pairwise interaction terms among these 5 variables were added in a stepwise fashion, a significant interaction term ($p < 0.05$) was found only between age and cough and sputum, indicating that the positive relation between dropout status and cough and sputum was strongest for older men.

*(B) Dropouts and compliers, excluding all reinfarction (n = 539):* All 5 variables found to be independent risk factors for dropout status in analysis A were also statistically significant risk factors in analysis B; in addition, subjects with a history of angina were more likely to be dropouts than those without angina (Table I). Standardized coefficients, adjusted relative odds, and confidence intervals are detailed in Table II. An exploration of interactions among these 6 variables was performed in a manner similar to that for analysis A. The results showed that the interaction between age and cough and sputum remained statistically significant; in addition, the interaction between angina and systolic blood pressure was statistically significant ($p < 0.01$). The positive relation between dropout status and angina was strongest for subjects with relatively high levels of systolic blood pressure.

Finally, since the mean substitution method of handling missing data in these analyses may have diluted the statistical significance of changes in cholesterol, triglycerides, and ponderal index, the analyses were repeated for the subset of 317 subjects who had measured values for all 14 baseline variables. Cholesterol, triglyceride, and ponderal index remained nonsignificant in these analyses.

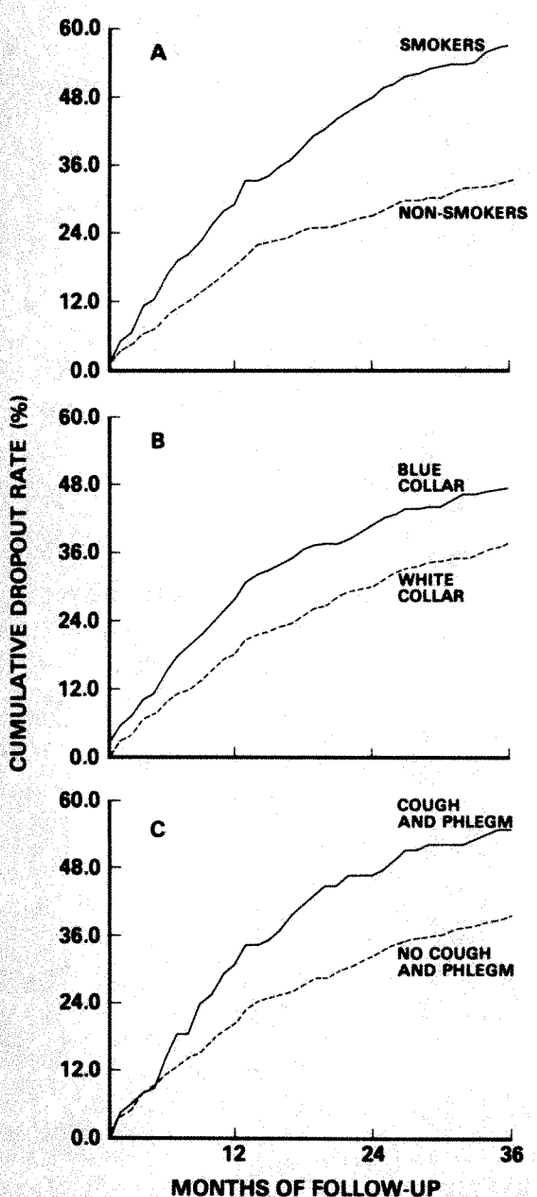



**FIGURE 2.** Month-by-month life-table cumulative dropout rate in the 618 subjects eligible for statistical analysis: **A,** in smokers and nonsmokers; **B,** in blue and white collar workers; and **C,** in subjects with and without cough and phlegm.

## Discussion

The OEHCS provided an opportunity to prospectively investigate dropout from 2 different supervised programs of physical activity after myocardial infarction. There was no difference in dropout between the 2 groups (high or low intensity exercise), suggesting that subjects tended to equally accept either high intensity exercise or what was essentially a "social encounter." Dropout may not be influenced by the prescribed activity itself but rather by other factors such as lack of

**TABLE II Standardized Coefficients,* Adjusted Relative Odds of Dropout, and 95% Confidence Intervals About the Adjusted Relative Odds**

| Variable | Standardized Coefficient | | Adjusted Relative Odds | | 95% Confidence Intervals | |
|---|---|---|---|---|---|---|
| | Analysis A† | Analysis B† | Analysis A | Analysis B | Analysis A | Analysis B |
| Smoking (yes versus no) | 4.98 ($p < 0.001$) | 4.98 ($p < 0.001$) | 2.46 | 2.75 | (1.73, 3.51) | (1.85, 4.08) |
| Occupation (blue versus white collar) | 2.98 ($p = 0.003$) | 2.83 ($p = 0.005$) | 1.66 | 1.71 | (1.18, 2.34) | (1.18, 2.48) |
| Systolic pressure (10 mm Hg) | 2.25 ($p = 0.02$) | 2.16 ($p = 0.03$) | 1.13 | 1.14 | (1.02, 1.06) | (1.01, 1.28) |
| Cough/sputum (yes versus no) | 2.03 ($p = 0.04$) | 2.25 ($p = 0.02$) | 1.60 | 1.81 | (1.02, 2.53) | (1.08, 3.02) |
| Age (10 yr) | −2.30 ($p = 0.02$) | −2.48 ($p = 0.01$) | 0.72 | 0.69 | (0.55, 0.95) | (0.52, 0.93) |
| Angina (yes/no) | ... | 2.19 ($p = 0.03$) | ... | 1.56 | ... | (1.05, 2.32) |

* Standardized coefficient is logistic coefficient/standard error. † Analysis A (n = 618), reinfarctions ignored; analysis B (n = 539), reinfarctions excluded.

spouse support, inconvenience, or program factors such as uninterested staff.[10] Previous trials[3–5] have demonstrated no significant difference in reduction of recurrent myocardial infarction between exercising or control subjects, perhaps because of an insufficient study population.[5] As the OEHCS reported similar recurrence rates in the high and low intensity groups,[6] the equal acceptance of endurance training and relaxation-recreation programming seen in this trial has important rehabilitation implications. There is evidence that the supportive aspects of group interaction, whether emotional, social, educational, or some other known or unknown factors, together with modification of coronary-prone behavior, including an increase in exercise habits, are important in minimizing the incidence and severity of complication after myocardial infarction.[11] Thus, the long-term behavioral benefits from such rehabilitation programs focusing on exercise may be more important than physiologic changes, such as in maximal oxygen consumption.

The overall 3-year dropout rate was 46.5%, a figure considerably lower than that reported at 3 years in the Swedish[3] or at 1 year in the Finnish[4] trials, but considerably higher than that reported in the 3-year National Exercise Heart Disease Program (NEHDP).[5] However, the NEHDP had a built-in "preliminary pre-randomization program of low level exercise of 6 weeks duration that was designed to identify and exclude likely nonadherers to the planned exercise program . . ." [5]; if the OEHCS early dropouts (≤3 months) are allowed for, the subsequent rate was similar to the NEHDP. The greatest rate of dropout in the OEHCS occurred within the first 6 months of the trial; the dropout rate decreased thereafter (Fig. 1), supporting observations of a decreasing dropout over time previously made by ourselves[7,12] and other investigators in rehabilitation programs,[3,13,14] in preventive exercise programs[15] and in health care programs in general.[16] As suggested by Andrew et al,[10] 1 of the factors which can easily be instituted to reduce early dropout is a regular continued education program for the staff members and the continued involvement of the spouse in certain aspects of the program. The reasons for dropout in the OEHCS are similar to those previously reported in considerably more detail.[10]

Because recurrent myocardial infarction compounded the problem of defining a dropout, we took 2 different approaches to the classification of dropouts in the analysis of the data. In both analyses the importance of smoking and occupational status in predicting the potential dropout corroborates earlier observations made in a smaller sample from the OEHCS.[7,12] As there was no interaction between smoking and occupational status, the relative odds for these 2 variables may be multiplied to show that the estimated odds for dropout are more than 4 times higher for blue collar smokers than for white collar nonsmokers. In addition, younger age, higher resting systolic blood pressure, and presence of cough and sputum on entry were also consistently associated with dropout. One factor, angina, was significantly associated with dropout only when myocardial infarction was excluded (Table II). In analysis A (myocardial infarction status ignored) patients reinfarcting while in the study were classified as compliers. Clearly this classification might obscure any true relation of angina to volitional dropout, because angina is frequently associated with a poor postinfarction prognosis.[17] In analysis B (reinfarctions excluded), this bias did not pertain and angina was significantly associated with dropout. This is not surprising, since most patients with angina have symptoms during exercise. While it may be difficult to predict individual response, these data suggest that subgroups with a high likelihood of dropout can be identified.

Continued smoking after an infarction is an indicator of poor compliance with health behavior change and is associated with dropout from exercise studies,[7,12,13,18] although this has not been an invariable finding.[19] With regard to occupation, blue collar workers may have a poorer understanding both of the disease and the rehabilitation process than white collar workers[20] and they often have a greater anxiety level, possibly because of concern about their ability to continue working.[21] Moreover, if the blue collar worker perceives the exercise intensity to be lower than in his daily work, he may be likely to question the need for the extra, "unneces-

sary" exercise. Blue collar workers comprised more than 40% of this study population and a significant proportion dropped out of the OEHCS.[7,12] This has not been reported in other rehabilitation programs, perhaps because white collar workers make up the majority of other study populations.[22,23] The presence of cough or sputum as a predictor of dropout is somewhat more difficult to explain but it is possible that exercise makes this symptom worse and thus leads to a greater rate of withdrawal from the program in older men bothered by coughing on entering the study. Although it showed an effect which was independent of current smoking, this symptom may indicate past smoking habits in patients who gave up smoking at the time of their infarction.

We have identified a number of characteristics that distinguish dropouts from compliers. The more important appear to be smoking, blue collar occupation, and angina. It may be difficult to generalize from results observed in a randomized trial to nonexperimental exercise programs having different motivational and programmatic features. However, the factors reported here should not only be given consideration when referring patients to an exercise rehabilitation program but also need to be kept in mind when studies to improve compliance are being designed.

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## References

1. **Froelicher VF, Brown P.** Exercise and coronary heart disease. J Cardiac Rehab 1981;1:277–288.
2. **Sackett DL.** Bias in analytic research. J. Chronic Dis 1979;32:51–63.
3. **Sanne H, Elmfeldt D, Grimby G, Rydin G, Wilhelmsen L.** Exercise tolerance and physical training of non-selected patients after myocardial infarction. Acta Med Scand [Suppl] 1973;551:1–124.
4. **Kentala E.** Physical fitness and feasibility of physical rehabilitation after myocardial infarction in men of working age. Ann Clin Res 1972;(Suppl 9)4:1–84.
5. **Shaw L,** for The National Exercise Heart Disease Project Staff. Effects of a prescribed supervised exercise program on mortality and cardiovascular morbidity in patients after a myocardial infarction. Am J Cardiol 1981;48: 39–46.
6. **Rechnitzer PA, Cunningham DA, Andrew G, Buck C, Jones NL, Kavanagh T, Oldridge NB, Parker JO, Shephard RJ, Sutton JR.** The relationship of exercise to the recurrence rate of myocardial infarction in men—Ontario Exercise-Heart Collaborative Study. Am J Cardiol 1982;50:65–69.
7. **Oldridge NB.** Compliance of post myocardial infarction patients to exercise programs. Med Sci Sports 1979;11:373–375.
8. **Rechnitzer PA, Sangal S, Cunningham DA, Andrew G, Buck C, Jones NL, Kavanagh T, Parker JO, Shephard RJ, Yuhasz MS.** A controlled prospective study of the effect of endurance training on the recurrence rate of myocardial infarction. Am J Epidemiol 1975;102:358–365.
9. **Anderson S, Auguier A, Hanck WW, Oakes D, VanDale W, Welsberg NI.** Statistical Methods for Comparative Studies. New York: John Wiley, 1980:161–177.
10. **Andrew G, Oldridge NB, Parker JO, Cunningham DA, Rechnitzer PA, Jones NL, Buck C, Kavanagh T, Shephard RJ, Sutton JR, McDonald W.** Reasons for dropout from exercise programs in post-coronary patients. Med Sci Sports Exerc 1981;12:164–168.
11. **Doehrman SR.** Psycho-social aspects of recovery from coronary heart disease: a review. Soc Sci Med 1977;11:199–218.
12. **Oldridge NB, Wicks JR, Hanley C, Sutton JR, Jones NL.** Non-compliance in an exercise rehabilitation program for men who have suffered a myocardial infarction. Can Med Assoc J 1978;118:361–364.
13. **Bruce EH, Frederick R, Bruce RA, Fisher LD.** Comparison of active participants and dropouts in CAPRI cardiopulmonary rehabilitation programs. Am J Cardiol 1976;37:53–60.
14. **Carmody TP, Senner JW, Malinow MR, Matarozzo JD.** Physical exercise rehabilitation: long-term dropout rate in cardiac patients. J Behav Med 1980;3:163–168.
15. **Mann GV, Garrett HL, Farhi A, Murray H.** Exercise to prevent coronary heart disease. An experimental study of the effects of training on risk factors for coronary heart disease in men. Am J Med 1969;46:12–27.
16. **Sackett DL, Snow JC.** The magnitude of compliance and noncompliance. In: Haynes RB, Sackett DL, Taylor DW, eds. Compliance with Therapeutic Regimens. Baltimore: John Hopkins University Press, 1979:11–22.
17. **Moss AJ.** Factors influencing prognosis after myocardial infarction. Curr Probl Cardiol 1980;4:10–11.
18. **Nye GR, Poulsen WT.** An activity programme for coronary patients: a review of morbidity, mortality and adherence after five years. NZ Med J 1974; 79:1010–1013.
19. **Shephard RJ, Corey P, Kavanagh T.** Exercise compliance and the prevention of a recurrence of myocardial infarction. Med Sci Sports Exerc 1981;13:1–5.
20. **Hackett TP, Cassem NH.** White-collar and blue-collar responses to heart attack. J Psychosom Res 1976;20:85–95.
21. **Byrne DG.** Effect of social context on psychological responses to survived myocardial infarction. Int J Psychiatry Med 1980–1981;10:23–31.
22. **Kavanagh T, Shephard RJ, Chisholme AW, Qureshi S, Kennedy J.** Prognostic indexes for patients with ischemic heart disease enrolled in an exercise-centered rehabilitation program. Am J Cardiol 1980;44:1230–1240.
23. **Stern MJ, Cleary P.** The National Exercise and Heart Disease Project. Long-term psychosocial outcome. Arch Intern Med 1982;142:1093–1097.

# Ventricular Electrical Instability: A Predictor of Death After Myocardial Infarction

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**The results of a prospective study of ventricular electrical instability after myocardial infarction (MI) are presented. Ventricular electrical stability was assessed using a standardized protocol of programmed stimulation in 165 hemodynamically stable patients 6 to 28 days after acute MI. Ventricular electrical instability was defined as induction at programmed stimulation of ventricular fibrillation (VF) or ventricular tachycardia (VT) lasting at least 10 seconds. Of 165 MI survivors, 38 (23%) had ventricular electrical instability. No significant differences were noted between stable and unstable patients in terms of coronary prognostic index, elevation of serum creatine phosphokinase, coronary anatomy, site of MI, or frequency of VT within 48 hours of MI. The mean follow-up period was 8 months (range 0 to 12).**

**There were 7 deaths in stable patients (5 from cardiogenic shock, 1 from septicemia, and 1 unwitnessed) and 10 deaths in unstable patients (8 instantaneous, 1 from cardiogenic shock, and 1 unwitnessed) during the subsequent year. In addition, 2 of 127 stable patients and 4 of 38 unstable patients had spontaneous VT from which they were satisfactorily resuscitated. Thus, the sensitivity of ventricular electrical instability as a predictor of instantaneous death or spontaneous VT was 86% and the specificity 83%. The predictive accuracy of the absence of ventricular electrical instability as an indicator for the absence of instantaneous death or spontaneous VT was 98%. The predictive accuracy of the presence of ventricular electrical instability as a predictor of instantaneous death or spontaneous VT was 32%.**

**Thus, patients with ventricular electrical instability after MI have a high risk of instantaneous death within 1 year; patients without ventricular electrical instability after MI have a low risk of instantaneous death within 1 year; prospective studies of antiarrhythmic therapy and measures to prevent reinfarction and optimize left ventricular performance are required to determine whether instantaneous death can be prevented in unstable patients; and therapy to prevent reinfarction and optimize left ventricular performance may offer the best chance to improve prognosis in stable patients.**

The overall probability of death after acute myocardial infarction (MI) is related to age, presence of previous MI, and left ventricular dysfunction.[1–4] However, approximately half of all deaths during the year after MI are sudden,[1,3–12] are due to ventricular fibrillation (VF) or ventricular tachycardia (VT),[13] and are not necessarily associated with clinical evidence of acute myocardial ischemia or postmortem evidence of reinfarction.[14]

Greene et al[15] in 1978 reported that repetitive ventricular beats (1 nonstimulated ventricular beat after programmed stimulation with a single ventricular extrastimulus introduced during atrial drive) indicated ventricular electrical instability[15] and predicted VT and sudden death after MI.[10] However, the clinical significance of repetitive ventricular beats has since been questioned by several investigators,[16–18] and controversy remains regarding the predictive value of programmed stimulation after MI.[19] This report presents a new protocol of programmed stimulation and a new definition of ventricular electrical instability. The aim of this study was to ascertain the value of ventricular electrical instability as a predictor of death after MI.

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## Methods

Ventricular electrical stability was assessed by programmed stimulation in 165 patients 6 to 28 days (mean 10) after acute MI. These patients comprised a subgroup of 341 consecutive patients admitted to Westmead Hospital with acute MI between March 1980 and May 1981. Of the original 341 patients, 37 died within 5 days of admission. Ventricular electrical

**TABLE I Clinical Profiles of Assessed and Nonassessed Patients**

| | Assessed (n = 165) | Nonassessed (n = 139) | p* |
|---|---|---|---|
| Age (yr) | 54 ± 1 | 64 ± 1 | <0.001 |
| Male (%) | 82 | 62 | <0.001 |
| Maximal CK (IU/liter) | 1,649 ± 121 | 1,232 ± 108 | NS |
| CPI | 4.0 ± 0.2 | 6.2 ± 0.3 | <0.001 |
| VF or VT in 48 hours (%) | 16 | 13 | NS |
| Transmural infarction (%) | 75 | 53 | <0.001 |
| Anterior infarction (%) | 44 | 62 | <0.02 |
| Diseased vessels (n) | 1.5 ± 0.1 (n = 78) | 1.6 ± 0.1 (n = 22) | NS |
| Ventricular aneurysm (%) | 19 (15/78) | 14 (3/22) | NS |
| Ejection fraction | 0.55 ± 0.02 (n = 63) | 0.62 ± 0.14 (n = 19) | NS |

* Values given are mean ± standard error of the mean. NS = not significant.

stability was not assessed in 139 (nonassessed patients) of the remaining 304 patients, because consent for study was either refused or not requested (because of persistent ischemia, uncontrolled cardiac failure, or cardioactive medication).

Written informed consent was obtained and the administration of all cardioactive medications ceased at least 5 days before study. Patients were postabsorptive but not sedated. Quadripolar electrode catheters were introduced into the right ventricle through femoral venipunctures. Drive trains of 8 stimuli followed by single and paired extrastimuli at twice diastolic threshold and 20 mA (rectangular pulses 2 ms in duration from a Medtronic 5325 programmable stimulator) were applied at the right ventricular apex and outflow tract. The drive cycle length ($S_1$-$S_1$) was set as long as possible, usually about 600 ms (only 1 drive cycle length was tested), and single extrastimuli ($S_2$) were introduced during diastole from 300 ms in 10 ms decrements to the ventricular effective refractory period (ERP). With paired extrastimuli, $S_1$-$S_2$ was set at ERP plus 10 ms and the second extrastimulus ($S_3$) was introduced during diastole from 300 ms in 10 ms decrements to ventricular refractoriness. This sequence was applied first at the right ventricular apex and then at the right ventricular outflow tract in each case at twice diastolic threshold. The entire sequence was then repeated at 20 mA. The protocol was terminated prematurely if VF or VT lasting more than 10 seconds occurred. Such patients were classified as unstable (ventricular electrical instability). All of these were converted promptly to sinus rhythm without neurologic or other sequelae. The remaining patients were classified as stable (ventricular electrical stability).

Ventricular electrical stability (or instability) was noted but not used to influence subsequent management. However, if a patient exhibited spontaneous VT or VF, antiarrhythmic therapy was introduced. Other data recorded before hospital discharge included a Norris Coronary Prognostic Index[1] (CPI) and a maximal serum level of creatine phosphokinase (CK). Left ventricular ejection fractions[20] were calculated from right anterior oblique cineventriculograms in 82 of 100 patients who underwent ventriculography (ejection fractions were not calculated in 18 patients with ventricular aneurysms). The presence of a ventricular aneurysm was noted if paradoxical systolic wall motion was observed in the right anterior oblique cineventriculogram. Coronary arteries were reported as significantly diseased when there was a >50% reduction in the luminal diameter of the left main coronary artery or a >75% reduction in luminal diameter in any of the other major coronary arteries. Angiography was not performed routinely in all postinfarct patients, and indications for angiography were not the same in all cases.

Patients were followed for up to 12 months (mean 8) and survival rates were determined by the life table method.[21,22]

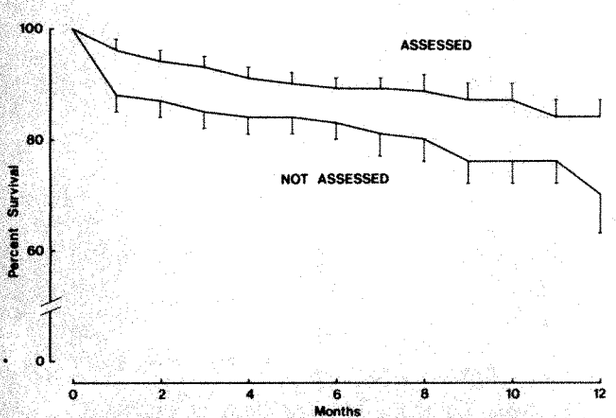



**FIGURE 1.** Actuarial survival curves for assessed and nonassessed patients. **Bars** indicate 1 standard error of the mean for estimation of survival rates at each month.

## Results

Clinical profiles of assessed and nonassessed patients before hospital discharge are summarized in Table I. The assessed group consisted of more male patients, more patients with transmural infarction (appearance of new Q waves on the 12-lead electrocardiogram), and fewer patients with anterior infarctions than did the nonassessed group. The mean age and CPI[1] were higher in nonassessed patients, reflecting exclusion from study of some older patients and those with uncontrolled cardiac failure. No significant differences were noted in the incidence of VF or VT within 48 hours of admission (no patients had exhibited spontaneous VF or VT between the 48 hours after infarction and programmed stimulation), in the maximal recorded value of CK, in coronary anatomy, or in the incidence of ventricular aneurysm. Ejection fractions were similar in assessed and nonassessed patients. The results of life table analysis of 1-year survival of assessed and nonassessed patients are illustrated in Figure 1.

**TABLE II Clinical Profiles of Stable and Unstable Patients**

| | Stable (n = 127; 77%) | Unstable (n = 38; 23%) | p* |
|---|---|---|---|
| Age (yr) | 54 ± 1 | 54 ± 2 | NS |
| Male (%) | 81 | 74 | NS |
| Maximum CK (IU/liter) | 1,550 ± 100 | 1,994 ± 220 | NS |
| CPI | 3.8 ± 0.2 | 4.4 ± 0.5 | NS |
| VF or VT in 48 hours (%) | 16 | 16 | NS |
| Transmural infarction (%) | 71 | 89 | <0.025 |
| Anterior infarction (%) | 45 | 39 | NS |
| Diseased vessels (n) | 1.5 ± 0.1 (n = 57) | 1.7 ± 0.2 (n = 21) | NS |
| Ventricular aneurysm (%) | 19 (11/57) | 19 (4/21) | NS |
| Ejection fraction | 0.58 ± 0.02 (n = 46) | 0.47 ± 0.03 (n = 17) | <0.01 |

* Values given are mean ± standard error of the mean. NS = not significant.

The relatively low first-month survival rate among nonassessed patients (log-rank test,[22] $p < 0.01$) occurred because of exclusion from assessment of patients with uncontrolled cardiac failure or persistent ischemia. Survival rates for individual months 2 through 12 were not significantly different. The cumulative 1-year survival rates for assessed and nonassessed patients were 84 and 70%, respectively. The majority of deaths in nonassessed patients (16 of 28) were due to cardiogenic shock, 4 were virtually instantaneous with no evidence of acute ischemia or cardiac failure, 4 were noncardiac, and 4 were unwitnessed. There were 17 deaths in the assessed patients: 8 were instantaneous, 6 were from cardiogenic shock, 1 was noncardiac, and 2 were unwitnessed.

Assessed patients were classified unstable or stable according to whether or not VF or VT (lasting at least 10 seconds) was induced at programmed stimulation. The clinical profiles of stable and unstable patients are summarized in Table II.

The incidence of transmural infarction was higher (unstable 89%, stable 71%) and ejection fractions (unstable 0.47, stable 0.58), when measured, tended to be lower among unstable patients (range of ejection fractions: unstable patients, 0.17 to 0.66; stable patients, 0.21 to 0.66), but the groups were similar in all other respects. The life table analysis of 1-year survival of stable and unstable patients is illustrated in Figure 2.

Although the cumulative 1-year survival rate for stable patients was 91%, it was only 65% for unstable patients ($p < 0.001$). There were significant differences also in survival rates for individual months 4 ($p < 0.01$) and 5, 6, and 9 ($p < 0.05$).

The clinical profiles of stable and unstable survivors and nonsurvivors are compared in Table III. There were

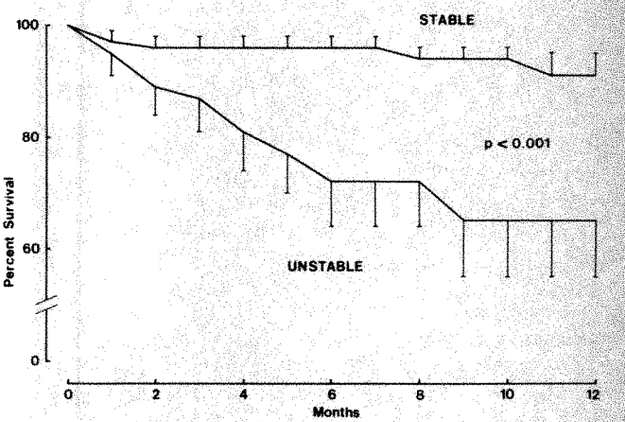



**FIGURE 2.** Actuarial survival curves for stable and unstable patients. **Bars** indicate 1 standard error of the mean for estimation of survival rates at each month.

**TABLE III Clinical Profiles of Survivors and Nonsurvivors**

| | Stable | | Unstable | |
|---|---|---|---|---|
| | Alive (n = 120) | Dead (n = 7) | Alive (n = 28) | Dead (n = 10) |
| Age (yr | 54 ± 1 | 59 ± 4 | 52 ± 2 | 61 ± 3 |
| Maximal CK (IU/liter) | 1,546 ± 104 | 1,628 ± 373 | 2,108 ± 277 | 1,653 ± 287 |
| CPI | 3.7 ± 0.2 | 5.3 ± 1.2 | 3.6 ± 0.6 | 6.7 ± 0.9 |
| VF or VT in 48 hours (%) | 15 | 29 | 14 | 20 |
| Transmural infarction (%) | 70 | 86 | 89 | 90 |
| Anterior infarction (%) | 46 | 29 | 32 | 60 |
| Diseased vessels (n) | 1.5 ± 0.1 (n = 56) | 2.0 (n = 1) | 1.6 ± 0.2 (n = 19) | 2.5 ± 0.5 (n = 2) |
| Ventricular aneurysm (%) | 11/56 | 0/1 | 3/19 | 1/2 |
| Ejection fraction | 0.59 ± 0.02 (n = 45) | 0.55 (n = 1) | 0.47 ± 0.03 (n = 16) | 0.37 (n = 1) |

significant differences between unstable survivors and nonsurvivors in terms of age ($p < 0.02$) and coronary prognostic index ($p < 0.01$). However, the range of the CPI among unstable nonsurvivors was wide (1.0 to 9.7). Of the 10 nonsurvivors, 7 had CPI <9. There was a higher incidence of death among unstable patients than among stable patients with transmural ($p < 0.01$) and anterior ($p < 0.001$) infarcts. These differences did not apply between stable and unstable patients with nontransmural or inferior infarcts. The mean ejection fraction for unstable survivors (n = 16) was less than that for stable (n = 45) survivors ($p < 0.01$). During the year no stable patient with ventricular aneurysm and only 1 unstable patient with a ventricular aneurysm died.

At the final review (or death), 20% of assessed patients were taking regular beta-adrenoceptor blocking drugs, 8% were receiving some other regular antiarrhythmic therapy, and 13% had undergone coronary artery bypass grafting (Table IV). There was no significant difference in survival of patients with or without medical or surgical therapy. The predictive value of ventricular electrical instability after myocardial infarction is indicated in Table V.

Death occurred in 7 stable patients; 5 died in cardiogenic shock, 1 patient had septicemia, and 1 death was unwitnessed. There were 10 deaths in unstable patients; 8 died virtually instantaneously without evidence of acute ischemia or cardiac failure (VF was documented in 5 of these patients during unsuccessful resuscitation), 1 patient died in cardiogenic shock after coronary artery bypass, and 1 death was unwitnessed. Thus, the sensitivity of ventricular electrical instability as a predictor of death after infarction was 59% and the specificity was 81%. The predictive accuracy of ventricular electrical stability, that is, the absence of instability, as a predictor of survival was 94% and the predictive accuracy of ventricular electrical instability, that is, the presence of instability, as a predictor of death was 26%. Because there were no instantaneous deaths among stable patients, the sensitivity of ventricular electrical instability as a predictor of instantaneous death was 100%. The predictive accuracy of ventricular electrical stability (absence of instability as an indicator for the absence of subsequent instantaneous death) was also 100%. The specificity of ventricular electrical instability as a predictor of instantaneous death was 81% and the predictive accuracy was 21%.

During the year 4 of 38 unstable patients exhibited spontaneous VT, in the absence of further acute ischemia. In contrast, only 2 of 127 stable patients exhibited spontaneous VT. In 1 patient a ventricular aneurysm had developed after reinfarction, and the patient was subsequently unstable in the laboratory when restudied. The other patient was asymptomatic, with an idioventricular rhythm that caused no hemodynamic embarrassment. Thus, the sensitivity of ventricular electrical instability as a predictor of instantaneous death or spontaneous VT was 86% and the specificity was 83%. The predictive accuracy of ventricular electrical stability was 98% and of instability 32%.

## Discussion

The major finding of this study is that although patients with ventricular electrical instability after myocardial infarction have a high risk of death from spontaneous VF, patients without ventricular electrical instability have a very low risk of death from spontaneous VF. Of unstable patient deaths, 80% (8 of 10) were instantaneous and VF was documented in 5 of these. A further 11% of unstable patients (4 of 38) were resuscitated from spontaneous VT during the year. In contrast,

**TABLE IV Therapy in Stable and Unstable Patients**

| | Stable | | Unstable | | |
|---|---|---|---|---|---|
| | Alive (n = 120) | Dead (n = 7) | Alive (n = 28) | Dead (n = 10) | p |
| BB (20%) | 27 | 0 | 6 | 0 | NS |
| AA (8%) | 6 | 0 | 5 | 2 | NS |
| CABG (13%) | 18 | 0 | 3 | 1 | NS |

AA = medical antiarrhythmic therapy other than beta-adrenoceptor blockade; BB = beta-adrenoceptor blockade; CABG = coronary artery bypass graft.

**TABLE V Value of Programmed Stimulation As a Predictor of Death, Instantaneous Death, and Spontaneous VT**

| | | | Predictive Accuracy of | |
|---|---|---|---|---|
| | Sensitivity | Specificity | Stability | Instability |
| All deaths (%) | 59 | 81 | 94 | 26 |
| Instantaneous deaths (%) | 100 | 81 | 100 | 21 |
| Instantaneous death or spontaneous VT (%) | 86 | 83 | 98 | 32 |

Sensitivity = number of events predicted by ventricular electrical instability (true-positives)/true-positives + number of events falsely predicted by ventricular electrical stability (false-negatives); specificity = number of events predicted by ventricular electrical stability (true-negatives)/true-negatives + number of events falsely predicted by ventricular electrical instability (false-positives); predictive accuracy of stability = true-negatives/true-negatives + false-negatives; predictive accuracy of instability = true-positives/true-positives + false-positives.

none of the deaths in stable patients were instantaneous and in only 2% did spontaneous VT develop (1 patient had VT after reinfarction and development of a left ventricular aneurysm, and 1 patient had an asymptomatic idioventricular rhythm without hemodynamic embarrassment). It remains to be determined whether therapeutic intervention of any kind improves prognosis in unstable patients. A prospective randomized study of antiarrhythmic therapy in unstable patients is being conducted at an institution as a first step toward answering this question.

The problems for patients without ventricular electrical instability appear to be different. Because most deaths among stable patients were due to cardiogenic shock (5 of 7), therapy aimed at preventing reinfarction and optimizing left ventricular performance may offer the best chance to improve prognosis in these patients.

The only significant differences between stable and unstable patients before hospital discharge occurred in the incidence of transmural infarction (71% stable, 89% unstable) and the mean ejection fraction (0.58 stable, 0.47 unstable). Notwithstanding these differences, most assessed patients had survived transmural MI and none had severely depressed left ventricular function. Ventricular electrical stability was assessed in the absence of acute ischemia[23] 6 to 28 days after MI. In contrast to previous reports,[10,16,18] we defined ventricular electrical instability as VF or VT lasting at least 10 seconds. This definition was chosen because of controversy[19] concerning the clinical significance of repetitive ventricular beats[10] (1 or a few nonstimulated beats) after programmed stimulation.

Our standardized protocol of programmed stimulation was developed to provide a simple and rapid means of assessing ventricular electrical stability. Left ventricular stimulation was not included because of the additional potential complications and additional time required for study. The 2 right ventricular stimulation sites were chosen because catheter manipulation could be readily achieved using anteroposterior X-ray control only. Stimulation with 20 mA (the maximal output of the Medtronic 5325 stimulator) as well as twice diastolic current threshold stimulation, may have resulted in some false-positive results. However, omission of 20 mA stimulation would have resulted in some false-negative results (3 unstable patients who died instantaneously and 1 patient who had spontaneous VT had exhibited ventricular electrical instability at 20 mA only). The optimal current intensity for stimulation for demonstrating ventricular electrical instability has not been defined.

Nevertheless, the predictive value of the present protocol is clear. The absence of ventricular electrical instability was associated with a high probability of survival for 1 year (91%, Fig. 2), whereas its presence was associated with a significantly ($p < 0.001$) lower probability of survival (65%, Fig. 2).

Schulze et al,[4] studying 81 survivors of acute MI during a 10-month period, found that patients with an ejection fraction (biplane radionuclide) <40% had a higher incidence of sudden death (8 of 45, 18%) than did patients with an ejection fraction ≥40% (0 of 36). These investigators found complicated ventricular arrhythmias (modified Lown class: III, multifocal ventricular premature contractions [VPC]; IV, coupled or bigeminal VPC; and V, VT or R on T VPC) during continuous 24 hour Holter monitoring in 3 patients with an ejection fraction ≥40% and in 26 with an ejection fraction <40%. Complicated ventricular arrhythmias were present in all patients who died suddenly. No patient without complex arrhythmia (modified Lown class: 0, no VPC; I, unifocal PVC <30/h in all hours; and II, unifocal PVC >30/h in any hour) died. Sudden death occurred in 8 of 29 patients (28%) with complicated ventricular arrhythmias. All 8 patients who died suddenly were in the subgroup of 26 patients with an ejection fraction <40% and complicated arrhythmias. These data are similar to those of Bigger et al,[24] who studied 430 MI survivors and observed sudden death in 11 of 50 (22%), with VT (≥3 consecutive ventricular complexes) on Holter monitoring. However, 75% of patients who died suddenly had not exhibited VT and their death would not have been predicted by Holter monitoring.

The data of Bigger et al[24] show that VT on Holter monitoring is not a necessary or sufficient condition to predict death or sudden death. The data of Schulze et al[4] imply that complicated VPC on Holter monitoring and an ejection fraction less than 40% are necessary conditions for predicting sudden death. However, these investigators showed that low ejection fraction is not a sufficient condition to predict death or sudden death. Our own data appear to indicate that ventricular electrical instability is probably a necessary but not sufficient condition for predicting sudden death.

The subsets of patients at high risk for sudden death in the aforementioned series[4,24] and our own must, to some extent, overlap. In the future it may be possible to use a combination of noninvasive and invasive tests to identify more specifically the subset of MI survivors at highest risk for sudden death.

Sudden death from spontaneous VT or VF during the first year after MI requires the presence of at least 2 conditions: (1) A ventricular substrate that can sustain VT or VF in the absence of acute myocardial ischemia. Intraventricular reentrant circuits could provide this substrate. (2) Some perturbation to initiate VT or VF. Such perturbations may include spontaneous VPC or spontaneous changes in conduction velocities or refractory periods within reentrant circuits.

Probably a critical mass of infarct is required to have within it or around it potential reentrant circuits. Hearts with larger infarcts may be more likely to incorporate intraventricular reentrant circuits than hearts with small infarcts. Hence, it is not surprising that left ventricular dysfunction (low ejection fraction) and complicated ventricular arrhythmias on Holter monitoring are associated with spontaneous VT, VF, and sudden death in many but not all cases.

The crucial determinant of predisposition to VT or VF (and sudden death) is the capacity to sustain VT or VF in the presence of spontaneous VPC. Ventricular electrical instability as described herein may be that determinant.

We conclude that (1) patients with ventricular electrical instability after myocardial infarction have a high risk of sudden death within 1 year; (2) patients without ventricular electrical instability after myocardial infarction have a very low risk of sudden death within 1 year; (3) prospective studies (of antiarrhythmic therapy and measures to prevent reinfarction and optimize left ventricular performance) are required to determine whether sudden death can be prevented in unstable patients; (4) therapy to prevent reinfarction and optimize left ventricular performance may offer the best chance to improve prognosis in stable patients.

## References


1. **Norris RM, Caughey DE, Deeming LW, Mercer CJ, Scott PJ.** Coronary prognostic index for predicting survival after recovery from acute myocardial infarction. Lancet 1970;2:485–487.
2. **Norris RM, Caughey DE, Mercer CJ, Scott PJ.** Prognosis after myocardial infarction. Six year follow-up. Br Heart J 1974;36:786–790.
3. **Helmers C, Lundman T.** Sudden coronary death after acute myocardial infarction. Predictive value of data registered in the coronary care unit. Adv Cardiol 1978;25:176–182.
4. **Schulze RA, Strauss HW, Pitt B.** Sudden death in the year following myocardial infarction. Relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction. Am J Med 1977;62: 192–199.
5. **Vismara LA, Amsterdam EA, Mason DT.** Relation of ventricular arrhythmias in the late hospital phase of acute myocardial infarction to sudden death after hospital discharge. Am J Med 1975;59:6–12.
6. **Doyle JT.** Profile of risk of sudden death in apparently healthy people. Circulation 1975;52:Suppl 3:176–179.
7. **Moss AJ, de Camilla J, Davis H.** Cardiac death in the first 6 months after myocardial infarction: potential for mortality reduction in the early post hospital period. Am J Cardiol 1977;39:816–820.
8. **Bigger JT, Heller CA, Wenger TL, Weld FM.** Risk stratification after acute myocardial infarction. Am J Cardiol 1978;42:202–210.
9. The Anturane Reinfarction Trial Research Group. Sulfinpyrazone in the prevention of sudden death after myocardial infarction. N Engl J Med 1980;302:250–256.
10. **Greene HL, Reid PR, Schaeffer AH.** The repetitive ventricular response in man. A predictor of sudden death. N Engl J Med 1978;299:729–734.
11. **Moss AJ, Davis HT, de Camilla J, Bayer LW.** Ventricular ectopic beats and their relation to sudden and non-sudden cardiac death after myocardial infarction. Circulation 1979;60:998–1003.
12. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801–807.
13. **Cobb LA, Baum RS, Alvarez HA, Schaffer WA.** Resuscitation from out-of-hospital ventricular fibrillation: four years follow-up. Circulation 1975; 51,52:Suppl III:III-223–III-228.
14. **Friedman M, Manwaring JH, Rosenman RH, Donlon G, Ortega P, Grube SM.** Instantaneous and sudden deaths: clinical and pathological differentiation in coronary artery disease. JAMA 1973;225:1319–1328.
15. **Greene HL, Reid PR, Schaeffer AH.** The repetitive ventricular response in man. An index of ventricular electrical instability (abstr). Am J Cardiol 1978;41:400.
16. **Mason JW.** Repetitive beating after single ventricular extrastimuli: incidence and prognostic significance in patients with recurrent ventricular tachycardia. Am J Cardiol 1980;45:1126–1131.
17. **Farshidi A, Michelson EL, Greenspan AM, Spielman SR, Horowitz LN, Josephson ME.** Repetitive responses to ventricular extrastimuli: incidence, mechanism, and significance. Am Heart J 1980;100:59–68.
18. **Ruskin JN, DiMarco JP, Garan H.** Repetitive responses to single ventricular extrastimuli in patients with serious ventricular arrhythmias: incidence and clinical significance. Circulation 1981;63:767–772.
19. **Akhtar M.** The clinical significance of the repetitive ventricular response (editorial). Circulation 1981;63:773–775.
20. **Kennedy JW, Trenholme SE, Kasser IS.** Left ventricular volume and mass from single-plane cineangiocardiograms. A comparison of anteroposterior and right anterior oblique methods. Am Heart J 1970;80:343–352.
21. **Cutler SJ, Ederer F.** Maximum utilization of the life table method in analyzing survival. J Chronic Dis 1958;8:699–712.
22. **Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG.** Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977;35:1–39.
23. **Wellens HJ, Lie KI, Durrer D.** Further observations on ventricular tachycardia as studied by electrical stimulation of the heart. Chronic recurrent ventricular tachycardia and ventricular tachycardia during acute myocardial infarction. Circulation 1975;49:647–653.
24. **Bigger JT, Weld FM, Rolnitzky LM.** Prevalence, characteristics and significance of ventricular tachycardia (three or more complexes) detected with ambulatory electrocardiographic recording in the late hospital phase of acute myocardial infarction. Am J Cardiol 1981;48:815–823.

# Status of the Major Epicardial Coronary Arteries 80 to 150 Days After Percutaneous Transluminal Coronary Angioplasty

## Analysis of 3 Necropsy Patients

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**Certain clinical and necropsy cardiac findings are described in 3 men who had percutaneous transluminal coronary angioplasty (PTCA) of the left anterior descending (LAD) coronary artery 80, 90, and 150 days before sudden death. Each patient had a decrease in the mean transstenotic coronary gradient (17, 38, and 43 mm Hg) and an angiographic increase in the LAD luminal diameter (55, 60, and 65%). At necropsy, the LAD coronary artery in the area of the PTCA in each patient was narrowed 76 to 95% in cross-sectional area by atherosclerotic plaques. No cracks in plaques or other lesions which may have resulted from the PTCA procedure were identified histologically in the LAD coronary artery of any patient.**

Several studies have described morphologic changes early (≤60 days) in coronary arteries in humans[1–3] and in animals[4–6] after PTCA. Although several reports[7–10] have described angiographic appearances of coronary arteries late (>60 days) after PTCA, morphologic observations have not been reported in coronary arteries subjected to PTCA >60 days before death. In this report, clinical and necropsy cardiac findings are described in 3 men who died suddenly 80, 90, and 150 days, respectively, after PTCA.

### Patients Studied

**Clinical observations:** Each patient had exertional angina pectoris for only 1 to 2 months before PTCA. Coronary angiography and PTCA performed 80, 90, and 150 days, respectively, before death disclosed severe (76 to 95% diameter reduction) luminal narrowing of the LAD coronary artery and insignificant (<50% diameter reduction) narrowing of the left main, left circumflex, and right coronary arteries (Table I, Fig. 1 to 3). At PTCA, the LAD in each patient was dilated 55, 60, and 65%, respectively (Table I), and the mean coronary pressure gradient fell 17, 38, and 43 mm Hg, respectively, in the 3 patients. Exercise treadmill testing in each patient 1 to 11 days after PTCA disclosed electrocardiographic changes of J point depression in 2 patients (Patients 2 and 3) and no changes in the third patient. No patient developed angina pectoris during or within an hour of the exercise test.

Angina pectoris did not recur after PTCA in Patients 1 and 2. Patient 3 remained pain-free for the first 105 days after PTCA, but during the last 45 days he had 3 episodes of mild exertional angina relieved promptly by nitroglycerin. After PTCA, all 3 patients thereafter received long-term administration of dipyridamole; 2 (Patients 1 and 2) received salicylates; 2 (Patients 2 and 3) received isosorbide dinitrate; and 1 patient each received verapamil (Patient 1) and nifedipine (Patient 2). Two patients (Patients 2 and 3) died suddenly at home or work without apparent chest pain. Patient 1 was killed during an automobile accident while intoxicated (alcohol).

**Morphologic observations:** At necropsy, no foci of myocardial fibrosis or necrosis were present. In all 3 patients, the 4 major epicardial coronary arteries were excised from the heart and cut transversely into 5-mm segments; a Movat-stained histologic section was prepared from each segment and examined. The results of the quantitative studies, representing the consensus of 3 observers (BFW, BMM, JCK), are summarized in Figure 4.

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**TABLE I Observations in 3 Necropsy Men Who Died >60 Days After Percutaneous Transluminal Coronary Angioplasty (PTCA)**

| Observation | Patient 1 | 2 | 3 |
|---|---|---|---|
| Age (yr) at death | 33 | 48 | 57 |
| Systemic pressure (mm Hg) | 135/90 | 110/80 | 150/90 |
| Interval (days) from PTCA to death | 80 | 90 | 150 |
| Maximal coronary narrowing by angiography (% diameter reduction) | | | |
| LM | 0 | 0 | 0 |
| LAD | 80 | 85 | 85 |
| LC | ≤50 | ≤25 | ≤25 |
| R | ≤50 | 0 | ≤25 |
| Change (% diameter reduction) in LAD | 80 → 25 | 85 → 25 | 85 →20 |
| Mean intracoronary pressure (mm Hg) before → after dilation | | | |
| Proximal | 104 → 85 | . . . | 80 → 80 |
| Distal | 52 → 50 | . . . | 25 → 68 |
| Gradient | 52 → 35 | 50 → 12 | 55 → 12 |
| Maximal coronary narrowing at necropsy (% cross-sectional area) | | | |
| LM | 26–50 | 0–25 | 0–25 |
| LAD | 76–95 | 76–95 | 76–95 |
| LC | 76–95 | 26–50 | 51–75 |
| R | 76–95 | 76–95 | 51–75 |
| Cororary narrowing at necropsy at site of PTCA (% cross-sectional area) | 76–95 | 76–95 | 75–95 |
| Heart weight (g) | 450 | 490 | 415 |

LAD = left anterior descending; LC = left circumflex; LM = left main; R = right.

The site of the PTCA was determined from the area of maximal diameter reduction on the pre-PTCA coronary angiogram (Fig. 1). The catheter diameter just proximal to its tip was measured (in millimeters) on a black and white glossy print of 1 frame of the cineangiogram. A right anterior oblique angiographic view was used to view the bifurcation of the LAD and left circumflex coronary arteries. A magnification correction factor was determined by dividing the angiographic catheter diameter by the actual catheter diameter (provided by the manufacturer). The angiographic distance (in millimeters) from the origin of the LAD from the left main coronary artery to the site of maximal diameter reduction was measured. To locate this area of the LAD at necropsy, the distance measured on the angiogram was divided by the magnification correction factor. The LAD length was then measured at necropsy starting at the origin of the LAD from the left main coronary artery. The 5-mm coronary artery segment containing this area was recorded.

In each patient, at least 1 of the 4 major coronary arteries was narrowed 76 to 95% in cross-sectional area by atherosclerotic plaques: the LAD in all 3 patients, the right in Patients 1 and 2, and the left circumflex in Patient 1. The site of the PTCA in the LAD coronary artery in each patient was narrowed 76 to 95% in cross-sectional area by atherosclerotic plaque. The 5-mm segment of LAD containing the site of PTCA in each patient was serially sectioned at 10 $\mu$m intervals; every fifth section was stained. A total of 72 histologic sections in the area of PTCA was examined (26 in Patient 1, 34 in Patient 2, and 12 in Patient 3). Of the total 153 5-mm coronary segments from the 3 patients, none was narrowed 96 to 100%, 14 (9%) were narrowed 76 to 95%, and 34 (22%) were narrowed 51 to 75% in cross-sectional area by athero-

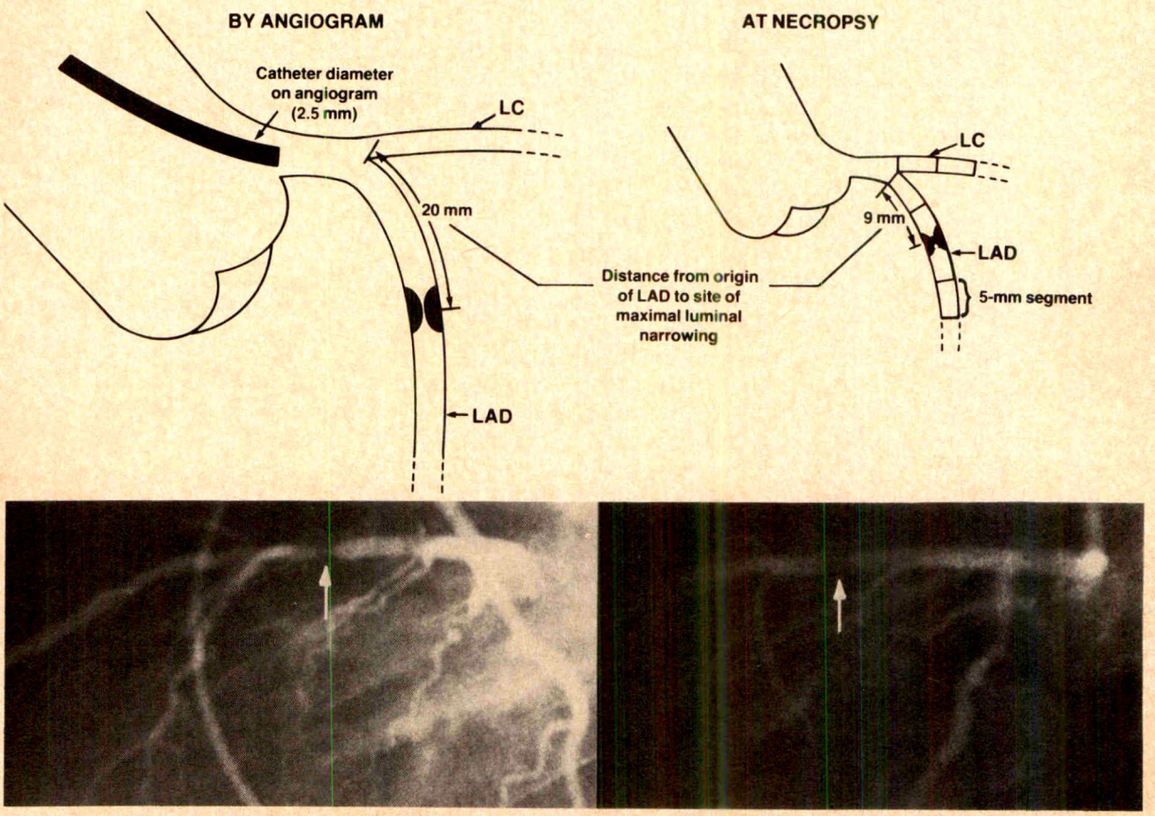



**FIGURE 1.** Patient 1. **Top panel,** diagram illustrating method of determining at necropsy the site of PTCA during life. **Bottom panels,** frames of coronary angiogram showing an increase in diameter of the left anterior descending (LAD) artery after PTCA (**arrows**). LC = left circumflex coronary artery.

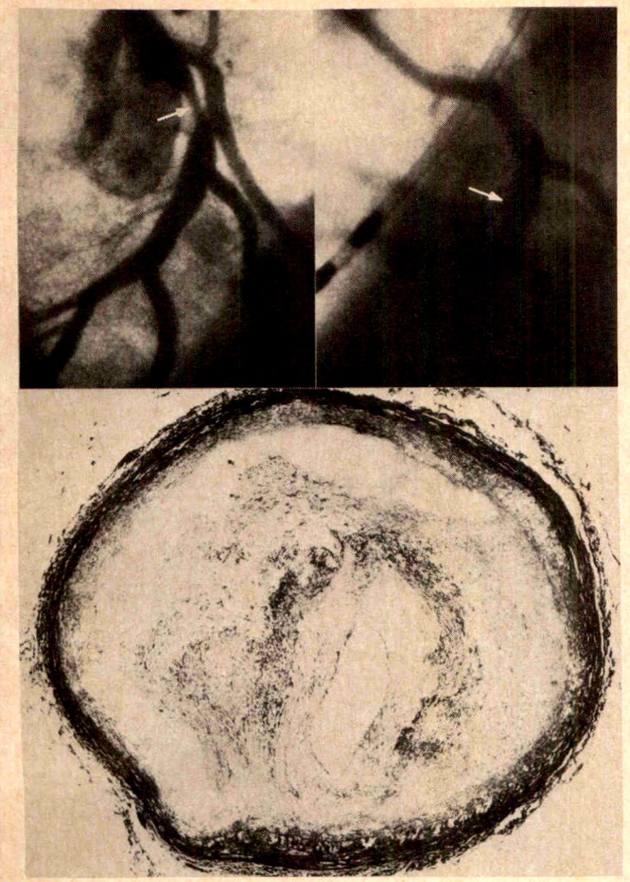


**FIGURE 2.** Patient 2. **Top panels,** frames of coronary angiogram 90 days before death showing an increase in diameter of the LAD artery after PTCA (**arrows**). **Bottom panel,** histologic section of the LAD artery at the site of previous PTCA procedure, showing severe luminal narrowing by atherosclerotic plaque (Movat stain; magnification ×22).

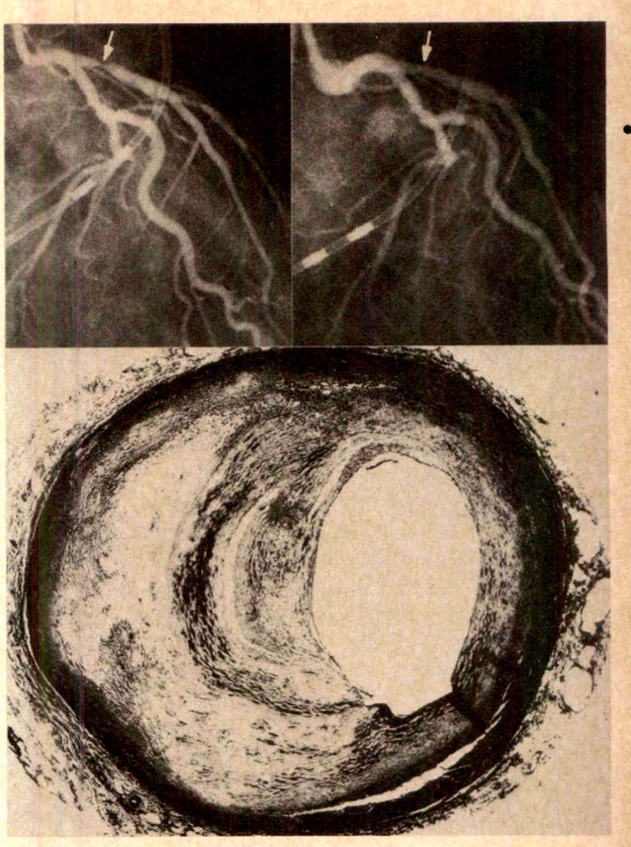


**FIGURE 3.** Patient 3. **Top panels,** frames of coronary angiogram 150 days before death showing an increase in diameter of the LAD artery after PTCA (**arrows**). **Bottom panel,** histologic section of the LAD artery at the site of a previous PTCA procedure, showing severe luminal narrowing by atherosclerotic plaque (Movat stain; magnification ×23).

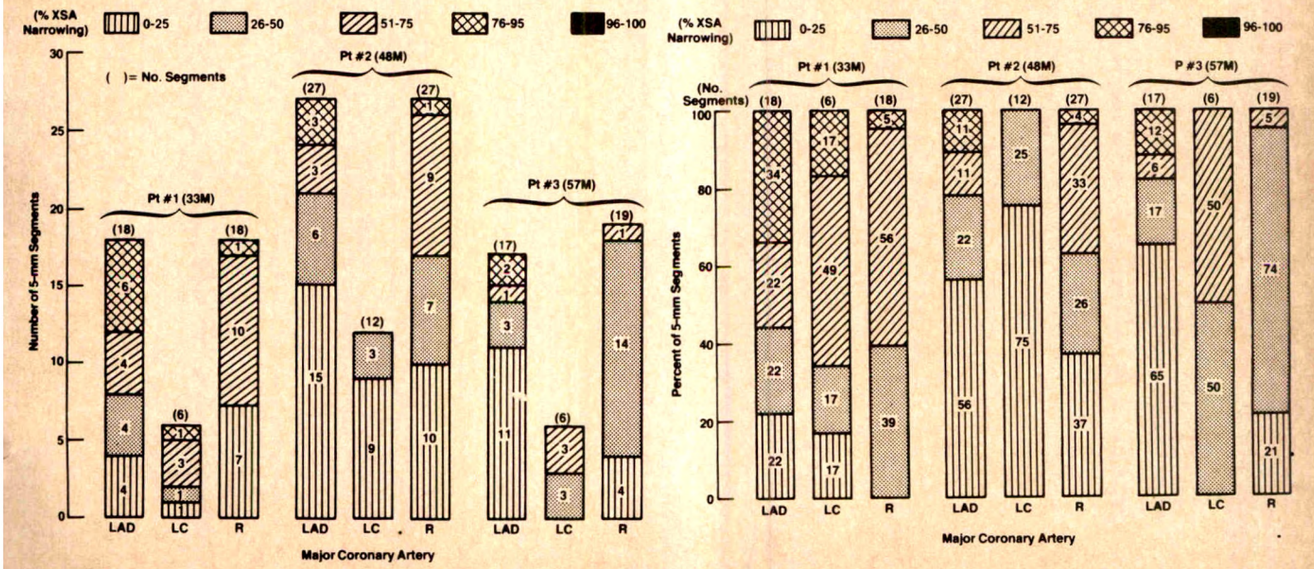



**FIGURE 4.** Number (**left panel**) and percent (**right panel**) of 5-mm segments of the LAD, left circumflex (LC), and right (R) coronary arteries narrowed to various degrees in cross-sectional area (XSA) by atherosclerotic plaques in the 3 necropsy patients.

sclerotic plaques (Fig. 4). In each patient, the LAD coronary artery had the most segments narrowed 76 to 95%: 6 of 8 in Patient 1, 3 of 4 in Patient 2, and 2 of 2 in Patient 3. Histologic assessment of the atherosclerotic plaque in the area of the PTCA compared with other areas of atherosclerotic plaque in the same artery or other coronary arteries in the same patient disclosed no distinctive morphologic difference.

## Comments

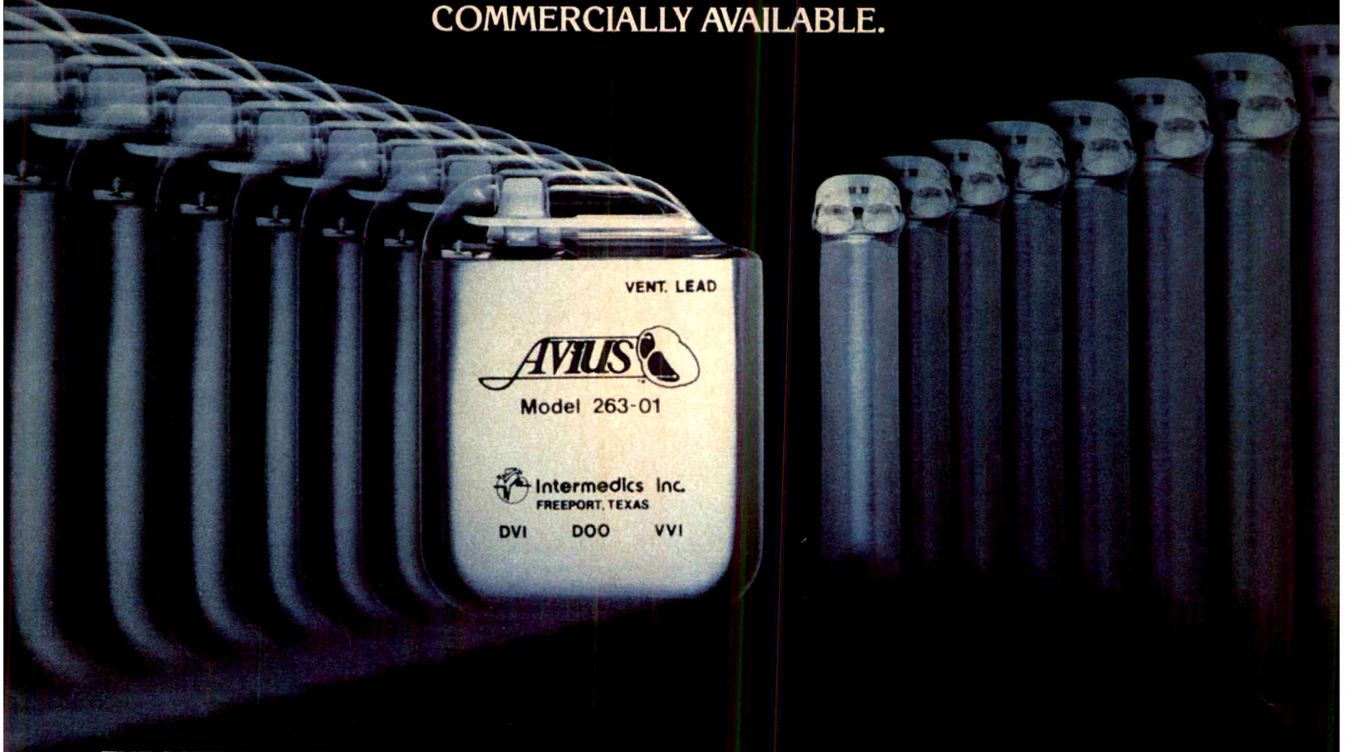
The 3 men described above had PTCA of the LAD coronary artery 80, 90, and 150 days before death; each had a decrease in the mean transstenotic coronary gradient and an angiographic increase in the lumen of the LAD coronary artery. Only 1 had angina pectoris after the PTCA procedure, and each died suddenly. At necropsy, each patient had 76 to 95% cross-sectional area narrowing by atherosclerotic plaques in the area of the PTCA procedure. Despite examination of numerous sections of the coronary artery, histologic study of the atherosclerotic plaques in the area of the PTCA did not disclose any morphologic lesions attributable to the PTCA procedure. Indeed, comparison of the composition of the plaques at the site of the PTCA with plaques in other areas of the LAD and with those in the other major coronary arteries in the same patient did not disclose any distinctive differences. While splits, tears, and breaks have been described histologically in coronary arteries of humans and in animals immediately after the PTCA procedure,[1–6] these distinctive morphologic lesions were not recognized late in our 3 patients.

## References


1. **Lee G, Ikeda RM, Joye JA, Bogren HG, DeMaria AN, Mason DT.** Evaluation of transluminal angioplasty of chronic coronary artery stenosis. Value and limitations assessed in fresh human cadaver hearts. Circulation 1980; 61:77–83.
2. **Block PC, Myler PK, Stertzer S, Fallon JT.** Morphology after transluminal angioplasty in human beings. N Engl J Med 1981;305:382–385.
3. **Baughman KL, Pasternak RC, Fallon JT, Block PC.** Transluminal coronary angioplasty of postmortem human hearts. Am J Cardiol 1981;48:1044–1047.
4. **Block PC.** Histological and ultrastructural studies in animals. In: Proceedings of the Workshop on Percutaneous Transluminal Coronary Angioplasty. Hyattsville, MD: DHEW publication no. (NIH)80–2030, March 1980:155–156.
5. **Block PC, Baughman KL, Pasternak RC, Fallon JT.** Transluminal angioplasty: correlation of morphologic and angiographic findings in an experimental model. Circulation 1980;61:778–785.
6. **Block PC, Fallon JT, Elmer D.** Experimental angioplasty: lessons from the laboratory. Am J Radiol 1980;135:907–912.
7. **Gruntzig AR, Senning A, Siegenthaler WE.** Nonoperative dilatation of coronary artery stenosis. N Engl J Med 1979;301:61–68.
8. **Cowley MJ, Vetrovec GW, Wolfgang TC.** Efficacy of percutaneous transluminal angioplasty: technique, patient selection, salutary results, limitations and complications. Am Heart J 1981;101:272–280.
9. **Kent KM, Bonow RD, Rosing DR, Ewels CJ, Lipson LC, McIntosh CL, Bacharach S, Green M, Epstein SE.** Improved myocardial function during exercise after successful percutaneous transluminal angioplasty. N Engl J Med 1982;306:441–446.
10. **Kent KM, Bentivoglio LG, Block PC, Cowley MJ, Dorros G, Gosselin AJ, Gruntzig A, Myler RK, Simpson J, Stertzer SH, Williams DO, Fisher L, Gillespie MJ, Detre K, Kelsey S, Mullin SM, Mock MB.** Percutaneous transluminal coronary angioplasty: report from the registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1982;49:2011–2020.

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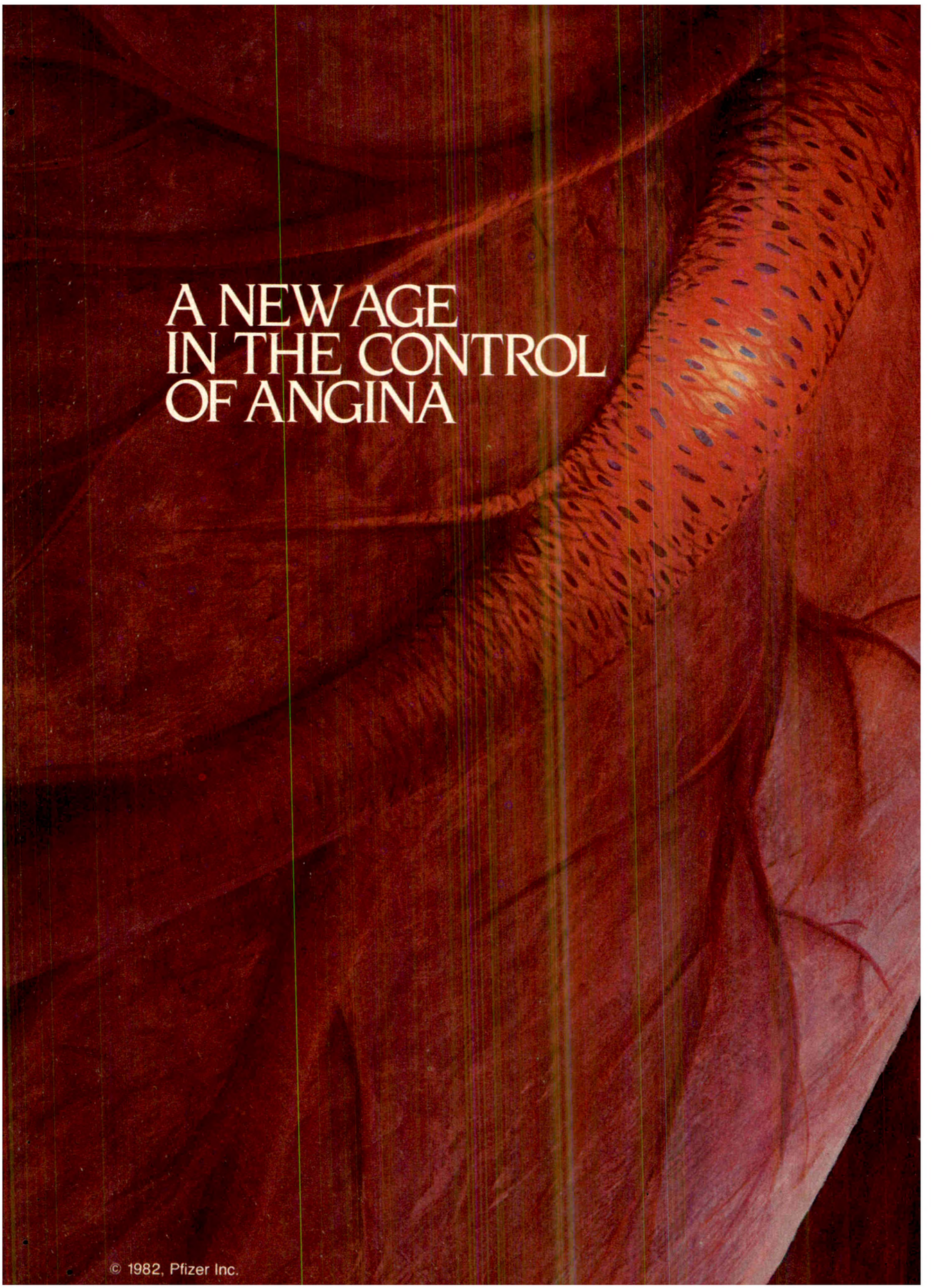
**Our Business is Life.®**

INDICATIONS FOR USE: Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, and heart block unresponsive to drug therapy.

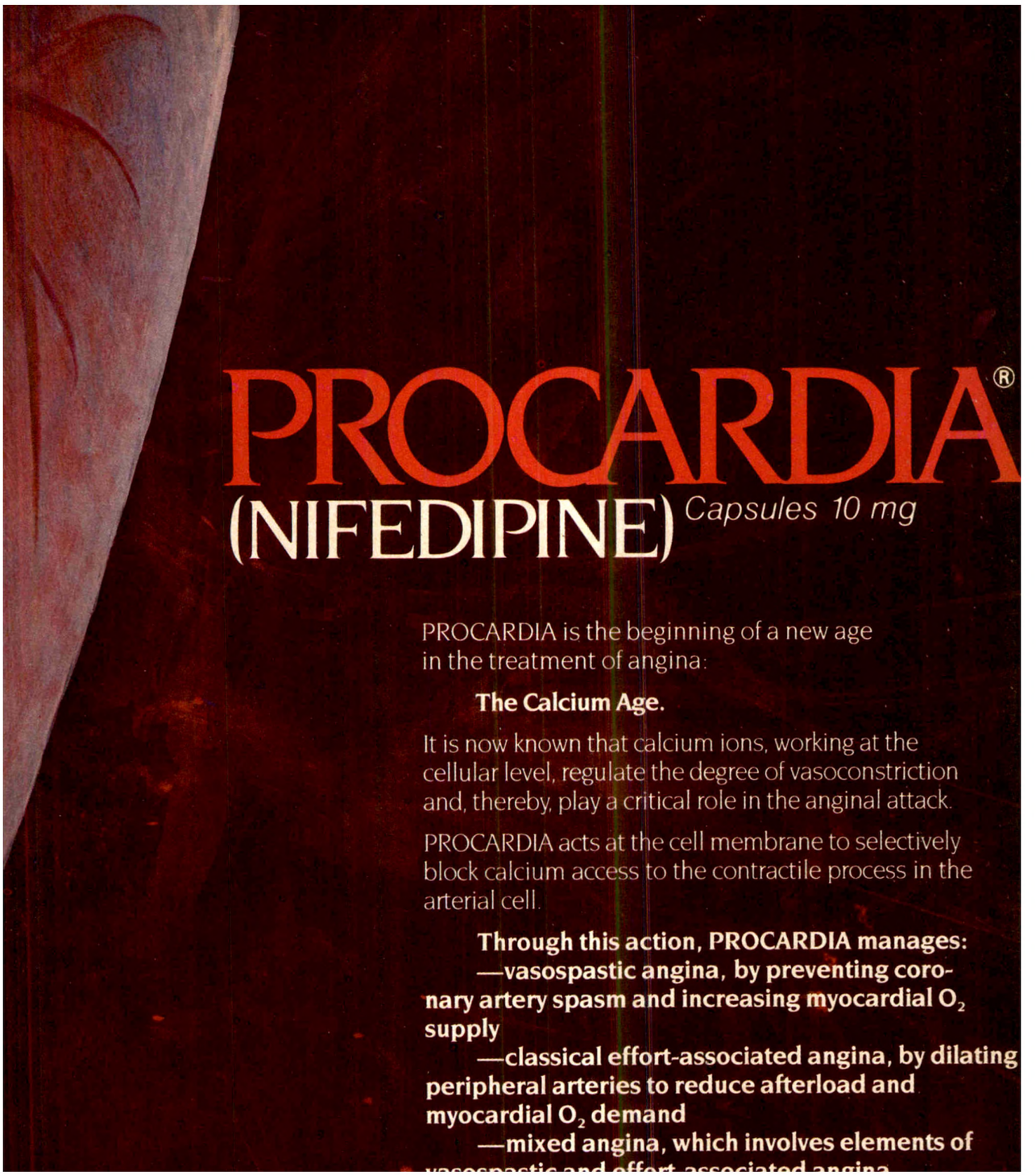
A-V sequential pacing is specifically indicated for treatment of conduction disorders that require restoration of both rate and atrio-ventricular synchrony. A-V sequential pacing may also be indicated for patients with extensive myocardial infarction with A-V block and sinus bradycardia.

CONTRAINDICATIONS AND SIDE EFFECTS: There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

PRECAUTIONS: See the "Cautionary notes" section of the Physicians' Manual for the Intermedics cardiac pulse generator to be implanted. Discussion includes Possible Complications, Environmental Hazards (electrocautery, diathermy, defibrillation, therapeutic radiation, home appliances, and industrial and special environments), and Effects of Drugs.




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PROCARDIA®
(NIFEDIPINE) Capsules 10 mg
PROCARDIA is the beginning of a new age in the treatment of angina:
The Calcium Age.
It is now known that calcium ions, working at the cellular level, regulate the degree of vasoconstriction and, thereby, play a critical role in the anginal attack.
PROCARDIA acts at the cell membrane to selectively block calcium access to the contractile process in the arterial cell.
Through this action, PROCARDIA manages:
—vasospastic angina, by preventing coronary artery spasm and increasing myocardial $O_2$ supply
—classical effort-associated angina, by dilating peripheral arteries to reduce afterload and myocardial $O_2$ demand
—mixed angina, which involves elements of

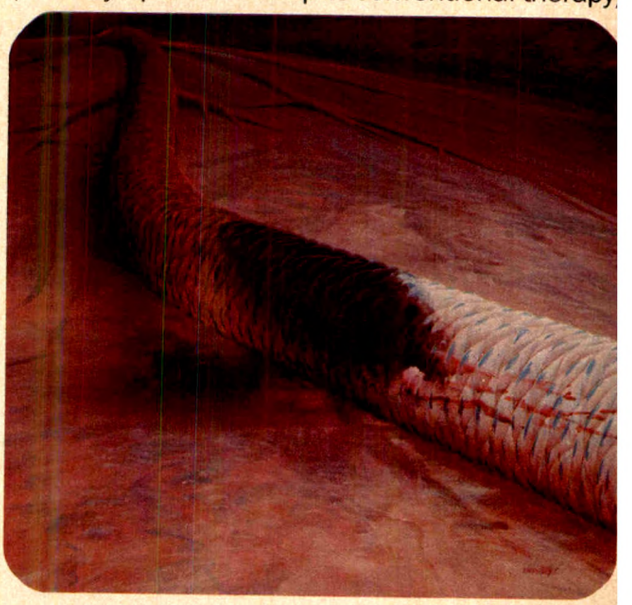
# PROCARDIA®
## (NIFEDIPINE) *Capsules 10 mg*

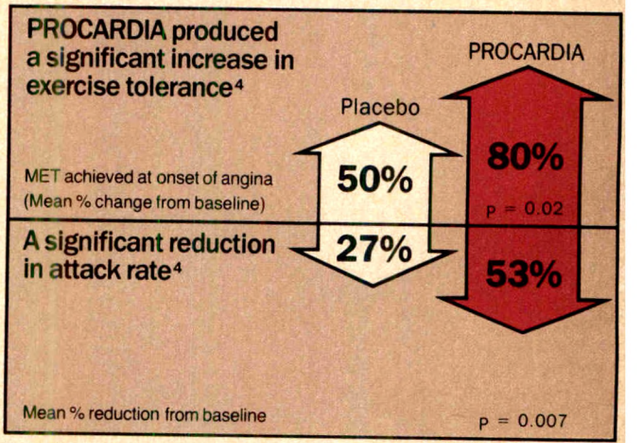
# PROVEN EFFECTIVE ACROSS THE SPECTRUM OF ANGINA

Contemporary medical opinion holds that the pathophysiology of angina is a spectrum ranging from pure, fixed atherosclerotic lesion to pure coronary artery spasm. Many patients, however, are believed to have a combination of both lesion and spasm.[2,3]

Angina due to pure fixed lesion can be prevented by reducing oxygen demand. Angina due to coronary artery spasm can be treated by preventing the spasm itself, thereby increasing oxygen supply. With this new understanding of angina, optimal antianginal therapy should provide this dual action: increasing $O_2$ supply while reducing $O_2$ demand.

## In effort angina*
(when symptomatic despite conventional therapy)



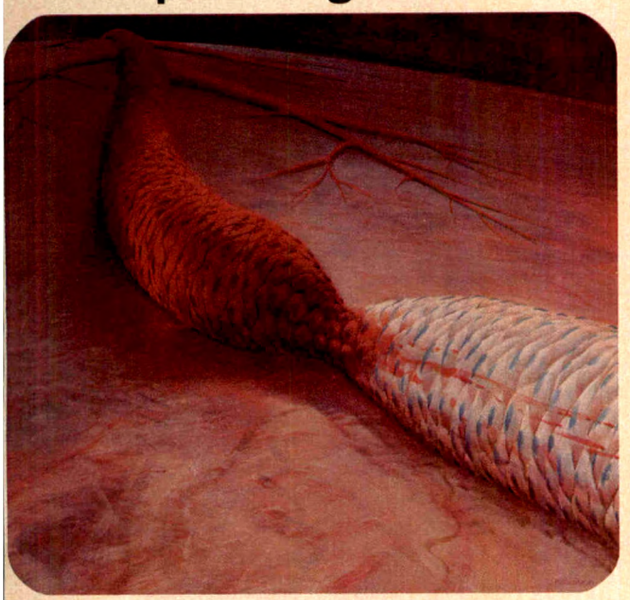



Double-blind, placebo-controlled, crossover 20-week study of 32 patients (27 evaluated for attack rate; 19 for exercise tolerance). Mean PROCARDIA dosage: 51 mg/day.

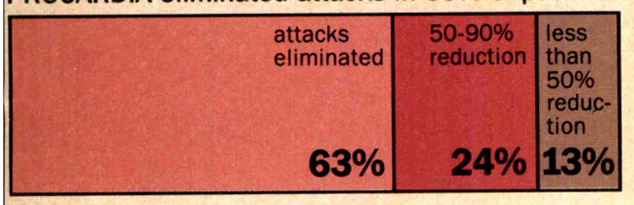
*In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

*Please see PROCARDIA Brief Summary on last page.*

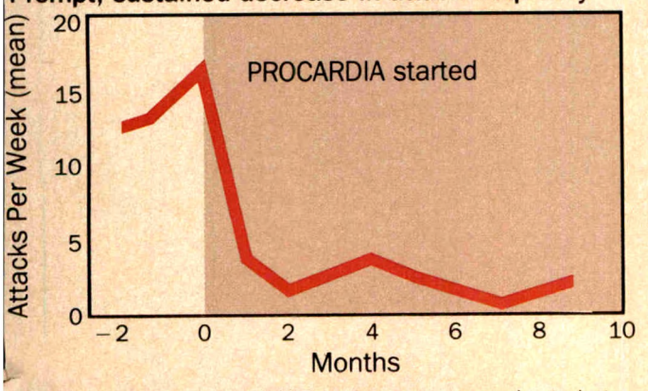
## In vasospastic angina



**PROCARDIA eliminated attacks in 63% of patients[5]**

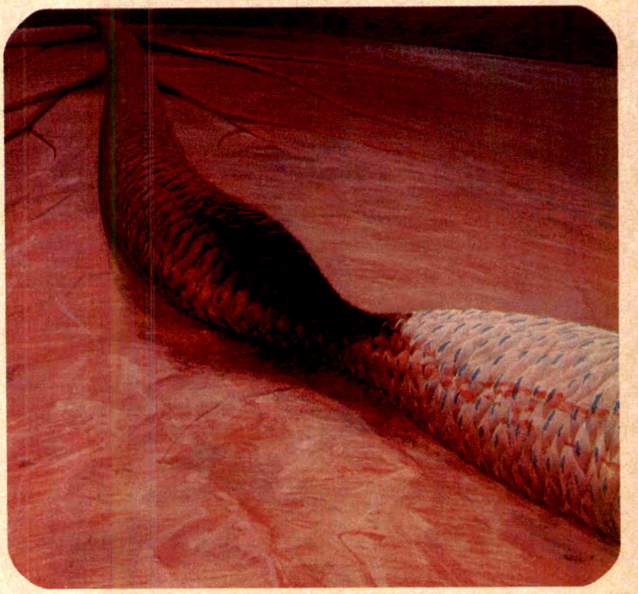


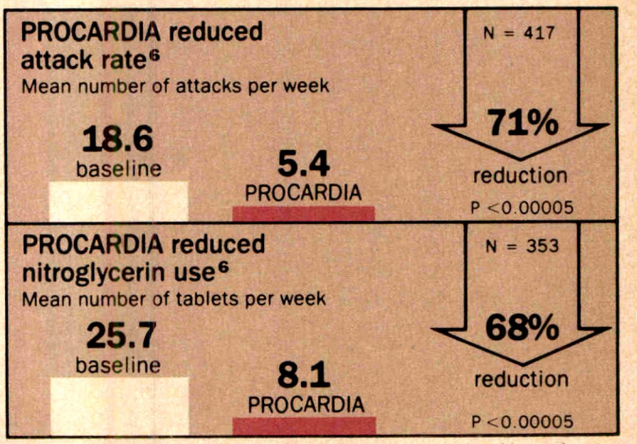

**Prompt, sustained decrease in attack frequency[5]**




Long-term, open study of 127 patients unresponsive to beta blockers and/or nitrates with symptoms of myocardial ischemia and demonstrated coronary artery spasm. PROCARDIA dosage: 40 to 160 mg/day.

## In mixed angina (fixed lesion and spasm)






Studies of patients with mixed angina characterized by pain at rest and effort. Most patients (89%) were initiated on nitrate and/or beta blocker therapy but remained symptomatic. Minimum duration of nifedipine treatment two months. Nifedipine dosage: 30 to 120 mg/day.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

# PROCARDIA®
## (NIFEDIPINE) *Capsules 10 mg*

# ANGINA MANAGEMENT BEYOND BETA BLOCKERS

—Beta blockers prevent angina primarily by lowering myocardial oxygen demand. Like these agents, PROCARDIA reduces myocardial oxygen demand. However, PROCARDIA provides an added dimension of angina control by increasing myocardial oxygen supply where coronary artery spasm is present.

—Beta blockers can actually cause spasm. PROCARDIA prevents spasm.

—Beta blockers decrease myocardial perfusion in poststenotic areas. PROCARDIA increases myocardial perfusion to both normal and poststenotic areas.

—Beta-blocker treatment is limited in patients with myocardial dysfunction, COPD, asthma, bundle branch blocks, and diabetes. PROCARDIA can be given safely in all these groups of patients.

—The hypotensive effect of PROCARDIA is usually modest and well tolerated, however, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or subsequent upward dosage adjustment, and may be more likely with concomitant beta blockers.

—Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA, or at the time of dosage increases. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers, if possible, rather than stopping them abruptly before beginning PROCARDIA.

—Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

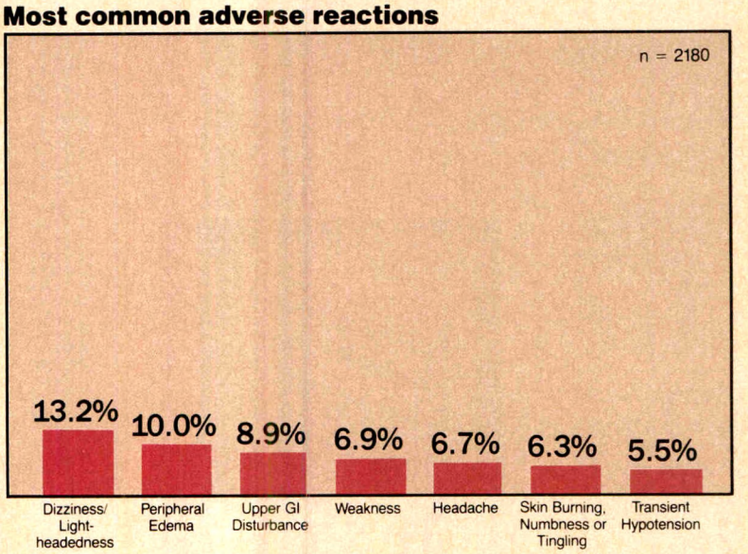
*Please see PROCARDIA Brief Summary on last page.*



# THE FIRST ORAL CALCIUM CHANNEL BLOCKER...

# PROVIDES PROTECTION WITH A MILD SIDE-EFFECT PROFILE

**Most common adverse reactions**




Information is drawn from a large uncontrolled experience in 2180 patients and presents the most frequent side effects reported with PROCARDIA.

# AN ADDED ADVANTAGE: COMPATIBILITY

—MAY BE USED WITH A WIDE VARIETY OF OTHER AGENTS

—CAN BE USED WITH NITRATES AND BETA BLOCKERS WITH CAUTION (See Warnings and Precautions)

# THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA

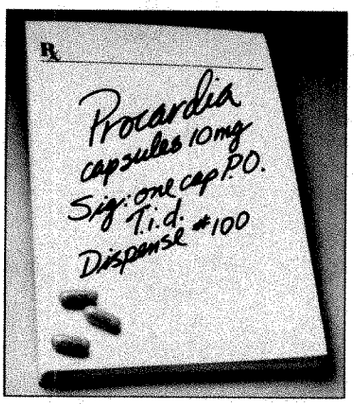
# PROCARDIA®
## (NIFEDIPINE) *Capsules 10 mg*

Proven effective when used alone.

Enhanced effectiveness when combined with beta blockers.

Convenient dosing

| | | |
|---|---|---|
| Start with: | 1 | 10-mg capsule *t.i.d.* |
| Titrate to: | 2 | 10-mg capsules *t.i.d.* |
| Titrate to: | 3 | 10-mg capsules *t.i.d.* |




For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely. Maximum dose: 180 mg/day.


**References**

1. Lichtlen PR, Engel H-J, Wolf R, et al: Regional myocardial blood flow in patients with coronary artery disease after nifedipine. in Lichtlen PR, Kimura E, Taira N (eds): *International Adalat® Panel Discussion: New Experimental and Clinical Results*. Tokyo, Excerpta Medica, 1978, pp 69–85.
2. Maseri A, Chierchia S: Angina pectoris—a new dimension, a new approach: Part 2. *Primary Cardiol* 6:123–136, October 1980.
3. Braunwald E: *Introduction: New Concepts in Ischemic Heart Disease: The Role of Coronary Artery Spasm*. New York, Science & Medicine, Inc, 1980, p 1.
4. Mueller HS, Chahine RA: Interim report of multicenter double-blind, placebo-controlled studies of nifedipine in chronic stable angina. *Am J Med* 71:645-657, October 1981.
5. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: experience in 127 patients. *N Engl J Med* 302:1269–1273, June 5, 1980.
6. Braunwald E (moderator): Procardia® (nifedipine) in clinical practice. Presented at symposium following the Thirty-First Annual Scientific Session of the American College of Cardiology, Atlanta, Georgia, April 29, 1982.


## PROCARDIA® CAPSULES (nifedipine) For Oral Use

**BRIEF SUMMARY**

**INDICATIONS AND USAGE: I. Vasospastic Angina:** PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

**II. Chronic Stable Angina (Classical Effort-Associated Angina):** PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

**CONTRAINDICATIONS:** Known hypersensitivity reaction to PROCARDIA.

**WARNINGS: Excessive Hypotension:** Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

**Increased Angina/Beta Blocker Withdrawal:** Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

**Congestive Heart Failure:** Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

**PRECAUTIONS: General:** Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

**Pregnancy:** Category C.

**ADVERSE REACTIONS:** The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

**Laboratory tests:** Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms.

**HOW SUPPLIED:** Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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# Electrophysiologic Testing in the Management of Survivors Of Out-of-Hospital Cardiac Arrest

FRED MORADY, MD, MELVIN M. SCHEINMAN, MD, DAVID S. HESS, MD, RUEY J. SUNG, MD, EDWARD SHEN, MD, and WILLIAM SHAPIRO, MD

**Forty-five patients survived a cardiac arrest due to ventricular tachycardia (VT) or ventricular fibrillation (VF). Programmed ventricular stimulation was performed with the patients taking no antiarrhythmic medications. Sustained VT was induced in 26 patients (58%) and nonsustained VT in 8 (18%). With treatment aimed at the underlying heart disease (plus empiric antiarrhythmic therapy in 2 patients), the 11 patients who had no inducible VT have had no recurrence of symptomatic VT or cardiac arrest over a follow-up period of 19 ± 9 months (mean ± standard deviation). Conventional antiarrhythmic drugs suppressed the induction of VT and were used for chronic treatment in 9 of 34 patients (26%) with inducible VT. Three of these 9 patients had recurrent VT or sudden death, whereas 6 have had no recurrence over follow-up of 20 ± 7 months. In the 25 of 34 patients in whom the induction of VT was not suppressed by conventional antiarrhythmic drugs, 23 were treated with amiodarone (daily dose 550 ± 120 mg), and 2 underwent coronary artery bypass grafting with either aneurysmectomy or map-directed endocardial resection. One of the latter 2 patients died suddenly 12 months after surgery. Among the 23 patients treated with amiodarone, 2 had fatal VT or sudden death and 21 (91%) did not, over 18 ± 14 months of follow-up.**

**In survivors of a cardiac arrest, the chief value of electrophysiologic testing is in identifying patients without inducible VT, who appear to have a low risk of recurrent sudden death with treatment directed at the underlying heart disease. Serial electropharmacologic testing with conventional antiarrhythmic drugs is disappointing, with a low incidence of arrhythmia suppression.**

Of patients who have survived an episode of out-of-hospital cardiac arrest, 29 to 74% have been reported to have inducible VT with programmed ventricular stimulation.[1-3] Only 1 study has reported long-term follow-up events in patients who had aborted cardiac arrest and in whom chronic antiarrhythmic therapy was based on the results of electropharmacologic testing. Ruskin et al[2] reported no recurrence of cardiac arrest over a mean follow-up of 15 months in 19 patients treated with drugs that suppressed the induction of VT. We performed electrophysiologic testing in 45 survivors of out-of-hospital cardiac arrest; the results of therapy guided by electropharmacologic drug testing are reported herein.

From the Department of Medicine and the Cardiovascular Research Institute, University of California, San Francisco. Manuscript received June 8, 1982; revised manuscript received August 27, 1982, accepted August 27, 1982.

Address for reprints: Fred Morady, MD, Room 573, Moffitt Hospital, San Francisco, California 94143.

## Methods

Forty-five patients (Table I) survived an out-of-hospital episode of cardiac arrest. The earliest rhythm documented before direct-current cardioversion was VF in 30 and VT in 12; in 3 patients the rhythm before direct-current cardioversion was not documented. At the time of the cardiac arrest, 31 of 45 patients had been taking 1 of the following antiarrhythmic drugs orally: quinidine, 0.8 to 1.2 g/day; procainamide, 2 to 3 g/day; disopyramide, 0.6 g/ day; or phenytoin, 300 mg/day. In addition, 14 patients were taking propranolol, 80 to 240 mg/day.

Coronary angiography was performed within 3 weeks of the episode of aborted cardiac arrest in 31 of 45 patients, including 26 of 36 patients who had ischemic heart disease. Left ventricular (LV) ejection fraction was determined either by contrast or radionuclide angiography in 41 of 45 patients.

Patients with evidence of a new myocardial infarction in association with the episode of aborted cardiac arrest were excluded from the study. In addition, patients with the congenital long Q-T syndrome were excluded because of the previous finding that programmed ventricular stimulation seldom results in VT induction in these patients.[4]

**Electrophysiologic study protocol:** After informed consent had been obtained, an electrophysiologic study was performed 5 days to 6 weeks after the episode of cardiac arrest. All antiarrhythmic medications were discontinued for at least 4 half-lives before electrophysiologic study. Studies were performed in the fasting, unsedated state. Two quadripolar electrode catheters were inserted percutaneously into a femoral vein; 1 was positioned across the tricuspid valve for recording the His bundle electrogram, and the other was positioned against the apex of the right ventricle. In patients undergoing left ventricular stimulation, a bipolar electrode catheter was inserted percutaneously into a femoral artery and positioned against the apex of the left ventricle. Electrocardiographic leads $V_1$, I, and III and intracardiac electrograms were recorded using a VR-12 Electronics for Medicine recorder. Ventricular stimulation was performed with 2 ms pulses, delivered by a programmable stimulator (Bloom) at a constant current of 5 mA.

The following stimulation protocol was used. Right ventricular drive was instituted at a cycle length of 500 ms and diastole was scanned with 1, 2, and then 3 extrastimuli. Short bursts of right ventricular overdrive pacing were then performed at cycle lengths of 600 to 300 ms. If VT was not induced with right ventricular stimulation, left ventricular stimulation was performed, except in 1 patient who had a prosthetic aortic valve and 3 patients we studied early in our experience. In patients who did not have ischemic heart disease, if VT was not induced with this protocol, ventricular stimulation was repeated during continuous infusion of 1 to 5 μg/min of isoproterenol, titrated to maintain a heart rate of 120 beats/min.

In patients who did not have inducible VT, a standard atrial pacing protocol was used to rule out rapid supraventricular tachycardia as a cause of cardiac arrest. Sustained VT was defined as VT at least 30 seconds in duration or requiring direct-current cardioversion or overdrive pacing for termination. Nonsustained VT was defined as VT of 6 beats to 30 seconds in duration.

**Electropharmacologic testing:** Drugs were tested based on each patient's history of drug intolerance and previous clinical response. The following drugs were tested acutely in the electrophysiology laboratory after intravenous administration: procainamide, 750 to 1,500 mg; propranolol, 0.2 mg/kg; lidocaine, loading dose of 225 mg over 20 minutes, concomitant with a 2 mg/min continuous infusion; propafenone, loading dose of 2 mg/kg, concomitant with a 1 to 2 mg/min continuous infusion. The following oral agents were tested during the last 1 to 2 hours of the dosing interval, after administration of a sufficient number of doses to attain a steady-state serum drug level: procainamide, 3 to 8 g/day; quinidine, 1.2 to 1.6 g/day; disopyramide, 400 to 600 mg/day; propranolol, 160 to 480 mg/day; tocainide, 0.8 to 1.2 g/day; nadolol, 240 to 300 mg/day.

Electropharmacologic testing was usually performed until VT could no longer be induced by both right and left ventricular stimulation, even when VT had been induced by right ventricular stimulation in the baseline study; however, in 4 patients studied early in our experience and in whom VT was induced by right ventricular stimulation, left ventricular stimulation was not performed during electropharmacologic testing. If high-dose procainamide was not successful in suppressing VT induction, quinidine and disopyramide were generally not tested.

When the induction of VT could not be suppressed by 1 or more of the aforementioned drugs, treatment was begun with amiodarone, 800 mg/day orally, except in 2 patients who underwent a surgical procedure. Because of the observation by ourselves and others that ventricular stimulation studies are not predictive of clinical response in patients treated with amiodarone, patients treated with this drug did not undergo repeat studies.[5-7]

**TABLE I Clinical Characteristics of 45 Survivors of Cardiac Arrest***

| | |
|---|---|
| Age (yr) | 56 ± 16† |
| Males/females | 39/6 |
| Heart disease | |
| Ischemic | 36 (78) |
| Single-vessel CAD | 3 |
| Double-vessel CAD | 3 |
| Triple-vessel CAD | 16 |
| LMCA disease | 3 |
| Coronary spasm | 1 |
| Catheterization not done | 10 |
| Previous myocardial infarction | 30 |
| Previous CABG | 5 |
| Congestive cardiomyopathy | 3 (7) |
| Valvular | 3 (7) |
| Mitral valve prolapse | 2 (4) |
| Hypertrophic cardiomyopathy | 1 (2) |
| No heart disease | 1 (2) |
| Ejection fraction | 0.42 ± 0.15† |
| Congestive heart failure | |
| NYHA I or II | 14 (31) |
| NYHA III or IV | 11 (24) |
| Previous episode of cardiac arrest | 6 (13) |

* Numbers in parentheses represent percentages. † Mean ± standard deviation. CABG = coronary artery bypass grafting; CAD = coronary artery disease; LMCA = left main coronary artery; NYHA = New York Heart Association functional class.

**TABLE II Surgical Procedures Performed in 45 Survivors of Cardiac Arrest**

| Patients (n) | Heart Disease | Operative Procedure |
|---|---|---|
| | Before Electrophysiologic Testing | |
| 1 | Aortic stenosis | Aortic valve replacement |
| 2 | Stenosis of LMCA | CABG |
| | After Electrophysiologic Testing | |
| 1 | Stenosis of LMCA | CABG and aneurysmectomy |
| 1 | Triple-vessel CAD | CABG and map-directed endocardial resection |
| 1 | Triple-vessel CAD | CABG |

CABG = coronary artery bypass grafting; CAD = coronary artery disease; LMCA = left main coronary artery.

**Surgical therapy:** After their episodes of cardiac arrest, 3 patients underwent a surgical procedure before electrophysiologic testing and 3 afterwards (Table II).

**Chronic drug therapy and follow-up:** Patients were followed on a regular basis by either 1 of the investigators or by the patient's referring physician. Drug therapy was adjusted to yield serum drug levels that matched drug levels found to be successful in suppressing VT induction in the laboratory. In patients treated with amiodarone, the dose was tapered to 600 mg/day after 6 weeks of therapy; subsequent adjustments in the dose depended on the clinical response and development of adverse effects.

Twenty-four–hour ambulatory electrocardiographic recordings were obtained every 3 to 4 months. Sudden death was defined as unexpected natural death occurring during sleep or within 1 hour of the patient's collapse.

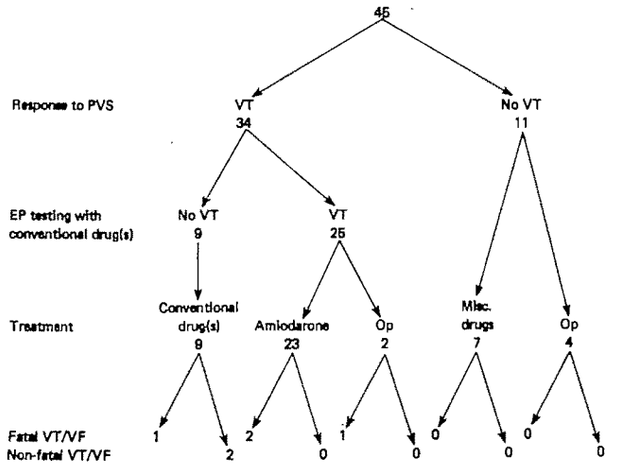



**FIGURE 1.** Results of electrophysiologic testing and clinical follow-up in 45 survivors of cardiac arrest. EP = electropharmacologic; Misc. = miscellaneous (see text for details); Op = operation (as listed in Table II); PVS = programmed ventricular stimulation.

**Statistical analysis:** Values are expressed as mean ± 1 standard deviation. Patients in whom VT induction was suppressed by conventional agents were compared with those in whom VT induction was not suppressed using Fischer's exact test and Student's *t* test.

## Results

During the baseline electrophysiologic study, sustained VT was induced in 26 of 45 patients (58%). Mean cycle length of VT was 273 ± 77 ms. The VT morphology was that of right bundle branch block in 18, left bundle branch block in 5, and polymorphic in 3. VT was induced with right ventricular stimulation in all but 3 patients who required left ventricular stimulation. VT was induced with burst pacing in 3 patients, with 1 extrastimulus in 1 patient, with 2 extrastimuli in 9 patients, with 3 extrastimuli in 12 patients, and with 3 extrastimuli during isoproterenol infusion in 1 patient. Direct-current cardioversion was required to terminate VT in 15 of 26 patients; in the remaining 11 patients, VT was terminated with overdrive pacing.

Nonsustained VT was induced in 8 of 45 patients (18%). The mean duration of VT was 29 ± 18 beats (range 8 to 65); the mean cycle length was 224 ± 19 ms. The VT morphology was that of right bundle branch block in 4 patients, left bundle branch block in 1, and polymorphic in 3. In all cases, nonsustained VT was induced with right ventricular stimulation; 2 extrastimuli were necessary in 2 patients, and 3 extrastimuli in 6.

Overall, VT was induced with programmed ventricular stimulation in 34 of 45 patients (76%). Of the 30 patients who had VF at the time of resuscitation, VT was induced in 23 (77%); of the 12 patients who had VT at the time of resuscitation, VT was induced in 10 (83%).

VT could not be induced with programmed ventricular stimulation in 11 patients (24%). Two of these patients had undergone coronary artery bypass grafting because of stenosis of the left main coronary artery, and 1 had undergone aortic valve replacement for aortic stenosis. A fourth patient had had a cardiac arrest 2 weeks after initiation of quinidine for prevention of atrial fibrillation; an electrocardiogram obtained several days before the cardiac arrest showed a Q-T interval of 0.52 seconds ($Q\text{-}T_c$ = 0.58 second). A fifth patient who had coronary artery disease (CAD) had no inducible VT despite frequent episodes of spontaneous VT before and after electrophysiologic study. Of the other 6 patients, 5 had CAD and 1 had coronary artery spasm. Three of these patients were engaged in strenuous exertion at the time of the cardiac arrest. One patient had no underlying heart disease.

**Clinical follow-up in patients with no inducible VT during baseline study (Fig. 1):** Eleven patients with no inducible VT have had no recurrence of symptomatic VT or VF over a mean follow-up period of 19 ± 9 months (range 9 to 34). Four patients underwent coronary artery bypass grafting or aortic valve replacement (before the electrophysiologic study in 3 patients and afterwards in 1). The patient who had coronary artery spasm was treated with nitrates. Three patients who had CAD but who either refused or were not suitable candidates for coronary artery bypass grafting were treated with nitrates and beta-adrenergic blocking agents aimed at preventing myocardial ischemia; 1 of these patients was also treated with encainide for suppression of asymptomatic premature ventricular beats. The patient who had been treated with quinidine and had Q-T interval prolongation before a cardiac arrest was treated with procainamide (for paroxysmal atrial fibrillation); no VT could be induced while taking procainamide. The patient who had no inducible VT but who had frequent spontaneous episodes of VT was treated with amiodarone. The patient without underlying heart disease was initially treated empirically with nadolol for 6 months and has subsequently taken no medication over an additional 7 months of follow-up.

**Results of electropharmacologic drug testing and clinical follow-up (Fig. 1):** VT could no longer be induced after administration of a conventional antiarrhythmic drug in 9 of 34 patients (26%) who had inducible VT during the baseline electrophysiologic study. Induction of VT was suppressed by procainamide in 4 patients (mean serum level 10.3 ± 5.9 μg/ml), quinidine in 1 (serum level 3.2 μg/ml), nadolol or propranolol in 2, and a combination of procainamide (serum level 6.4 ± 0.9 μg/ml) and propranolol in 2. These patients were treated chronically with the drug(s) that suppressed the induction of VT. One patient died suddenly after 1 month of treatment. Another patient (who did not undergo left ventricular stimulation during electropharmacologic testing) had an episode of symptomatic VT after 1 week of treatment, underwent coronary bypass grafting, and has had no recurrence of VT or cardiac arrest over 21 months of follow-up. A third patient had recurrence of aborted cardiac arrest after 17 months of treatment, and subsequently underwent insertion of an

automatic internal defibrillator. The remaining 6 of 9 patients had no recurrence of cardiac arrest or symptomatic VT over a mean follow-up period of 20 ± 7 months.

During electropharmacologic testing with conventional antiarrhythmic drugs, VT remained inducible in 25 of 34 (74%) patients who had inducible VT during the baseline electrophysiologic study. These patients underwent an average of 1.8 drug trials each. Twenty-one of these 25 patients failed testing with intravenous procainamide (mean serum level 12.9 ± 6.8 μg/ml). There was no significant difference in the proportion of patients with ischemic heart disease (20 of 25 versus 5 of 9) or mean ejection fraction (0.38 ± 0.10 versus 0.46 ± 0.15) in these 25 patients and the 9 in whom VT induction was suppressed by a conventional antiarrhythmic drug. One of these 25 patients underwent coronary artery bypass grafting and aneurysmectomy and died suddenly 12 months after surgery. Another patient underwent coronary artery bypass grafting and map-directed endocardial resection and has remained well for 39 months. The remaining 23 of 25 patients were treated with amiodarone (mean dose 550 ± 120 mg) either alone (17 patients) or in combination with procainamide (in 6 patients procainamide slowed the rate of induced VT). One patient died suddenly after 1 month of treatment, and another patient died from refractory VT after 3 months of treatment. The remaining 21 of 23 patients (91%) who were treated with amiodarone have had no recurrence of cardiac arrest or symptomatic VT over a mean follow-up period of 18 ± 14 months (range 7 to 65).

Overall, in the 45 patients who survived a cardiac arrest and underwent electrophysiologic testing, 4 of 45 patients (9%) died due to VT or VF at 4.2 ± 5 months of follow-up, 2 of 45 (4%) had a nonfatal recurrence of VT at 1 week and 17 months of follow-up, and 39 of 45 (87%) have had no recurrence of symptomatic VT or VF over a follow-up period of 18 ± 12 months.

## Discussion

Previous studies have shown that patients who survive an episode of cardiac arrest in the absence of a transmural myocardial infarction and who are treated with conventional antiarrhythmic drugs in a nonstandardized fashion have a mortality of 34 to 36% at 1 year of follow-up.[8–10] In comparison, in the present series of 45 patients in whom therapy was guided by the results of electrophysiologic testing and in whom amiodarone was used in 50% of patients, the mortality from VT or VF was only 9% at 1.5 years of follow-up. The lower mortality in the present series suggests that electrophysiologic testing and/or the use of amiodarone may play a role in improving survival in a group of patients at high risk of sudden death.

The finding of inducible VT in 76% of patients who survived a cardiac arrest is similar to the findings of Josephson,[3] Ruskin,[2] and their co-workers, who reported inducible VT in 60 and 74% of such patients, respectively. In contrast, Myerburg et al[1] found that only 29% of patients who had survived a cardiac arrest had inducible VT. However, in the last series, only 1 extrastimulus was used in the ventricular stimulation protocol, compared with 2 extrastimuli in the series of Josephson and Ruskin and 3 extrastimuli in our series. Thus, programmed ventricular stimulation should be performed with at least 2 extrastimuli to avoid false-negative results. The relative sensitivity and specificity of 2 versus 3 extrastimuli remain to be determined.

Left ventricular stimulation was required to induce VT in approximately 10% of patients who had inducible VT. However, we performed right ventricular stimulation at only 1 site, the apex. It is possible that right ventricular stimulation at more than 1 site may at times eliminate the need for left ventricular stimulation. In any case, to maximize the yield of VT induction studies, ventricular stimulation should be performed at more than 1 site.

In the patients in this series who did not have inducible VT with programmed ventricular stimulation, possible reasons for its lack include the following: (1) The spontaneous arrhythmia may have been due to abnormal automaticity rather than reentry and thus may not be provocable with programmed stimulation. This is the most likely explanation in the patient who had no inducible VT despite having frequent spontaneous episodes of VT before and after the electrophysiologic study. (2) The onset of spontaneous VT or VF may have been related to transient myocardial ischemia that was not present at the time of the ventricular stimulation study. This is a likely explanation in the patient who had coronary spasm, in the 2 patients who had stenosis of the left main coronary artery and underwent coronary artery bypass grafting before the ventricular stimulation study, and in the 3 patients with CAD who experienced a cardiac arrest during strenuous exertion. (3) The spontaneous episode of VT or VF was related to an abnormality that was corrected by the time of the electrophysiologic study (for example, hypokalemia, quinidine-induced Q-T prolongation, or aortic stenosis). Thus, in 2 of our patients the lack of inducible VT can be attributed to discontinuation of quinidine in 1 and aortic valve replacement in the other. In patients who survive a cardiac arrest and do not have inducible VT, another possible explanation for the lack of inducible VT may be that the patient has the congenital long Q-T syndrome; VT can be induced with programmed stimulation in only a minority of these patients.[4]

In the series by Ruskin et al,[2] 6 patients who had survived a cardiac arrest did not have inducible VT; these patients were not treated with antiarrhythmic drugs and had no recurrence of cardiac arrest over a mean follow-up of 15 months. However, no details of their treatment, such as surgery or antianginal drugs, were given. The 11 patients in our series who did not have inducible VT also have had no recurrence of symptomatic VT or VF. Only 2 of 11 patients were treated with antiarrhythmic drugs specifically aimed at suppressing ventricular arrhythmias. Thus, in patients who have survived a cardiac arrest, electrophysiologic testing may be helpful in identifying those with

a low risk of recurrent VT or VF when treatment is directed toward the underlying heart disease without specific antiarrhythmic therapy.

In the patients in whom VT was induced with programmed ventricular stimulation, electropharmacologic testing with conventional antiarrhythmic drugs was disappointing, with suppression of VT induction in only 26%. Of the patients in whom the induction of VT could not be suppressed, 21 of 25 were tested with large doses of procainamide. Although most of these patients were not tested with a second type I antiarrhythmic drug, it is unlikely that such testing would have been successful in suppressing the induction of VT, since Waxman et al[11] reported that in 63 patients who had inducible VT with procainamide, only 9% of 144 additional drug trials with conventional agents were successful in suppressing VT induction. Similarly, in the series by Ruskin et al,[2] conventional antiarrhythmic drugs were successful in suppressing the induction of VT in only 34% of patients undergoing electropharmacologic testing. Electrophysiologic testing is therefore helpful in the management of patients with aborted cardiac arrest by identifying the large subgroup of patients who should be treated wtih investigational drugs or surgery.

Of the 9 patients who were treated with conventional drugs that suppressed the induction of VT during electropharmacologic testing, 3 had a recurrence of VT or VF despite continued treatment with the original drug regimen. Thus, the suppression of inducible VT during electropharmacologic testing in patients who have survived a cardiac arrest may not guarantee a successful long-term clinical response. Discordance between the results of acute drug testing and the chronic clinical response may be a result of progression of the underlying heart disease or fluctuations in other variables that may influence the propensity to develop VT or VF, such as sympathetic tone and the degree of myocardial ischemia.

Of the 23 patients who were treated with amiodarone, 92% have remained free of symptomatic VT or VF over 18 months of follow-up. Previous studies have also reported an excellent response to amiodarone in patients with recurrent VT or VF.[6,12,13] We and others have demonstrated that the induction of VT during chronic oral amiodarone therapy does not preclude a good clinical response.[5–7] Therefore, in our series no further electropharmacologic testing was performed when patients were treated with amiodarone.

In light of the excellent response in the subgroup of patients treated with amiodarone, an alternate approach to electropharmacologic testing in the management of patients who have survived a cardiac arrest might be simply to treat all such patients empirically with amiodarone. This approach was employed by Peter et al[14] in 27 patients who had survived a cardiac arrest; these patients were treated empirically with amiodarone without undergoing an electrophysiologic study. The recurrence rate of VT or VF was only 7% at the end of 1 year of treatment. The principal disadvantage of this approach is that those patients who would have responded to conventional drugs are exposed to the risks of therapy with an experimental agent.

In summary, the following conclusions can be drawn from our study of 45 patients who survived a cardiac arrest: (1) VT can be induced in 76% of patients. (2) The lack of inducible VT may identify patients who have a low risk of recurrent VT or sudden death when therapy is directed toward the underlying cardiac abnormality. (3) Electropharmacologic testing with conventional antiarrhythmic drugs is disappointing, with a minority (26%) of patients responding to these drugs. (4) In the patients who do not respond to electropharmacologic testing with conventional drugs, treatment with amiodarone is associated with a low recurrence rate of VT or sudden death. If the favorable outcome of amiodarone therapy in these patients is confirmed, empiric trials with this drug would be indicated, obviating serial electropharmacologic testing.

## References


1. **Myerburg RJ, Conde CA, Sung RJ, Mayorga-Cortes A, Mallon SM, Sheps DS, Appel RA, Castellanos A.** Clinical, electrophysiologic and hemodynamic profile of patients resuscitated from prehospital cardiac arrest. Am J Med 1980;68:568–576.
2. **Ruskin JN, DiMarco JP, Garan H.** Out-of-hospital cardiac arrest. Electrophysiologic observations and selection of long-term antiarrhythmic therapy. N Engl J Med 1980;303:607–613.
3. **Josephson ME, Horowitz LN, Spielman SR, Greenspan AM.** Electrophysiologic and hemodynamic studies in patients resuscitated from cardiac arrest. Am J Cardiol 1980;46:948–955.
4. **Morady F, Scheinman MM, Hess DS, Chen R, Stanger P.** Clinical characteristics and results of electrophysiologic testing in young adults with ventricular tachycardia or ventricular fibrillation. Am Heart J, In press.
5. **Morady F, Scheinman MM, Hess DS.** Amiodarone in the management of patients with malignant ventricular arrhythmias (abstr). Circulation 1981; 64:Suppl IV:IV-36.
6. **Heger JJ, Prystowsky EW, Jackman WM, Naccarelli GV, Warfel KA, Rinkenberger RL, Zipes DP.** Amiodarone. Clinical efficacy and electrophysiology during long-term therapy for recurrent ventricular tachycardia or ventricular fibrillation. N Engl J Med 1981;305:539–545.
7. **Hamer AW, Finerman WB, Peter T, Mandel WJ.** Disparity between the clinical and electrophysiologic effects of amiodarone in the treatment of recurrent ventricular tachyarrhythmias. Am Heart J 1981;102:992–1000.
8. **Liberthson RR, Nagel EL, Hirschman JC, Nussenfeld SR.** Prehospital ventricular defibrillation. Prognosis and follow-up course. N Engl J Med 1974;291:317–321.
9. **Cobb LA, Baum RS, Alvarez H III, Schaffer WA.** Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow-up. Circulation 1975; 51-52:Suppl III:III-223–III-228.
10. **Schaffer WA, Cobb LA.** Recurrent ventricular fibrillation and modes of death in survivors of out-of-hospital ventricular fibrillation. N Engl J Med 1975; 293:259–262.
11. **Waxman HL, Sadowki LM, Josephson ME.** Response to procainamide during electrophysiologic study for sustained ventricular tachycardia predicts response to other drugs (abstr). Circulation 1981;64:Suppl IV:IV-87.
12. **Podrid PJ, Lown B.** Amiodarone therapy in symptomatic, sustained refractory atrial and ventricular tachyarrhythmias. Am Heart J 1981;101: 374–379.
13. **Kaski JC, Girotti LA, Messuti H, Rutitzky B, Rosenbaum MB.** Long-term management of sustained, recurrent, symptomatic ventricular tachycardia with amiodarone. Circulation 1981;64:273–279.
14. **Peter T, Hamer A, Weiss D, Mandel W.** Sudden death survivors: experience with long-term empiric therapy with amiodarone (abstr). Circulation 1981;64:Suppl IV:IV-36.

# Quinidine for Ventricular Arrhythmias: Value of Electrophysiologic Testing

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**Quinidine was evaluated during serial electrophysiologic testing with programmed ventricular stimulation in 89 patients with life-threatening ventricular arrhythmias. In 30 of the 89 patients, quinidine therapy prevented the initiation of ventricular tachycardia (VT) during programmed ventricular stimulation. In 8 additional patients no single drug tested was effective, and quinidine in combination with either mexiletine (7 patients) or propranolol (1 patient) prevented the initiation of VT during electrophysiologic testing. The mean serum concentrations of quinidine in the patients who responded and those who failed to respond were 2.9 ± 0.8 and 2.8 ± 1.1 μg/ml, respectively; however, but nonresponders were characterized by more severe congestive heart failure and an increased incidence of digitalis use. During chronic therapy (24 ± 3 months) with quinidine either alone or in combination with a second antiarrhythmic drug in the 38 patients whose arrhythmia had been suppressed during electrophysiologic testing, 32 (84%) remain symptom-free while 3 have had recurrent arrhythmia and 3 discontinued quinidine because of adverse effects. These data demonstrate that quinidine, when selected on the basis of electrophysiologic testing, provides effective long-term prophylaxis against recurrent ventricular arrhythmia and that approximately 40% of patients tested are likely to respond either to quinidine alone or quinidine in combination with another antiarrhythmic agent.**

Quinidine, a cinchona alkaloid, has been known to have electrophysiologic effects for over 200 years.[1] Its successful use in the treatment of VT was reported early in this century. Since that time it has remained one of the principal drugs used for prophylaxis against recurrent VT.[2,3] Within the last 10 years, electrophysiologic testing with programmed ventricular stimulation has become established as a method for assessing antiarrhythmic therapy in patients with ventricular arrhythmias. In this report we describe the effects of quinidine observed during electrophysiologic testing in 89 patients with ventricular arrhythmias.

## Methods

We administered quinidine to 89 patients with a history of 1 or more clinical episodes of either VT or ventricular fibrillation (VF) during an evaluation that utilized intracardiac electrophysiologic techniques. In 86 of 89 patients, VT or VF had been initiated by programmed cardiac stimulation during a baseline study performed 48 or more hours after discontinuation of any previous antiarrhythmic therapy. In the remaining 3 patients, multiple episodes of VT or VF occurred when attempts were made to withdraw therapy; these 3 patients underwent the initial electrophysiologic study while receiving quinidine. Patients referred to our laboratory with a history of an allergic reaction to quinidine were not rechallenged with the drug. Patients who had previously had VT or VF during chronic therapy with quinidine were also excluded if documentation of an adequate serum level at the time was available. The clinical characteristics of the 89 patients included in this report are listed in Table I.

**Electrophysiologic procedures:** The initial electrophysiologic evaluation was performed with the patient in a fasting, nonsedated state after informed consent had been obtained. Digoxin, if required for congestive heart failure or atrial fibrillation, and propranolol, if required for angina, were continued. Digoxin dosage was adjusted to maintain the serum concentration between 0.8 and 2.0 ng/ml throughout the study period. Two to 4 quadripolar electrode catheters with a 1 cm interelectrode distance were inserted percutaneously through femoral and antecubital veins and positioned with fluoroscopic guidance at multiple intracardiac sites. Intracardiac electrograms were filtered below 30 and above 500 Hz and displayed simultaneously with scalar electrocardiographic leads I, II, and $V_1$ on a multichannel oscilloscope (Electronics for Medicine, VR-12). Data were stored on frequency-modulated magnetic tape (A-R Vetter, Rebersburg, Pennsylvania) and later retrieved on photographic paper at speeds of 75 to 200 mm/s.

Ventricular stimulation was performed with a programmable constant current stimulator (Medtronic 5325) that

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delivered rectangular pulses of 2 ms duration. Ventricular stimulation was performed from 1 or more right ventricular sites at 4 to 5 times diastolic threshold (minimum 2 mA). The following stimulation protocol was used[4,5]: (1) atrial pacing at incremental rates of 100 to 300 beats/min; (2) premature atrial stimulation during atrial pacing at 1 or more basic cycle lengths; (3) ventricular pacing at incremental rates of 60 to 100 beats/min for 30 seconds; (4) premature ventricular stimulation with single ($S_2$) and double ($S_2$-$S_3$) extrastimuli during sinus rhythm and during fixed-rate ventricular pacing at multiple basic cycle lengths; (5) rapid ventricular pacing in brief bursts at rates of 100 to 280 beats/min: 3- to 5-beat pacing bursts were delivered at progressively shorter cycle lengths until 1:1 capture could no longer be achieved, sustained VT or VF occurred, or a paced rate of 280 beats/min was reached.

The same ventricular stimulation protocol was employed during both the initial study and during subsequent drug trials. The initiation of either sustained VT (>100 beats) or nonsustained VT (5 to 100 beats) was considered a significant response to stimulation.[4,5]

After the initial study, subsequent programmed stimulation trials were carried out using an indwelling bipolar electrode positioned at the right ventricular site from which VT had been initiated previously. Trials were conducted during steady-state quinidine therapy after serum concentrations of any previously used agent had dissipated. The mean total daily dose of quinidine base was 1,087 ± 204 mg with a range of 604 to 1,920 mg. Seventy-three patients received 3 or 4 divided doses/day of quinidine sulfate while 16 patients with gastrointestinal intolerance to quinidine sulfate received quinidine gluconate at similar intervals.

Quinidine therapy was evaluated during this in-hospital phase using 4 end points: (1) suppression of ability to initiate VT or VF by programmed ventricular stimulation; (2) initiation of VT or VF by programmed ventricular stimulation; (3) a clinical episode of spontaneous VT or VF before restudy with a simultaneous serum quinidine level of at least 2.0 μg/ml; or (4) intolerable early adverse effects. Patients who had an episode of symptomatic or sustained VT, cardiac arrest, or unexplained syncope during quinidine therapy were considered chronic treatment failures. During the first 24 to 48 hours of quinidine treatment, electrocardiographic rhythm strips were monitored and, if either marked Q-T prolongation (>+50% baseline), QRS widening (>+20% of baseline) or atrioventricular block was noted, quinidine was either discontinued or its dosage reduced.

Forty-nine patients received quinidine on only 1 dose schedule. The other 40 patients continued to manifest VT in response to ventricular stimulation during their initial trial with quinidine and were then begun on therapy at a higher dose. Thirty-one of these 40 patients underwent repeat programmed ventricular stimulation on the higher dose. The other 9 patients were unable to tolerate the higher dose because of adverse effects and were considered nonresponders to quinidine. All data presented represents that obtained during EP testing on the highest dosage of quinidine reached.

Quinidine was used in combination with a second antiarrhythmic agent only if both agents had been shown to be ineffective in preventing initiation of VT when each agent was used separately. Therapeutic trials involving quinidine in a combination with 1 or 2 other antiarrhythmic agents were performed in 35 patients.

Quinidine serum concentrations were determined at the time of electrophysiologic testing using fluorometric analysis after benzene extraction in a modification of the method of Cramer and Isaksson.[6,7] This method measures quinidine and dihydroquinidine and excludes polar metabolites.[7] The effects of quinidine in each individual patient were assessed using a $t$ test for matched pairs while comparisons between responders and nonresponders were made using a 1-tailed $t$ test for unmatched groups.

**TABLE I Clinical Characteristics of 89 Patients**

| | |
|---|---|
| Sex | 73 Male<br>16 Female |
| Age | 57 ± 12 Years |
| Cardiac diagnosis | 78 ASHD<br>5 Other HD<br>6 NSHD |
| Clinical presentation | 56 VT<br>21 VF<br>12 Syncope* |

* Ventricular tachycardia initiated by ventricular stimulation at initial electrophysiologic study. ASHD = atherosclerotic heart disease; HD = heart disease; NSHD = no structural heart disease.

## Results

**Initial electrophysiologic studies:** In 86 patients, programmed cardiac stimulation initiated VT or VF during the initial study of antiarrhythmic drugs. Three patients had 1 or more spontaneous episodes of VT when attempts to withdraw therapy were made. The tachycardia rate was 237 ± 30 (mean ± standard deviation) beats/min. All episodes of VT or VF ended spontaneously or were interrupted without complication using either ventricular pacing or transthoracic, direct-current countershock.

**Ventricular stimulation during quinidine therapy (Table II):** Between 36 and 72 hours after the initiation of quinidine therapy, but before repeat EP testing was performed, 5 patients had a spontaneous episode of VT or VF. The serum quinidine concentration determined at that time was 2 to 3.2 μg/ml in these 5 patients. Three other patients developed adverse effects after the first several doses of quinidine. These adverse effects included fever, atrioventricular block, and severe hypotension, each of which occurred in 1 patient. These 8 patients did not undergo repeat programmed ventricular stimulation while taking quinidine.

In 30 of the remaining 81 patients, quinidine prevented the initiation of VT or VF by programmed ventricular stimulation. Sample electrocardiograms obtained in a patient who responded to quinidine are shown in Figure 1. In the 30 patients who responded to quinidine, the mean serum quinidine concentration at the time of testing was 2.9 ± 0.8 μg/ml.

In 51 patients of the 81 patients tested, quinidine failed to prevent the initiation of a ventricular ar-

**TABLE II Electrophysiologic Testing With Quinidine**

| | |
|---|---|
| VT/VF suppression | 30 (34%) |
| VT/VF still inducible | 56 (63%) |
| Early adverse effects | 3 (3%) |
| Total patients | 89 |

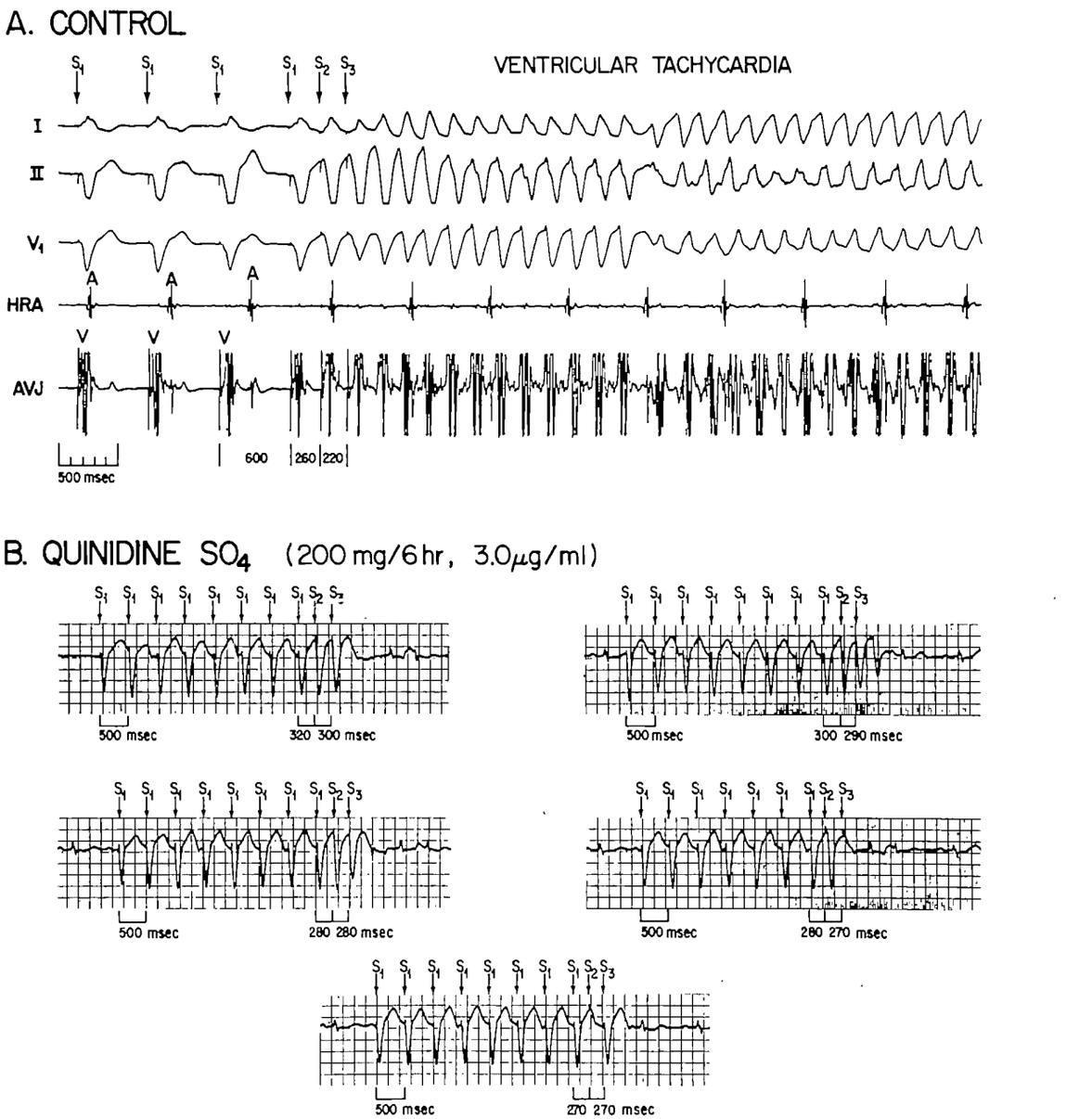



**FIGURE 1.** Response to quinidine in a patient with VT. **Panel A,** the tracings (**top to bottom**) represent surface electrocardiographic leads I, II, and $V_1$, and intracardiac recordings from the high right atrium (HRA) and the atrioventricular junction (AVJ). Two ventricular extrastimuli ($S_2$ and $S_3$) during fixed rate ventricular pacing at a cycle length ($S_1$-$S_1$) of 600 ms initiate sustained ventricular tachycardia. **Panel B,** all tracings represent surface electrocardiographic lead II. During quinidine therapy multiple attempts to initiate VT with double extrastimuli are unsuccessful and stimulation with shorter coupling intervals is impossible. Similar responses were noted to double extrastimuli at other basic cycle lengths and to bursts of rapid ventricular pacing (see Methods).

rhythmia by programmed ventricular stimulation. The mean serum concentration in the group of nonresponders was 2.8 ± 1.1 μg/ml and, as shown in Figure 2, the distribution of quinidine serum concentrations resembled that seen in those patients who responded to the drug. The effect of quinidine on the rate of induced VT observed is shown in Figure 3. Quinidine produced a modest decrease in the mean tachycardia rate from 222 ± 35 (mean ± standard deviation) to 196 ± 54 beats/min ($p < 0.001$). However, there was wide individual variation in the responses observed with changes of −120 to +60 beats/min noted in the rates of VT during therapy with quinidine. In 3 patients in whom a uniform morphology VT was initiated at the time of initial EP study, a more rapid polymorphic VT that degenerated rapidly to VF was observed during therapy with quinidine. In all 3 patients, serum quinidine concentrations were <3.0 μg/ml and none had markedly prolonged QRS durations or Q-Tc intervals (see Methods).

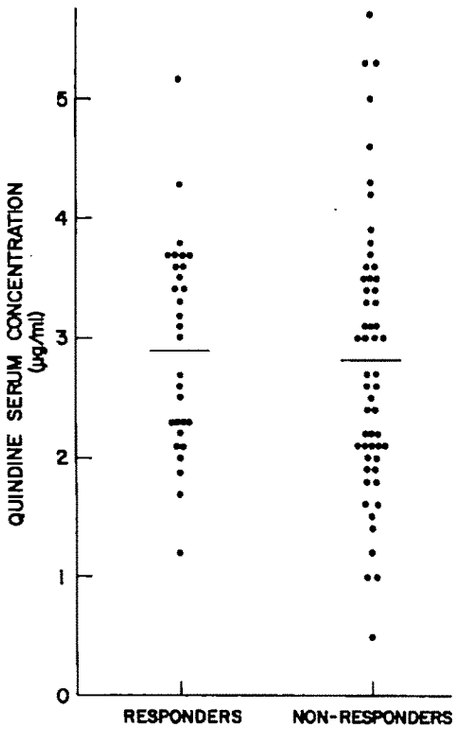



**FIGURE 2.** Quinidine serum concentrations in responders and nonresponders. **Each point** represents the serum concentration of quinidine in a patient at the time of repeat electrophysiologic study or failure before restudy. Only the highest concentration achieved is plotted for patients tested twice on different dosages.

**TABLE III Characteristics of Quinidine Responders and Nonresponders**

| | Responders (n = 30) | Nonresponders (n = 56) | p Value |
|---|---|---|---|
| LV ejection fraction (%)* | 53 ± 18 | 35 ± 17 | <0.002 |
| Digitalis therapy | 6/30 (20%) | 34/56 (61%) | <0.002 |
| Δ ERP RV (ms) | +35 ± 23 | +33 ± 22 | NS |
| Quinidine dose† (mg day$^{-1}$) | 1,053 ± 309 | 1,104 ± 300 | NS |
| Quinidine serum concentration (μg/ml) | 2.9 ± 0.8 | 2.8 ± 1.1 | NS |

* Determined by either radionuclide angiography or contrast left ventriculography. † Expressed as quinidine base. Δ ERP RV = change in effective refractory period at the right ventricular stimulation site; NS = not significant. All values are mean ± standard deviation.

**TABLE IV Results of Chronic Therapy**

| | Responders | | Nonresponders* | |
|---|---|---|---|---|
| Response During EP Study | Quin Alone | Quin and 2nd AAD | Quin Alone | Quin and 2nd AAD |
| Alive and well | 25 | 7 | 1 | 3 |
| Late VT or VF | 2 | 1 | 1 | 5 |
| Late adverse effects | 3 | 0 | 0 | 0 |

* Nonresponders during electrophysiologic (EP) testing on an antiarrhythmic regimen using quinidine who were discharged on that regimen when no effective regimen could be identified. AAD = antiarrhythmic drug; Quin = quinidine.

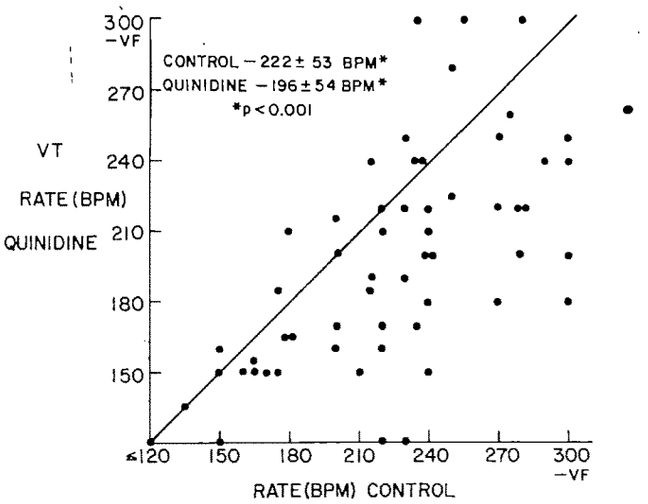



**FIGURE 3.** Effect of quinidine on VT rate. The **horizontal axis** represents the rate of VT observed at the initial study and the **vertical axis** represents the rate of the tachycardia during quinidine therapy. Although the usual effect was a decrease in tachycardia rate (points below the line of identity), in some patients acceleration was the observed effect (points above the line of identity).

Seven of the 31 patients (23%) tested at a second dosage level of quinidine responded to the increased dose. In all 7 the quinidine serum concentration had been ≤1.5 μg/ml (initial, 1.3 ± 0.2; final, 3.4 ± 0.9) at the time of the first trial. In the remaining 24 patients who underwent stimulation on 2 different dosage regimens, a higher serum concentration of quinidine at the second study (2.0 ± 0.5 versus 2.9 ± 1.1 μg/ml) did not increase drug efficacy. In the entire series there were 6 patients in whom serum concentrations ≥1.5 μg/ml could not be achieved without severe gastrointestinal adverse effects. This precluded higher dose therapy in these 6 patients and they are considered nonresponders.

**Combinations with other antiarrhythmic drugs:** Thirty-five patients who did not respond to quinidine alone were subsequently tested while receiving quinidine in combination with 1 or more antiarrhythmic drugs. Either mexiletine, propranolol, or amiodarone was the second drug used. Seven patients responded to a combination of quinidine and mexiletine and 1 patient's arrhythmia was suppressed with a combination of quinidine and propranolol during electrophysiologic testing.

**Characteristics of responders and nonresponders:** Table III compares the 30 patients who responded to quinidine alone with the 56 patients in whom quinidine therapy did not suppress spontaneous or stimulation-induced VT. The 3 patients with early adverse effects who did not undergo electrophysiologic testing while receiving quinidine are excluded. Quinidine produced a similar increase in the effective refractory period of the right ventricle in both groups. There was no significant difference between the 2 groups in either the dose of quinidine administered or the serum concen-

trations achieved. However, responders did have significantly higher left ventricular ejection fractions and were less likely to be receiving digitalis therapy than were nonresponders. Since in almost all cases digitalis therapy was used for the treatment of congestive heart failure, our data are insufficient to examine these 2 variables separately. However, serum digoxin levels were monitored during quinidine therapy; in only 1 case was a concentration >2.0 ng/ml detected.

**Results during chronic therapy (Table IV):** Chronic therapy with quinidine, either alone (30 patients) or in conjunction with a second antiarrhythmic drug (8 patients), was initiated in 38 patients whose arrhythmias were suppressed during programmed ventricular stimulation while receiving quinidine. The long-term results of this therapy are given in Table IV. Twenty-five of 30 patients receiving quinidine alone and 7 of 8 patients receiving quinidine in combination with another agent have remained free of VT, VF, or syncope during a mean follow-up of 24 ± 3 months. Three patients had adverse effects (severe diarrhea in 2 patients and fever in 1 patient) that necessitated discontinuation of quinidine therapy. Two patients receiving quinidine alone and 1 patient receiving quinidine in conjunction with mexiletine died suddenly during the follow-up period. These 3 deaths occurred 1, 3, and 12 weeks after hospital discharge. One of these 3 patients had stable but severe left ventricular dysfunction and the other 2 had severe angina and were awaiting coronary artery bypass surgery.

Ten patients whose inducible arrhythmias were not fully suppressed on any medical regimen tested were discharged on quinidine therapy. Eight received quinidine in combination with other agents while 2 received quinidine alone. Six of these 10 patients (60%) have had a recurrent symptomatic episode of VT or VF during the follow-up period.

If patients with adverse effects during chronic therapy are excluded, the results of programmed cardiac stimulation are seen to be highly predictive of long-term efficacy. When quinidine prevented the initiation of VT or VF during electrophysiologic testing, it subsequently proved effective during chronic therapy in 32 of 35 patients. In contrast, when quinidine therapy was predicted by electrophysiologic testing to be ineffective, only 4 of 10 patients remained free of symptomatic arrhythmia. The difference between these groups is highly significant ($p < 0.002$ by Fisher's test).

## Discussion

An evaluation of the acute phase efficacy of any form of antiarrhythmic therapy requires a reproducible end point that bears a direct relation to the goal of therapy. The suppression of the ability to initiate VT by means of programmed ventricular stimulation has been shown previously to predict future protection from recurrent ventricular arrhythmias.[5,8,9] In this study, serial electrophysiologic testing was employed to assess the efficacy of quinidine in the treatment of selected patients with serious ventricular arrhythmias. Our results demonstrate that 30 of 89 (34%) patients with VT at their initial electrophysiologic study failed to manifest any ventricular arrhythmia in response to programmed ventricular stimulation while receiving quinidine. In an additional 8 patients, full suppression was achieved when quinidine was used in combination with a second antiarrhythmic agent. Thus, on the basis of acute electrophysiologic testing, quinidine was predicted to provide or contribute to long-term protection from recurrent VT or VF in 38 of 89 (43%) consecutive patients in whom it was tested. Over a mean of 24 months clinical follow-up, 32 of these 38 (84%) patients were successfully treated, while failures occurred in 3 (7.9%) patients with intolerable adverse effects and 3 (7.9%) with recurrent arrhythmias.

Two previous series involving the use of programmed ventricular stimulation in patients with ventricular arrhythmias have included a group of patients studied while receiving quinidine. Horowitz et al[8] reported quinidine effective in 1 of 12 patients, while Mason and Winkle[9] reported that 5 of 14 patients (36%) responded favorably to the drug. Details correlating drug levels with efficacy are unavailable from these reports and some patients received only a single loading intravenous infusion before repeat programmed ventricular stimulation was performed. Several other studies have reported quinidine's efficacy in suppressing either spontaneous or exercise-induced ventricular ectopic activity. In 2 separate reports, Lown et al[10,11] reported that short-term administration of quinidine was effective in 7 of 23 and 10 of 18 patients with frequent or complex ventricular premature beats, respectively, for a combined success rate of 41% (17 of 41 patients). Gey et al,[12] using a single oral loading dose, found that quinidine was "partially or totally successful" in 9 of 19 patients with ventricular ectopic activity during exercise testing. Winkle et al[13] examined the effects of quinidine on ventricular ectopy and found quinidine to be effective in 8 of 13 patients during ambulatory monitoring and in 6 of 10 patients during exercise testing. However, as discussed by Winkle,[14] there are problems in the assessment of antiarrhythmic drug efficacy using such techniques due to the low reproducibility of arrhythmia on successive recordings during serial exercise or ambulatory monitoring periods. This factor limits the practical utility of the estimates made in the studies cited above. Responses to programmed ventricular stimulation during serial drug testing are highly reproducible,[15] and drug effects may be reliably assessed using this form of testing. In this series, when electrophysiologic techniques were used in a large group of patients, the efficacy rate of quinidine was comparable to that reported with other techniques[8–12] and the data obtained accurately predicted the outcome of chronic therapy.

The quinidine serum concentrations required to produce suppression of VT during repeat ventricular stimulation ranged from 1.2 to 5.1 μg/ml (2.9 ± 0.8, mean ± standard deviation). Ninety percent of the values were between 1.5 and 4.0 μg/ml, and all but 1 of the patients treated successfully during chronic follow-up were within this range. The fluorometric assay employed in this study yields results comparable to highly specific chromatographic techniques.[7,16] Thus,

these data may be used to define an approximate "therapeutic range" for quinidine in patients with VT or VF unassociated with acute myocardial infarction. However, if a less specific assay which includes other quinidine metabolites, such as the protein precipitation method of Brodie et al[17] or a less selective extraction procedure is employed, a higher range would have to be established for that particular laboratory. Previous investigators using a variety of criteria for antiarrhythmic efficacy reported similar mean levels in their patient groups with either atrial[18,19] or ventricular[20–22] arrhythmias; at least 2 reports observed that serum levels seen in responders and nonresponders were comparable.[21,22] These data confirm that antiarrhythmic drug therapy must be individualized for each patient. The success rate of only 30 to 40% observed in this series should serve to caution physicians initiating antiarrhythmic therapy with quinidine to define carefully criteria for efficacy and to anticipate that only a minority of individual patient trials are likely to be successful.

Recently, Engel et al[23] and Greenspan et al[24] reported that high dose procainamide therapy may achieve control of ventricular arrhythmias resistant to traditional therapy with that drug. Acute toxicity was not markedly increased. During therapy with quinidine, however, gastrointestinal side effects may become more prominent with even modest increases in dosage and added benefits from high dose programs may be difficult to achieve. However, there may be some patients able to tolerate such therapy in whom arrhythmia suppression can be maintained without toxicity.

The results of this study do not allow us to predict with certainty which patients with ventricular arrhythmias will respond to quinidine. Patients with congestive heart failure seem less likely to respond. This may be related to the concurrent use of digoxin in these patients even though serum digoxin concentrations were within the accepted therapeutic range. At the concentrations employed in this series of patients, quinidine has not been shown to affect myocardial contractility adversely.[25] The presence of heart failure, however, is a frequently noted determinant of an adverse prognosis in patients with ventricular arrhythmias[26–28]; it is possible that the electrophysiologic abnormalities in patients with ventricular dysfunction are more resistant to any pharmacologic therapy. Other factors may also affect the results of antiarrhythmic therapy. In this series, 2 patients without signs of congestive heart failure experienced a fatal arrhythmia in the setting of unstable angina pectoris despite arrhythmia suppression during acute electrophysiologic testing. These observations emphasize the fact that the severity of the underlying cardiac disease remains a critical determinant of both acute and chronic responses to therapy for ventricular arrhythmias and effective therapy must always be directed at multiple factors.

Prescription of antiarrhythmic therapy requires the use of appropriate criteria to predict long-term antiarrhythmic efficacy. The correlation demonstrated in this study between responses during electrophysiologic testing and clinical efficacy during long-term follow-up confirms the value of such studies in the prescription of prophylactic antiarrhythmic drug therapy with quinidine. When its use is guided by these techniques, quinidine remains a useful agent for long-term prophylaxis in selected patients with recurrent, life-threatening ventricular arrhythmias.

## References


1. **Willius FA, Keys TE.** Cardiac Clinics XCIV. A remarkably early reference to the use of cinchona in cardiac arrhythmia. Proc Staff Meet Mayo Clinic 1942;17:294–296.
2. **Bigger JT, Hoffman BF.** Antiarrhythmic drugs. In: Gilman AG, Goodman LS, Gilman A, eds. The Pharmacologic Basis of Therapeutics. 6th ed. New York: Macmillan Publishing, 1980:761–792.
3. **Singh BN, Mandel WJ.** Antiarrhythmic drugs: basic concepts of their actions, pharmacokinetic characteristics and clinical applications. In: Mandel WJ, ed. Cardiac Arrhythmias. Philadelphia: JB Lippincott, 1980:550–588.
4. **Ruskin JN, DiMarco JP, Garan H.** Out-of-hospital cardiac arrest: electrophysiologic observations and selection of long-term antiarrhythmic drug therapy. N Engl J Med 1981;303:607–613.
5. **DiMarco JP, Garan H, Harthorne JW, Ruskin JN.** Intracardiac electrophysiologic techniques in recurrent syncope of unknown cause. Ann Intern Med 1981;95:542–548.
6. **Cramer G, Isaksson B.** Quantitative determination of quinidine in plasma. Scand J Clin Lab Invest 1963;15:553–556.
7. **Greenblatt DJ, Pfeifer HJ, Ochs HR, Franke K, MacLaughlin DS, Smith TW, Koch-Weser J.** Pharmacokinetics of quinidine in humans after intravenous, intramuscular and oral administration. J Pharmacol Exp Ther 1977;202:365–378.
8. **Horowitz LN, Josephson ME, Farshidi A, Spielman SR, Michelson EL, Greenspan AM.** Recurrent sustained ventricular tachycardia. 3. Role of the electrophysiologic study in selection of antiarrhythmic regimens. Circulation 1978;58:986–997.
9. **Mason J, Winkle RA.** Electrode-catheter arrhythmia induction in the selection and assessment of antiarrhythmic drug therapy for recurrent ventricular tachycardia. Circulation 1978;58:971–985.
10. **Jelinek MV, Lohrbauer L, Lown B.** Antiarrhythmic drug therapy for sporadic ventricular ectopic arrhythmias. Circulation 1974;49:659–666.
11. **Gaughan CE, Lown B, Lanigan J, Voukydis P, Besser HW.** Acute oral testing for determining antiarrhythmic drug efficacy. I. Quinidine. Am J Cardiol 1976;38:677–684.
12. **Gey GO, Levy RH, Pettet G, Fisher L.** Quinidine plasma concentration and exertional arrhythmia. Am Heart J 1975;90:19–24.
13. **Winkel RA, Gradman AH, Fitzgerald JW, Bell PA.** Antiarrhythmic drug effect assessed from ventricular arrhythmia reduction in the ambulatory electrocardiogram and treadmill test: comparison of propranolol, procainamide and quinidine. Am J Cardiol 1978;42:473–480.
14. **Winkle RA.** Ambulatory electrocardiography and the diagnosis, evaluation and treatment of chronic ventricular arrhythmias. Prog Cardiovasc Dis 1980;23:99–129.
15. **Ruskin JN, DiMarco JP, Garan H.** Reproducibility of electrophysiologic response to programmed ventricular stimulation during serial drug testing in patients with recurrent ventricular tachycardia (abstr). Am J Cardiol 1981;47:449.
16. **Conrad KA, Molk BL, Chidsey CA.** Pharmacokinetic studies of quinidine in patients with arrhythmias. Circulation 1977;55:1–7.
17. **Brodie BB, Udenfriend S, Baer JE.** Analysis of basic organic compounds in biological tissues. I. Isolation prior to estimation. Fed Proc 1946;5:124–125.
18. **Rossi M, Lown B.** The use of quinidine in cardioversion. Am J Cardiol 1967;19:234–238.
19. **Sodermark T, Edhag O, Sjogren A, Jonsson B, Olsson A, Oro L, Danielsson M, Rosenhamer G, Wallin H.** Effect of quinidine on maintaining sinus rhythm after conversion of atrial fibrillation or flutter. Br Heart J 1975; 37:486–492.
20. **Carliner NH, Crouthamel WG, Fisher WL, Mugmou MA, Vassar DL, Narang PK, Plotnik GD.** Quinidine therapy in hospitalized patients with ventricular arrhythmias. Am Heart J 1976;98:708–715.
21. **Kessler KM, Lowenthal DT, Warner H, Gibson T, Briggs W, Riedenberg MM.** Quinidine elimination in patients with congestive heart failure or poor renal function. N Engl J Med 1974;290:706–709.
22. **Halkin H, Vered A, Millman P, Rabinowitz B, Neufeld HN.** Steady-state serum quinidine concentration: role in prophylactic therapy following acute myocardial infarction. Isr J Med Sci 1979;15:583–587.
23. **Engel TR, Meistler SG, Luck JC.** Modification of ventricular tachycardia by procainamide in patients with coronary artery disease. Am J Cardiol 1980;46:1033–1038.
24. **Greenspan AM, Horowitz LN, Spielman SR, Josephson ME.** Large dose procainamide therapy for ventricular tachyarrhythmia. Am J Cardiol 1980;46:453–462.
25. **Markiewicz W, Winkle RA, Bineth G, Kernoff R, Harrison DC.** Normal myocardial contractile state in the presence of quinidine. Circulation 1976;53:101–106.
26. **Ruberman W, Weinblatt E, Goldberg JD, Frank CW, Chaudhary BS, Shapiro S.** Ventricular premature complexes and sudden death after myocardial infarction. Circulation 1981;64:297–305.
27. **Davis HT, DeCamilla J, Bayer LW, Moss AJ.** Survivorship patterns in the posthospital phase of myocardial infarction. Circulation 1979;60:1252–1258.
28. **Swerdlow CD, Echt DS, Winkle RA, Griffin JC, Ross DL, Mason JW.** Clinical factors predicting antiarrhythmic drug efficacy at electrophysiologic study in patients with ventricular tachycardia (abstr). PACE 1982;5:307.

# Enhanced Parasympathetic Tone Shortens Atrial Refractoriness in Man

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**The purpose of this study was to determine the effects of enhanced vagal tone on human right atrial refractoriness in 12 patients. A specially built neck collar connected to a vacuum source was placed around the patient's neck and enhanced vagal tone was produced during neck suction using intracollar negative pressures of 50 to 60 mm Hg. Refractory periods were determined with a catheter electrode positioned in the high right atrium near the sinus node. Induced neck suction increased the spontaneous sinus cycle length from 837 ± 96 to 1,136 ± 273 ms ($p < 0.001$) and shortened the atrial effective refractory period from 241 ± 24 to 230 ± 20 ms ($p < 0.01$) and the atrial functional refractory period from 272 ± 32 to 262 ± 29 ms ($p < 0.01$). In 2 of 2 patients, collar-induced decreases in atrial refractoriness and increases in spontaneous cycle length were prevented after atropine (0.03 mg/kg) was given intravenously. It is concluded that enhanced vagal tone mediated through muscarinic receptors shortens atrial refractory periods in man.**

Vagal stimulation or the addition of acetylcholine[1–3] shortens atrial refractoriness, action potential duration, or both in rabbit, cat, and dog atria. Further, recent in vitro data[4] in normal human atrial tissue obtained at surgery demonstrate that ouabain shortens the action potential duration, an effect prevented by atropine. This observation suggests that the primary effect of ouabain was mediated through muscarinic receptors.

Because it is difficult to increase vagal tone in vivo without stimulating the vagal nerves directly, studies in patients to evaluate the effects of heightened vagal tone on atrial refractoriness have relied on indirect approaches such as inhibiting vagal tone with atropine or increasing vagal tone with ouabain. In conflict with the aforementioned data obtained during in vitro experiments or during in vivo animal experiments, Dhingra et al demonstrated in man that atropine shortened[5] and ouabain prolonged[6] atrial refractoriness. Interpretation of these results suggests that heightened vagotonia *prolongs* atrial refractoriness in man, a conclusion discordant with the previous data. However, in neither of these studies was the sympathetic nervous system blocked, and the results may have been due in part to the complex interactions of the parasympathetic and sympathetic nervous systems on the heart.[7–9] For example, acetycholine, by activating muscarinic receptors, can cause presynaptic inhibition of norepinephrine release from adrenergic nerves.[9] Atropine might remove vagal inhibition of sympathetic nerves and result in shortened atrial refractoriness due to a relative increase in adrenergic tone.[10] Likewise, ouabain, by increasing the effects of vagal tone on adrenergic nerves or by exerting an antisympathetic effect,[11] might prolong atrial refractoriness. The only certain way to determine the effects of cholinergic stimulation on atrial refractoriness is to increase vagal tone selectively.

Eckberg et al[12] developed a lead collar that can be placed around a patient's neck and through which

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negative pressures can be generated by vacuum suction. Intracollar negative pressure activates the carotid baroreflex and, during the first few seconds of suction, selectively increases vagal tone. Atropine but not propranolol blocks this response.[13,14] The purpose of this study was to investigate the effects on human atrial refractoriness of increased vagal tone induced by neck collar suction.

## Methods

Twelve patients undergoing electrophysiologic study for symptomatic atrioventricular block, ventricular tachyarrhythmias, syncope, or a combination of these (Table I) had atrial refractory periods determined before and during neck collar suction. No patient had a history of sinus nodal dysfunction, atrial arrhythmias, or electrocardiographic or echocardiographic evidence of atrial abnormalities. All had normal sinus nodal function on electrophysiologic testing. All patients were studied in the postabsorptive state and no patient was given sedatives before or during the time of study. No patient had been taking digitalis and all cardioactive medicines were discontinued 48 to 72 hours before the electrophysiologic procedure.

Two to 4 multipolar electrode catheters were inserted intravenously, using percutaneous technique, and positioned in multiple areas in the heart. Local anesthesia was obtained using a minimal amount[15] of 1% xylocaine. Atrial pacing was performed with a quadripolar catheter advanced to the heart from the right femoral vein. The interelectrode distance was 10 mm; the distal electrode pair was used for pacing and the proximal pair for recording atrial electrograms. In 11 of 12 patients, the distal electrode pair of the catheter used to determine atrial refractoriness was positioned near the area of the sinus node in the high right atrium at the junction of the atrium and superior vena cava, an area shown to have substantial parasympathetic innervation.[3,16,17] A stable catheter position near the sinus node could not be obtained for Patient 5 and the catheter was positioned in the high medial right atrium near the septum. A programmable stimulator (Medtronic 5325) delivered square wave stimuli 1.8 ms duration and twice late diastolic threshold. Data from multiple surface and intracardiac leads were displayed on a multichannel oscilloscopic recorder (Electronics for Medicine VR 12) and directly written out on photographic paper at 100 mm/s. Signals from the electrocardiographic surface leads were filtered at 0.1 to 20 Hz and from the intracardiac leads at 30 to 500 Hz.

**Enhanced vagal tone:** To assess the effects of reflex vagal stimulation (enhanced vagal tone) on atrial refractoriness and sinus nodal automaticity, a specially built neck suction device was used.[12] This device was constructed from lead stock and can be molded to fit subjects with different cervical anatomy. One line from the neck chamber connects to a vacuum source and one connects to a pressure gauge. The chamber was placed around the patient's neck and the degree of suction from the vacuum source was adjusted to produce neck suction at intracollar negative pressures of 50 to 60 mm Hg.

The vacuum source was turned on and kept at a constant level throughout the study but not connected to the patient. The patients were instructed to keep their mouths open during neck suction to prevent an inadvertent Valsalva maneuver. Intracollar negative pressure was obtained by manually opening a valve that connected the vacuum source to the neck collar; steady-state intracollar negative pressure occurred within 1 second after the valve was opened. The valve was then closed to remove intracollar negative pressure. Durations of neck suction were 2 seconds for sinus nodal testing and 2 to 3 seconds for atrial refractory period testing. It is important to note that previous data obtained by us[14] and others[13] demonstrate that during the first 3 seconds of neck suction increased vagal tone but not sympathetic withdrawal occur due to carotid baroreflex activation.

**TABLE I Patient Characteristics**

| Patient | Age (yr) & Sex | Cardiovascular Disease | Clinical Arrhythmias |
|---|---|---|---|
| 1 | 58M | PED | RMVT[23] |
| 2 | 51M | CAD | Nonsustained VT |
| 3 | 41F | MVP | Nonsustained VT |
| 4 | 65M | PED | Sustained VT |
| 5 | 33M | PED | Type I AV block |
| 6 | 15M | PED | Type I AV block |
| 7 | 52F | CAD | RBBB, LAFB |
| 8 | 52M | CM | VT/VF |
| 9 | 40M | CM | Nonsustained VT |
| 10 | 44F | PED | Syncope |
| 11 | 61F | PED | RMVT |
| 12 | 42M | CM | Nonsustained VT |

AV = atrioventricular; CAD = coronary artery disease; CM = idiopathic cardiomyopathy; LAFB = left anterior fascicular block; MVP = mitral valve prolapse; PED = primary electrical disease; RBBB = right bundle branch block; RMVT = repetitive monomorphic ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

The effect of intracollar negative pressure, induced for 2 seconds, on spontaneous sinus cycle length was obtained 3 times in each patient before atrial pacing. Then, atrial refractoriness was determined before and during neck suction by the following technique. The atria were paced at a constant cycle length ($S_1$-$S_1$) throughout refractory period testing and the drive train was not interrupted even after induced premature stimuli.[18] Thus, changes in heart rate that can affect refractoriness were avoided. After 30 seconds of pacing, premature stimuli ($S_2$) were induced after every eighth paced complex beginning with an $S_1$-$S_2$ interval initially too short to result in atrial depolarization. The $S_1$-$S_2$ interval was increased by 5 ms increments until $S_2$ produced an atrial response. The $S_1$-$S_2$ interval was increased further until the shortest $A_1$-$A_2$ interval was determined. Then, the effects of enhanced vagal tone on atrial refractoriness were evaluated. The $S_1$-$S_2$ interval was set at the longest premature interval at which $S_2$ tested 3 times did not result in an atrial depolarization. This $S_1$-$S_2$ interval was tested a fourth time, but 2 to 3 seconds before $S_2$ intracollar negative pressure was activated. If $S_2$ resulted in atrial depolarization during neck suction, the same $S_1$-$S_2$ interval was tested 3 additional times without induced neck suction to make sure that atrial capture during neck suction was not due to a change in the baseline atrial refractoriness. The premature coupling interval was decreased by 5 ms and tested 3 times before neck suction, during neck suction, and again 3 times after neck suction. This procedure was repeated at 5 ms $S_1$-$S_2$ decrements until an $S_1$-$S_2$ interval occurred that did not result in atrial depolarization on 3 attempts before and during induced neck suction. Thus, each $S_1$-$S_2$ interval was tested 6 times without neck suction and at least once with neck suction.

The control atrial effective refractory period was the longest $S_1$-$S_2$ interval at which $S_2$ consistently resulted in no atrial depolarization during the 6 times it was tested without neck suction. Atrial effective refractory period during neck suction was the longest $S_1$-$S_2$ interval at which $S_2$ on 3 consecutive attempts did not result in atrial depolarization. The atrial functional refractory period was defined as the shortest ob-

tainable $A_1$-$A_2$ interval during control or enhanced vagal tone. The paired $t$ test was used to analyze changes in sinus cycle length and atrial refractoriness before and after neck suction, and the data are reported as mean ±1 standard deviation.

## Results

During induced intracollar negative pressure, enhanced vagal tone prolonged the spontaneous sinus cycle length; for each patient the longest P-P interval obtained is shown in Table I. The maximum increase in P-P interval always was observed during the first 2 seconds of induced neck suction. For all patients except Patients 6, 7, and 10, spontaneous cycle length increased more than 20%, and the group cycle length was prolonged from 837 ± 96 to 1136 ± 273 ms (36%).

Enhanced vagal tone shortened atrial effective and functional refractory periods in 9 of 12 patients; in no patient was refractoriness increased (Table II, Fig. 1). For all patients, atrial effective refractory period was 241 ± 24 ms before and 230 ± 20 ms during induced intracollar negative pressure ($p < 0.01$). Atrial functional refractory period shortened during neck suction from 272 ± 32 to 262 ± 29 ms ($p < 0.01$). Atrial refractoriness did not change in Patients 5, 6, and 7. Patients 6 and 7 also had minimal increases in spontaneous cycle length during induced neck suction. Patient 5 was the only patient whose atrial pacing site was not near the area of the sinoatrial node.

Two patients received atropine intravenously (0.03 mg/kg) (Elkins-Sinn) and atrial refractoriness was retested using the same pacing cycle length. During atropine administration, induced intracollar negative pressure did not decrease refractoriness as it did in the control state. Furthermore, after atropine, neck suction had no effect on spontaneous cycle length.

## Discussion

This study demonstrates that atrial effective and functional refractory periods decrease in man during enhanced vagal tone, and supports previously published data in animals and in vitro data from human atria. To augment parasympathetic tone, we used a specially designed neck suction device.[12] Using this device, Eckberg et al[19] showed that during neck suction the first significant decrease in systolic arterial blood pressure occurred at 3 seconds and diastolic pressure fell at 2 seconds. During atrial pacing, we measured intraarterial

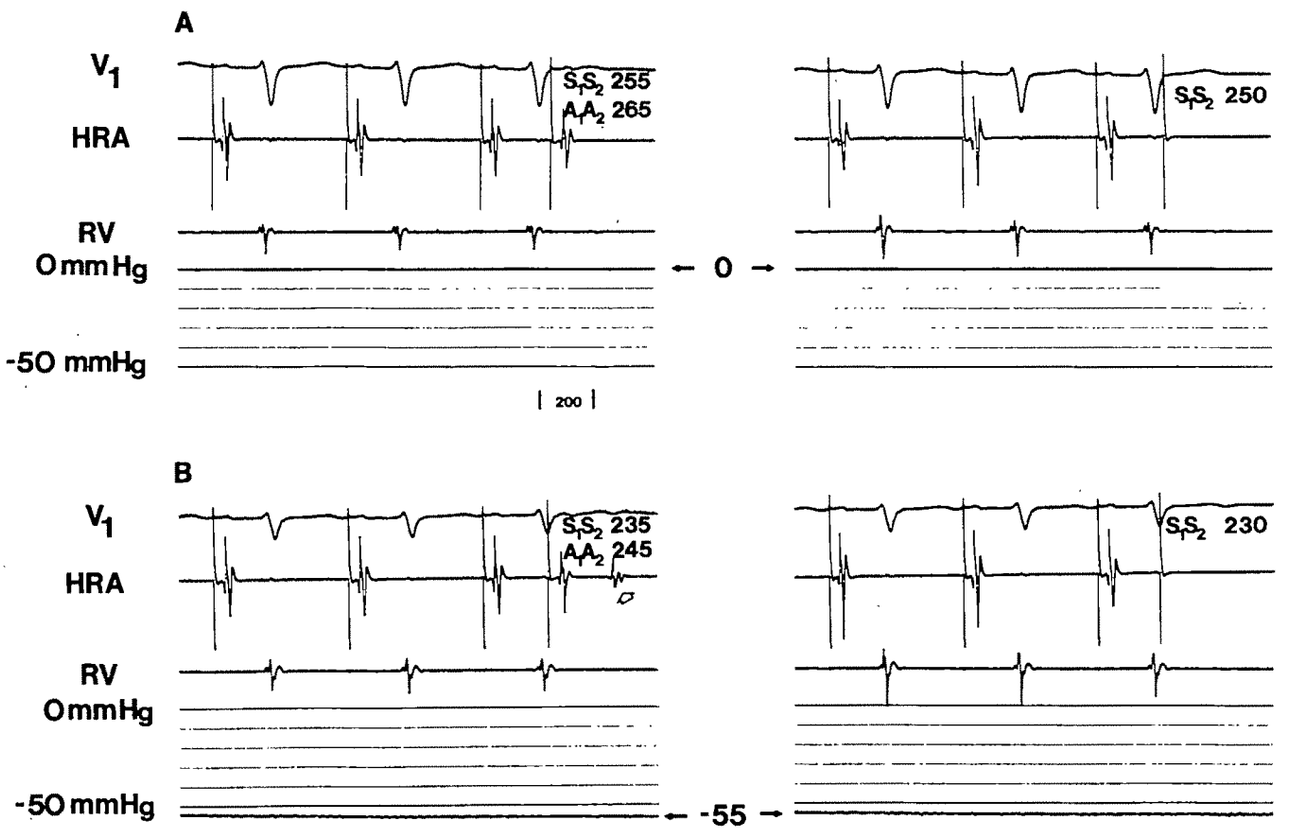



**FIGURE 1.** Change in atrial refractoriness during enhanced vagal tone. Atrial refractory period determinations were made before (**A**) and during (**B**) induced neck suction. Atrial effective and functional refractory periods were 250 and 265 ms, respectively, and shortened during neck suction (−55 mm Hg) to 230 and 245 ms, respectively. Note the repetitive atrial response (**arrow**) induced during neck suction. For all panels, the upper 3 recordings are standard electrocardiographic lead $V_1$ and intracardiac electrograms from the high right atrium (HRA) and right ventricle (RV). Intracollar pressure is noted on the bottom of the panels by the **heavy black line.**

**TABLE II Effect of Enhanced Vagal Tone on Spontaneous Cycle Length and Atrial Refractoriness (ms)**

| | Spontaneous Cycle Length | | | Atrial ERP | | Atrial FRP | |
|---|---|---|---|---|---|---|---|
| Patient | Control | EVT | PCL | Control | EVT | Control | EVT |
| 1 | 920 | 1,740 | 500 | 250 | 230 | 265 | 245 |
| 2 | 780 | 1,420 | 500 | 220 | 210 | 255 | 250 |
| 3 | 770 | 950 | 500 | 230 | 220 | 240 | 225 |
| 4 | 950 | 1,280 | 600 | 290 | 260 | 340 | 320 |
| 5 | 780 | 1,210 | 400 | 235 | 235 | 260 | 260 |
| 6 | 850 | 950 | 700 | 220 | 220 | 270 | 270 |
| 7 | 720 | 800 | 600 | 220 | 220 | 260 | 260 |
| 8 | 950 | 1,150 | 600 | 265 | 255 | 320 | 300 |
| 9 | 900 | 1,160 | 700 | 265 | 255 | 280 | 275 |
| 10 | 660 | 730 | 500 | 250 | 235 | 265 | 260 |
| 11 | 930 | 1,140 | 500 | 235 | 220 | 280 | 260 |
| 12 | 830 | 1,100 | 600 | 210 | 195 | 225 | 215 |
| Mean | 837 | 1,136 | ... | 241 | 230 | 272 | 262 |
| ± 1 SD | ±96 | ±273 | | ±24 | ±20 | ±32 | ±29 |
| p Value | <0.001 | | | <0.01 | | <0.01 | |

ERP = effective refractory period; EVT = enhanced vagal tone; FRP = functional refractory period; PCL = pacing cycle length; SD = standard deviation.

pressure in 2 patients through a cannula connected to a strain gauge pressure transducer; our results agreed with those of Eckberg et al.[19] Since it takes several seconds after hypotension for reflex autonomic changes to affect cardiac function,[20] the changes in atrial refractoriness induced during 2 to 3 seconds of neck suction did not result from an increase in reflex sympathetic tone. Additionally, previous data[13,14] demonstrate that atropine, but not propranolol, blocks the prolonged P-P interval that occurs during the first few seconds of induced neck suction.

Two additional observations indicate that the changes observed during neck suction were caused by increased vagal tone. First, neck suction caused no change in heart rate or atrial refractoriness in 2 of 2 patients after atropine was administered. Second, if enhanced reflex sympathetic tone, rather than parasympathetic tone, shortened atrial refractoriness during neck suction for ≤3 seconds, one would expect atrial refractoriness to shorten during more prolonged neck suction because of the time course of the sympathetic response. However, when neck suction was initiated 5 seconds before the premature atrial complex, atrial refractoriness usually did not change from control values. The inability to shorten atrial refractoriness during prolonged neck suction is more consistent with a cholinergic rather than an adrenergic response. Vagal tone during neck suction progressively decreases over time. The decrease in enhanced vagal tone during prolonged neck suction is consistent with the observation of Eckberg et al,[21] who showed that neck suction produced an initial decrease in heart rate that gradually returned to control values within 5 seconds.

The failure of enhanced vagal tone to shorten atrial refractoriness in Patient 5 may relate to the medial right atrial pacing site tested. Parasympathetic nerve terminals predominate in the area around the sinus node,[17] and Zipes et al[3] showed in the dog that vagal stimulation shortened atrial refractoriness at the sinus nodal area more than at any other atrial site. Since neck suction produced enhanced vagal tone in Patient 5, as demonstrated by a significant decrease in heart rate, it is reasonable to postulate that the inability of enhanced vagal tone to shorten atrial refractoriness in this patient may have occurred because the atrial site tested had relatively little parasympathetic innervation.

The differences between our results and the results obtained using atropine[5] may be explained in part by the complex interactions on the heart exerted by the parasympathetic and sympathetic nervous systems.[7–9] In particular, acetylcholine, by activation of muscarinic receptors, can cause presynaptic inhibition of release of norepinephrine from adrenergic nerves.[9] Since isoproterenol shortens human atrial refractoriness (unpublished results), the effect of atropine administration may depend on the baseline level of adrenergic and vagal tone, and on the amount of presynaptic vagal inhibition. If both substantial presynaptic inhibition and sympathetic tone are present, the overall effect of atropine might be to shorten atrial refractoriness. If minimal presynaptic inhibition and sympathetic tone are present, atropine might lengthen atrial refractoriness by reversing the direct (postsynaptic) effect of acetylcholine on atrial tissue. Of note, in the 2 patients given atropine, atrial refractoriness increased in 1 and decreased in the other.

Three patients demonstrated repetitive atrial responses to a single induced premature atrial complex, and repetitive atrial responses occurred only during enhanced vagal tone (Fig. 1). Induction of atrial fibrillation during atrial refractory period determination in man often is preceded by repetitive atrial responses, although atrial fibrillation did not occur in these patients. This potential arrhythmogenic consequence of enhanced vagal tone in man agrees with the well-known effect of heightened parasympathetic tone in facilitating atrial arrhythmias in animals. Alternatively, the induced repetitive atrial complexes in our patients may result from the shortened atrial functional refractory period.[22]

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## References


1. **Prystowsky EN, Grant AO, Wallace AG, Strauss HC.** An analysis of the effects of acetylcholine on conduction and refractoriness in the rabbit sinus node. Circ Res 1979;44:112–120.
2. **Burgen ASV, Terroux KG.** On the negative inotropic effect in the cat's auricle. J Physiol 1953;120:449–464.
3. **Zipes DP, Mihalick MJ, Robbins GT.** Effects of selective vagal and stellate ganglion stimulation on atrial refractoriness. Cardiovasc Res 1974;8: 647–655.
4. **Hordof AJ, Spotnitz A, Mary-Rabine L, Edie RN, Rosen MR.** The cellular electrophysiologic effects of digitalis on human atrial fibers. Circulation 1978;57:223–229.
5. **Dhingra RC, Amat-Y-Leon F, Wyndham C, Denes P, Wu D, Pouget JM, Rosen KM.** Electrophysiologic effects of atropine on human sinus node and atrium. Am J Cardiol 1976;38:429–434.
6. **Dhingra RC, Amat-Y-Leon F, Wyndham C, Wu D, Denes P, Rosen KM.** The electrophysiological effects of ouabain on sinus node and atrium in man. J Clin Invest 1975;56:555–562.
7. **Levy MN.** Sympathetic-parasympathetic interactions in the heart. Circ Res 1971;29:437–445.
8. **Watanabe AM, Besch HR.** Interaction between cyclic adenosine monophosphate and cyclic guanoside monophosphate in guinea pig ventricular myocardium. Circ Res 1975;37:309–317.
9. **Vanhoutte PM, Levy MN.** Prejunctional cholinergic modulation of adrenergic neurotransmission in the cardiovascular system. Am J Physiol 1980;238: H275–H281.
10. **Kralios FA, Millar CK.** Sympathetic neural effects on regional atrial recovery properties and cardiac rhythm. Am J Physiol 1981;240:H590–H596.
11. **Mendez C, Aceves J, Mendez R.** Inhibition of adrenergic cardiac acceleration by cardiac glycosides. J Pharmacol Exp Ther 1961;131:191–198.
12. **Eckberg DL, Cavanaugh MS, Mark AL, Abboud FM.** A simplified neck suction device for activation of carotid baroreceptors. J Lab Clin Med 1975;85:167–173.
13. **Eckberg DL.** Adrenergic-cholinergic baroreceptor interactions in man. In: Schwartz PJ, Brown AM, Malliani A, Zanchetti A, eds. Neural Mechanisms in Cardiac Arrhythmias. New York: Raven Press, 1978:335–338.
14. **Prystowsky EN, Jackman WM, Naccarelli GV, Rahilly GT, Heger JJ, Zipes DP.** Analysis of the effects of autonomic blockade on "post-vagal" tachycardia in man. Circulation 1981;64:Suppl IV:IV-239.
15. **Nattel S, Rinkenberger RL, Lehrman LL, Zipes DP.** Therapeutic blood lidocaine concentrations after local anesthesia for cardiac electrophysiologic studies. N Engl J Med 1979;301:418–420.
16. **Alessi R, Nusynowitz M, Abildskov JA, Moe GK.** Non-uniform distribution of vagal effects on atrial refractory period. Am J Physiol 1958;194:406–410.
17. **James TN, Spence CA.** Distribution of cholinesterase within the sinus node and AV node of the human heart. Anat Rec 1966;155:151–162.
18. **Prystowsky EN, Jackman WM, Rinkenberger RL, Heger JJ, Zipes DP.** Effect of autonomic blockade on ventricular refractoriness and atrioventricular nodal conduction in man. Evidence supporting a direct cholinergic action on ventricular muscle refractoriness. Circ Res 1981;49:511–518.
19. **Eckberg DL, Abboud RM, Mark AL.** Modulation of carotid baroreflex responsiveness in man: effects of posture and propranolol. J Appl Physiol 1976;41:383–387.
20. **Pickering TG, Gribbin B, Sleight P.** Comparison of the reflex heart rate response to rising and falling arterial pressure in man. Cardiovasc Res 1972;6:277–283.
21. **Eckberg DL.** Adaptation of the human carotid baroreceptor-cardiac reflex. J Physiol 1977;269:579–589.
22. **Wyndham CRC, Amat-Y-Leon F, Wu D, Denes P, Dhingra R, Simpson R, Rosen KM.** Effects of cycle length atrial vulnerability. Circulation 1977; 55:260–267.
23. **Rahilly GT, Prystowsky EN, Zipes DP, Naccarelli GV, Jackman WM, Heger JJ.** Clinical and electrophysiologic findings in patients with repetitive monomorphic ventricular tachycardia and otherwise normal electrocardiograms. Am J Cardiol 1982;50:459–468.

# Effect of Local Lidocaine Anesthesia on Ventricular Escape Intervals During Permanent Pacemaker Implantation In Patients With Complete Heart Block

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**Transient asystole is often noted during the course of permanent pacemaker implantation in patients with complete heart block. Since subcutaneous lidocaine is frequently used as the local anesthetic agent for permanent pacemaker implantation, the effect of this drug on ventricular escape intervals was studied. Ventricular escape intervals after transient cessation of pacing were studied in 9 patients with complete heart block before and 10, 30, and 45 minutes after subcutaneous lidocaine administration for permanent pacemaker implantation. The total lidocaine dose ranged from 170 to 400 mg (1.9 to 9.5 mg/kg of body weight). Therapeutic blood levels were achieved in 7 patients. The mean ventricular escape interval before lidocaine was 1.83 ± 0.32 seconds, which increased to 2.58 ± 1.24, 2.96 ± 1.06, and 2.68 ± 1.27 seconds at 10, 30, and 45 minutes after lidocaine ($p < 0.02$). The mean maximal escape interval before lidocaine was 2.06 ± 0.30 seconds, which increased to 3.80 ± 1.44 seconds ($p < 0.01$), a mean increase of 84%. The percent increase in maximal escape interval was related directly to the peak lidocaine level achieved. After lidocaine administration, 5 patients had asystole >4 seconds and 1 required resumption of pacing.**

**Thus, subcutaneous lidocaine contributes to the occurrence of asystole seen during permanent pacemaker implantation. It is advisable to limit the amount of lidocaine administered during permanent pacemaker implantation to the minimum necessary to achieve adequate local anesthesia. Strong consideration should be given to the use of a temporary pacemaker in patients with complete heart block during permanent pacemaker implantation even in the absence of previous asystole.**

Transient asystole is often noted during the course of permanent pacemaker implantation in patients with complete heart block. Asystole may occur when temporary pacing is momentarily halted for the measurement of pacing or sensing thresholds, even in patients who did not demonstrate pacer dependency before the procedure.

Subcutaneous lidocaine is frequently used as the anesthetic agent for permanent pacemaker implantation, and therapeutic blood concentrations of lidocaine have been demonstrated in patients in whom this agent is used for local anesthesia.[1] To assess whether lidocaine is responsible for the occurrence of asystole during pacemaker implantations, we studied the effects of the subcutaneous use of this drug upon serum lidocaine levels and ventricular escape intervals after transient cessation of pacing in patients with complete heart block.

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## Methods

The 9 patients, aged 57 to 83 years (mean 76), had complete heart block and permanent pacemakers implanted. Three patients had narrow QRS complexes of ≤0.08 second duration on a 12-lead electrocardiogram, whereas in 6 the complexes were widened. Of these, 4 had a right bundle branch pattern and 2 had a nonspecific intraventricular conduction delay. Eight patients had a history of syncope or near-syncope. None had abnormalities of liver function.

**TABLE I Data on 9 Patients With Complete Heart Block Undergoing Permanent Pacemaker Implantation**

| Patient | QRS Duration (s) | Total Lidocaine Dose (mg) | Lidocaine Dose (mg/kg) | Lidocaine Levels (μg/ml) | | | Mean Escape Intervals (s) ± Standard Deviation | | | | Maximal Escape Intervals (s) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 10′ | 30′ | 45′ | Baseline | 10′ | 30′ | 45′ | Baseline | At Maximal Lidocaine Level |
| 1 | 0.12 | 400 | 8.0 | 1.1 | 1.8 | 1.6 | 1.56 ±0.31 | 1.36 ±0.02 | 2.40 ±1.27 | 2.19 ±0.45 | 2.00 | 4.20 |
| 2 | 0.12 | 300 | 5.5 | 1.5 | 1.5 | 1.6 | 1.67 ±0.04 | 1.78 ±0.04 | 1.87 ±0.07 | 1.94 ±0.16 | 1.72 | 2.16 |
| 3 | 0.10 | 170 | ... | 0.1 | 0.3 | 0.3 | 1.95 ±0.06 | 2.18 ±0.14 | 2.12 ±0.04 | 2.32 ±0.12 | 2.02 | 2.48 |
| 4 | 0.08 | 350 | 6.7 | 0.9 | 1.9 | ... | 1.78 ±0.42 | 2.27 ±0.05 | 2.83 ±1.03 | ... | 2.15 | 4.30 |
| 5* | 0.08 | 200 | 1.9 | 0.0 | 0.1 | 0.3 | 2.42 ±0.10 | 2.51 0.08 | 2.66 0.16 | 2.49 ±0.11 | 2.56 | 2.64 |
| 6 | 0.08 | 200 | 2.9 | 1.8 | 1.9 | 2.4 | 2.16 ±0.24 | 5.47 ±0.68 | 5.32(P) ±0.19 | 5.80(P) ±0.31 | 2.47 | 6.12(P) |
| 7 | 0.12 | 350 | 5.1 | 1.7 | 2.1 | 1.9 | 2.04 ±0.04 | 3.53 ±0.65 | 3.84 ±1.16 | 2.39 ±0.29 | 2.08 | 5.46 |
| 8 | 0.12 | 400 | 6.5 | 0.7 | 2.2 | 2.0 | 1.59 ±0.24 | 2.00 ±0.06 | 3.61 ±0.91 | 2.21 ±0.15 | 1.76 | 4.34 |
| 9 | 0.12 | 400 | 9.5 | 1.7 | 1.9 | 1.3 | 1.31 ±0.37 | 2.09 ±0.15 | 1.95 ±0.11 | 2.09 ±0.05 | 1.74 | 2.10 |
| Mean ±SD | ... | 307 ±94 | 5.8 ±2.5 | 1.06 ±0.69 | 1.52 ±0.78 | 1.43 ±0.77 | 1.83 ±0.32 | 2.58† ±1.24 | 2.96† ±1.06 | 2.68† ±1.27 | 2.06 ±0.30 | 3.76‡ ±1.40 |

* Patient had pulse generator replacement only. † $p < 0.01$. ‡ $p < 0.02$. P = required resumption of ventricular pacing.

Eight patients were receiving their first pacemaker and each had a temporary pacemaker in place before the procedure. In 7 of these cases, the temporary pacer was inserted more than 24 hours before the study. One patient underwent pulse generator replacement and did not have a temporary unit.

In each patient, a constant physiologic pacing rate was maintained by means of the previously placed temporary or permanent pacemaker. An indwelling catheter was inserted into an arm vein to obtain serum lidocaine levels.

After the patient was appropriately prepared and draped, a baseline serum lidocaine level was drawn. Pacing was then transiently stopped and ventricular escape intervals were recorded. Cessation of pacing was accomplished by abruptly turning off the temporary pacemaker or by inhibiting the previously implanted permanent pacemaker by means of an externally applied pulsating electromagnet. Pacing was immediately resumed if a patient demonstrated presyncopal symptoms or other untoward effects. Under no circumstance was a patient allowed to have a pause of greater than approximately 6 seconds. Measurements were repeated 3 to 6 times in each patient, with approximately 1 minute of pacing between determinations. Recordings were made on a standard electrocardiograph at paper speeds of 25 and 50 mm/s.

After baseline determinations, the surgeon began the implantation procedure by infiltrating 1% lidocaine solution into the subcutaneous tissues of the deltopectoral region, being careful to avoid intravascular injection. The surgeon was instructed to employ standard operating techniques and to use as much lidocaine as was deemed necessary to attain adequate local anesthesia.

Serum lidocaine levels were drawn and escape intervals were measured 10, 30, and 45 minutes after the injection of lidocaine. In each patient, the number of determinations of escape intervals at each juncture was the same as that obtained in the control period. In 1 patient no data were obtained at 45 minutes.

Lidocaine levels were determined by the EMIT homogeneous enzyme immunoassay method.[2] Standard statistical techniques were utilized. A two-way analysis of variance was performed to compare escape intervals before and after lidocaine injection.

## Results

A summary of the data from each patient is given in Table I. The dose of lidocaine used ranged from 170 to 400 mg (mean 307) or 1.9 to 9.5 mg/kg of body weight (weight not available in 1 patient). The peak serum lidocaine levels ranged from 0.3 to 2.2 μg/ml and occurred either 30 or 45 minutes after injection. Therapeutic lidocaine levels of 1.1 to 2.4 μg/ml were achieved in 7 of the 9 patients. One of the patients (Patient 5) with a less than therapeutic level had a pulse generator replacement only.

Serum lidocaine levels and mean ventricular escape intervals before and 10, 30, and 45 minutes after lidocaine injection are shown in Table I. The mean ventricular escape interval in the control period was 1.83 ± 0.32 seconds. This increased to 2.58 ± 1.24, 2.96 ± 1.06, and 2.68 ± 1.27 seconds at 10, 30, and 45 minutes after lidocaine administration ($p < 0.02$, comparing each period with baseline). The mean escape intervals at 30 and 45 minutes were greater than the baseline values in every case. A representative example of escape interval prolongation is seen in Figure 1. Based on QRS morphology, 6 patients displayed a single escape focus

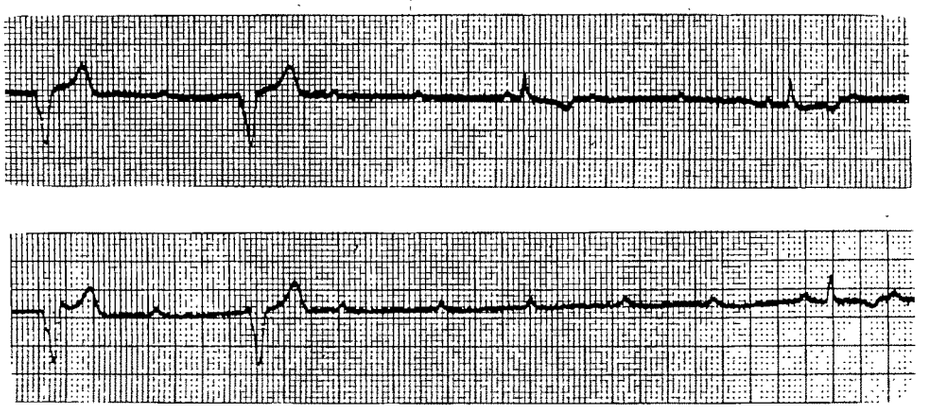


**FIGURE 1.** A representative lead II electrocardiographic tracing in Patient 4 demonstrating the effects of temporary cessation of pacing before (**top**) and after (**bottom**) lidocaine administration. The first 2 beats in both tracings are paced beats by way of bipolar temporary pacemaker. Paper speed is 25 mm/s.

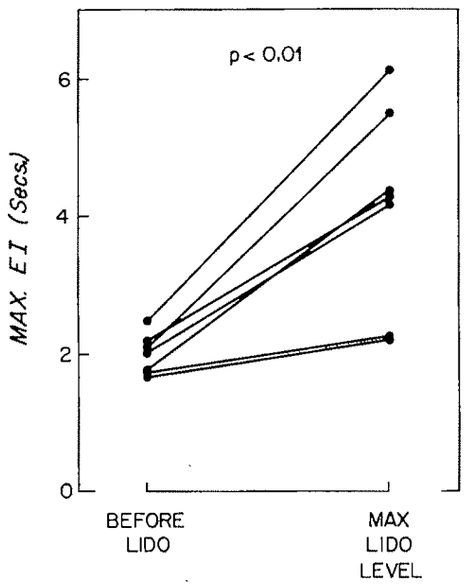



**FIGURE 2.** Maximal escape intervals (MAX EI) in 7 patients who achieved therapeutic lidocaine levels before lidocaine administration (BEFORE LIDO) and at maximal lidocaine level (MAX LIDO LEVEL).

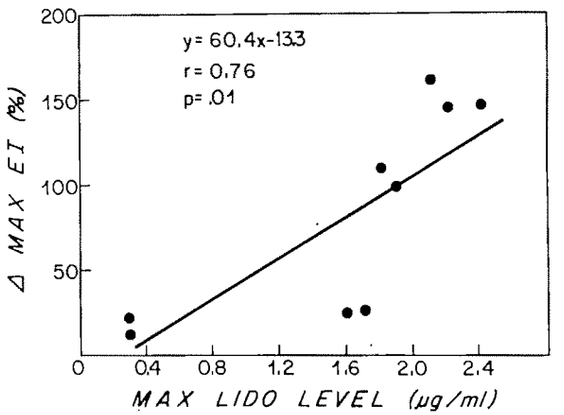



**FIGURE 3.** Relation between the change in maximal escape interval (Δ MAX EI) at the time of maximal lidocaine level (expressed as percent increase over control) and the serum lidocaine level at that time (MAX LIDO LEVEL).

during baseline studies and 3 patients had 2 foci. In only 1 instance did a patient have an escape focus after lidocaine injection which was not evident in the baseline. All patients with narrow QRS complexes on the initial electrocardiogram had escape foci whose QRS intervals were ≤0.09 second. Electrophysiologic studies were not performed to better identify the location of the escape foci.

The maximal ventricular escape intervals for each patient during the control period and at the time of maximal serum lidocaine levels are shown in Table I. These same values for the 7 patients who achieved therapeutic lidocaine levels are displayed in Figure 2. The mean maximal escape interval before lidocaine administration was 2.06 ± 0.30 seconds. At the time of peak lidocaine level, this increased to 3.80 ± 1.44 seconds ($p < 0.01$), a mean increase of 84%. In 6 of the 7 patients who achieved therapeutic drug levels, the longest escape interval observed occurred at the time of maximal lidocaine level. The degree of escape interval prolongation was directly related to the height of the serum lidocaine level. Figure 3 displays the percent increase in escape interval at peak lidocaine level as related to the drug level at that time. The correlation coefficient is 0.76 ($p = 0.01$). In the control period, no patient had asystole for longer than 2.56 seconds, and it was not necessary to turn the pacer back on in any patient. After lidocaine administration, 5 patients had asystole for >4 seconds and 1 required resumption of pacing after presyncopal symptoms or >6 seconds of asystole.

## Discussion

We have frequently observed asystole after transient cessation of pacing during a permanent endocardial pacemaker implantation procedure. This phenomenon generally occurs during the course of determining pacing and sensing thresholds. The occurrence of asystole may preclude the measurement or recording of the patient's intrinsic intracardiac QRS signal, thereby making it impossible to assess the sensing function of

a demand pacemaker. Furthermore, asystole may compromise the ability of the operator to reposition the electrode if there is no other means of maintaining an adequate heart rate. Asystole after the cessation of pacing has been observed even in patients who previously had been stable with only rare or minimal symptoms before pacemaker placement.

The achievement of therapeutic serum levels with the use of lidocaine for local anesthesia has been reported.[1] Since subcutaneous lidocaine is commonly used during pacemaker implantation, we investigated the possibility that this drug might be responsible for the emergence of pacer dependency.

In this study 7 of 9 patients achieved therapeutic drug levels after subcutaneous lidocaine administration during permanent pacemaker implantation. The level attained appeared to be related to the total dose administered, although the resulting maximal serum lidocaine levels were not as predictable as the results reported by Nattel et al.[1] In their study the peak lidocaine concentration could be predicted by multiplying the initial dose (in milligrams/kilogram) by 0.3. However, they noted the peak concentration to occur at an average of 62 minutes after subcutaneous injection, which was beyond the duration of our observations.

In unanesthesized dogs with complete heart block, Hayes et al[3] showed that lidocaine prolonged asystole after abrupt cessation of ventricular driving. Ryden and Korsgren[4] studied the effects of sudden cessation of pacing in 6 patients before and after 2 intravenous boluses of 1 to 2 mg/kg of lidocaine. In some patients this was followed by an intravenous drip of the medication, and blood levels were not measured. All of their patients reestablished an autonomous ventricular rhythm before lidocaine administration without any period of asystole of clinical importance. After lidocaine, 3 patients developed prolonged asystole which necessitated pacing after 8 seconds. Two of these patients had third-degree block and the remaining patient had second-degree atrioventricular block. Roos and Dunning[5] examined the acute effects of the rapid intravenous injection of 100 mg lidocaine in patients with a variety of conduction defects. Despite a mean arterial plasma level of 26.6 $\mu$g/ml, no effect was seen on the spontaneous firing rate of the escape focus in any of the 5 patients with complete heart block. This group included those with block distal and proximal to the His bundle.

Aravindakshan et al[6] administered lidocaine intravenously to 18 patients with complete atrioventricular block. They employed a bolus dose of 1.5 mg/kg followed by a 2 to 4 mg/min infusion. In 13 cases, there was little or no slowing of the escape rate. In the remaining 5 patients there was an abrupt slowing of the rates with resulting R-R intervals that grossly approximated multiples of the basic escape intervals, thus suggesting the occurrence of 2:1 or 3:1 exit block rather than slowing of the escape focus. They claimed that the development of exit block depended more on a critical degree of His-Purkinje conduction abnormality than on the plasma drug level achieved. Furthermore, they concluded that the basic QRS complex duration and escape rate were of no value in identifying those patients prone to abrupt rate slowing.

In the present study, lidocaine produced a lengthening of the mean and maximal escape intervals after the abrupt cessation of pacing in every patient. Of the 9 patients, the longest escape interval during the 3 to 6 determinations in the control period was 2.56 seconds. After lidocaine administration, 5 patients had escape intervals of >4 seconds at the time of their maximal drug concentration and 1 patient needed to have his pacemaker turned back on due to presyncopal symptoms or >6 seconds of asystole. The prolongation of escape interval was present by 10 minutes after injection and persisted for more than 45 minutes. The degree of prolongation of the escape interval was directly related to the maximal drug level achieved (Fig. 3), and the duration of asystole after lidocaine administration could not be predicted by the escape interval in the control state nor by the QRS duration. Three of our patients had QRS durations of $\leq$0.08 second; therapeutic levels of lidocaine were achieved in 2 of these patients. Both of these patients developed asystole lasting >4 seconds and 1 required the resumption of ventricular pacing. The lengths of the escape intervals before and after lidocaine injection do not suggest the existence of exit block.

Thus, prolonged asystole after abrupt cessation of pacing in patients with complete heart block is more likely to occur after lidocaine administration. Concentrations adequate to affect escape intervals are reached in a majority of patients undergoing routine permanent pacemaker implantation using local lidocaine anesthesia. To avoid problems related to asystole and allow proper threshold measurements, it is advisable to minimize the systemic concentration of this medication. This can be achieved by limiting the total dose used to the minimal amount necessary to achieve adequate local anesthesia. It is possible that the use of a vasoconstrictor mixed with the anesthesia may limit the distribution of the drug and thereby blunt or delay the peak systemic lidocaine concentration. However, the safety of such agents would need to be established in this patient population. Further study would also be necessary to assess the effects of alternate local anesthetic agents. Finally, strong consideration should be given to the routine use of temporary pacing in patients with complete heart block during permanent pacemaker implantation, even in the absence of prior asystole.

## References


1. **Nattel S, Rinkenberger RL, Lehrman LL, Zipes DP.** Therapeutic blood concentration after local anaesthesia for cardiac electrophysiologic studies. N Eng J Med 1979;301:418–420.
2. **Cobb ME, Buckly N, Hu MW, Miller JG, Singh P, Schneider RS.** Homogeneous enzyme immunoassay for lidocaine in serum (abstr). Clin Chem 1977;23:1161.
3. **Hayes JG, Ettinger E, Wanat FE, Killip T.** Evaluation of lidocaine in the treatment of ventricular arrhythmias (abstr). Circulation 1967;36:Suppl II: II-137.
4. **Ryden L, Korsgren M.** The effects of lidocaine on the stimulation threshold and conduction disturbances in patients treated with pacemaker. Circ Res 969;3:415–418.
5. **Roos JC, Dunning AJ.** Effects of lidocaine on impulse formation and conduction defects in man. Am Heart J 1975;89:686–689.
6. **Aravindakshan V, Kuo C, Gettes LS.** Effects of lidocaine on escape rates in patients with complete atrioventricular block. Am J Cardiol 1977;40: 177–183.

# Relation Between Late Potentials on the Body Surface and Directly Recorded Fragmented Electrograms in Patients With Ventricular Tachycardia

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**The relation between low-amplitude, late potentials on the body surface and directly recorded electrograms in 8 patients with and 11 patients without ventricular tachycardia (VT) was studied. Bipolar X,Y,Z leads were signal-averaged and filtered with a digital technique. All patients had catheter endocardial left ventricular maps. The VT group had medically intractable VT and an endocardial excision was performed for control of VT. Before bypass, epicardial maps were obtained in the operating room. All studies were performed during normal sinus rhythm.**

**Four patients without VT, each with a previous myocardial infarction, had fragmented endocardial electrograms recorded at 2.0 ± 1.2 sites. The latest electrogram for each patient ended 87 ± 8 ms after QRS onset, within the high-amplitude portion of the filtered QRS complex. All patients with VT had fragmented electrograms recorded at 6.1 ± 3.1 sites/patient. Eighty-eight percent of the fragmented electrograms were endocardial. The latest fragmented electrogram for each patient ended 161 ± 43 ms after QRS onset, significantly later than the fragmented electrograms from the patients without VT ($p = 0.002$).**

**Six VT patients had low-amplitude, late potentials at the end of the filtered QRS complex. In these patients, the last 40 ms of the filtered QRS complex contained a higher proportion of fragmented electrograms compared with earlier segments of the QRS complex (68% versus 27%, $p < 0.001$). Two patients with VT did not have late potentials. One patient with left bundle branch block had delayed left ventricular epicardial activation which masked the fragmented electrograms. The other had fragmented electrograms of brief duration which ended 80 ± 12 ms after QRS onset, during the time of normal ventricular activation.**

**It is concluded that the late potential corresponds to delayed, fragmented electrographic activity. Failure to record a late potential may arise from delayed ventricular activation at other sites from bundle branch block or fragmented electrograms of a brief duration.**

Delayed and fragmented electrograms have been recorded directly from the myocardium in patients and animals with ventricular arrhythmias.[1–9] The association of delayed electrical activity with VT suggests a reentrant mechanism. This concept is supported by the demonstration that the initiation and maintenance of the arrhythmias depends on the delayed electrogram spanning diastole before the onset of the first and between subsequent complexes of the tachycardia.[2,4–6,8]

In recent years, investigators working with signal averaging techniques have detected low-amplitude potentials on the body surface in patients and animals with ventricular arrhythmias.[10–19] These potentials occur at the end of or just after the QRS complex; in animals with experimental infarcts, the late potentials correlated in time to directly recorded fragmented electrograms.[10–17]

In previous work, we demonstrated that 90% of patients with VT after myocardial infarction (MI) had a distinctive low-amplitude, late potential that was continuous with the earlier portions of the QRS complex.[16,18,19] A similar potential was found in only 6% of patients without serious ventricular arrhythmias after MI. The purpose of this work was to identify the origin of the low-level late potential by correlation with directly recorded epicardial and endocardial ventricular electrographic maps.

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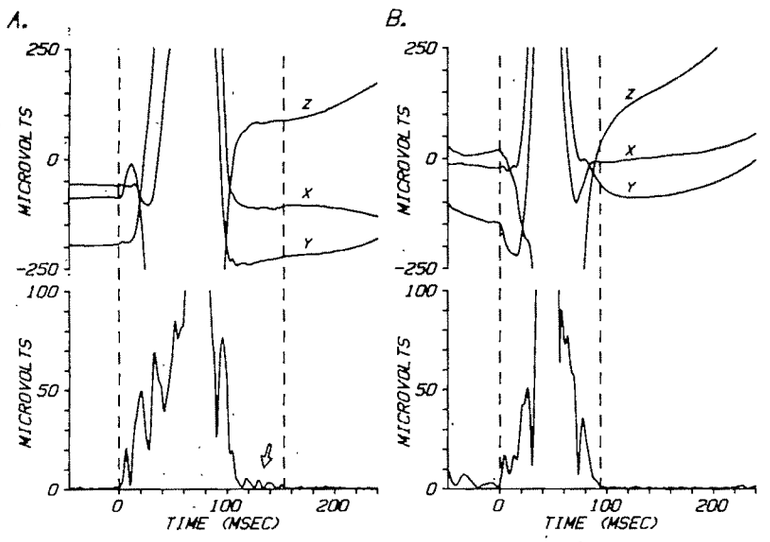



**FIGURE 1.** Patients 4 and 15. Signal processing in patients with (**A**) and without (**B**) VT. Signal-averaged X, Y, Z leads are shown at high gain on the top. The filtered QRS complex is on the bottom. The **dashed lines** are the end points of the filtered QRS complex as determined by the computer. The **arrow** points to a low-amplitude (4 $\mu$V), late potential at the end of the filtered QRS complex from the patient with VT. Both patients had anterior myocardial infarctions.

## Methods

**Patient population:** Nineteen patients were studied. Eight patients had VT; all had a prior MI. They were referred to our institution for recurrent, symptomatic VT which was inducible in the clinical electrophysiology laboratory with 1 to 3 ventricular premature depolarizations.[20] In each patient, the VT could not be controlled with antiarrhythmic agents,[21] and an endocardial excision with or without an aneurysmectomy was performed for control of the arrhythmia.[22,23] Endocardial and epicardial mapping and a signal-averaged electrocardiograph was performed in each patient.

Eleven other patients were studied with a signal-averaged electrocardiogram and endocardial mapping. These patients were referred to the catheterization laboratory for evaluation of chest pain, and they volunteered for a research study of endocardial activation. The patients had no history of VT or complex ventricular arrhythmias. Holter monitoring was performed for 24 hours in 8 patients and showed 0 to 10 unifocal ventricular premature beats/hour and the absence of multiform ventricular premature beats, couplets, or VT.

Table I lists the clinical data on all patients. Each patient gave informed consent. The research protocols were approved by the University of Pennsylvania Committee on Studies Involving Human Beings.

**Signal-averaged electrocardiograms:** A signal-averaged electrocardiogram was recorded from bipolar X,Y,Z leads with previously described techniques.[16] Ectopic and grossly noisy beats were rejected by a template algorithm. A mean of 142 ± 12 beats was averaged. Each lead was filtered with a bidirectional, high-pass digital filter which was designed to eliminate filter ringing.[16] The bandpass was 25 to 250 Hz and the rate of highpass attenuation was 24 dB/octave. The filtered X,Y,Z leads were combined into a vector magnitude—$\sqrt{(X^2 + Y^2 + Z^2}$—a measure which sums the high-frequency information from all 3 leads and which is termed the "filtered QRS complex" in this study. The end points of the filtered QRS complex were determined by a computer algorithm.[16]

Figure 1 shows results of signal processing in patients with and without VT. In previous studies,[16,18,19] a prolonged filtered QRS duration and a low voltage in the last 40 ms of the filtered QRS complex were found to identify patients with VT; those variables were used in the present study to quantify the filtered QRS complex. In this study a "late potential" is defined as a low-amplitude signal (<25 $\mu$V) in the last 40 ms of the filtered QRS complex (Fig. 1, arrow). It is called late because it typically occurs after end of the QRS complex in the standard electrocardiogram.

Left ventricular endocardial electrograms were recorded in the catheterization laboratory by bipolar electrodes with an interelectrode distance of 1 cm. The amplifier bandpass was 30 to 500 Hz. An attempt was made to record from 12 preselected endocardial sites with methods previously described[24]; occasionally, a preselected site could not be reached. Additional recordings were made, if possible, from the edges of aneurysms or infarcts, Table I lists the number of endocardial sites for each patient. There was no difference in the

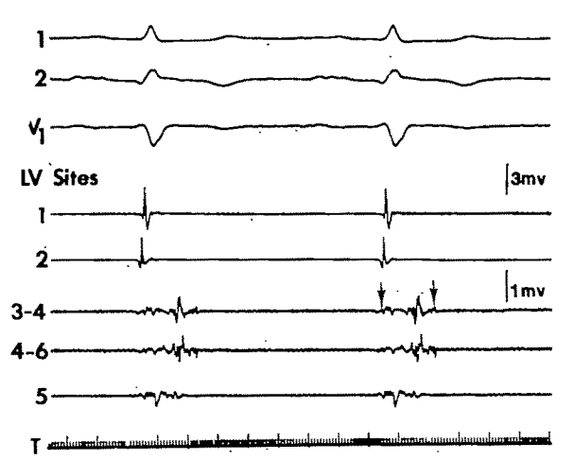



**FIGURE 2.** Examples of electrogram classification. **Top,** 3 surface electrocardiographic leads; **bottom,** 5 endocardial electrograms. Electrograms from sites 1 and 2 (apex) were normal. Electrograms from the other sites were fragmented. The **arrows** indicate the end points of a fragmented electrogram. Sites 3 through 6 are in the inferobasal portion of the heart. The voltage calibration is 3 mV for the normal electrograms and 1 mV for the fragmented electrograms. LV = left ventricular.

**TABLE I Patient Characteristics**

| Patient | Age (yr) & Sex | Cardiac Diagnosis | Location of Wall Motion Abnormalities | Ventricular Aneurysm | ECG | Endocardial Sites Studied (n) | Endocardial Sites (n) With Fragmented Electrograms |
|---|---|---|---|---|---|---|---|
| | | | Patients With Ventricular Tachycardia | | | | |
| 1 | 58M | CAD | INF | No | IMI | 16 | 9 |
| 2 | 57M | CAD | INF, ANT | Yes | IMI, AMI | 12 | 4 |
| 3 | 44M | CAD | ANT | Yes | AMI | 11 | 6 |
| 4 | 51M | CAD | ANT | Yes | AMI | 12 | 3 |
| 5 | 51M | CAD | ANT | Yes | AMI | 12 | 8 |
| 6 | 69M | CAD | INF | Yes | IMI | 13 | 5 |
| 7 | 49M | CAD | ANT | Yes | AMI, IVCD | 11 | 4 |
| 8 | 53M | CAD | ANT, LAT | Yes | LBBB | 10 | 4 |
| | | | Patients Without Ventricular Tachycardia | | | | |
| 9 | 50M | CAD | INF | No | IMI | 16 | 3 |
| 10 | 59F | CAD | INF | No | NL | 11 | 1 |
| 11 | 58M | CAD | ANT | No | AMI | 11 | 0 |
| 12 | 55M | CAD | None | No | NL | 13 | 0 |
| 13 | 51F | CAD | ANT | No | AMI | 11 | 3 |
| 14 | 43M | CAD | INF | No | IMI | 10 | 0 |
| 15 | 50M | CAD | ANT | No | AMI | 12 | 1 |
| 16 | 43M | CAD | ANT | No | NL | 16 | 0 |
| 17 | 59M | CAD | None | No | NL | 13 | 0 |
| 18 | 17M | NL | None | No | NL | 12 | 0 |
| 19 | 39M | NL | None | No | NL | 12 | 0 |

Patients 5 and 6 had, in addition, fragmented electrograms at 4 and 2 epicardial sites, respectively. AMI = anterior myocardial infarction; ANT = anterior; CAD = coronary artery disease; ECG = electrocardiogram; IMI = inferior myocardial infarction; INF = inferior; LAT = lateral; LBBB = left bundle branch block; NL = normal.

number of endocardial sites studied for the patients with and without VT ($p = 0.36$). Sites were identified with multiplane fluoroscopy. These methods have been validated by comparison with intraoperative data.[25]

In the operating room, epicardial electrograms were recorded from the patients with VT under halothane anesthesia before cardiopulmonary bypass as previously described.[22,23] A roving, bipolar electrode with a 1.5 mm interelectrode distance was used. The amplifier bandpass was 30 to 500 Hz. Recordings were made from 54 predetermined sites (29 left ventricular sites) in each patient. Intraoperative right bundle branch block temporarily developed in 3 patients, and the right ventricular sites were not analyzed further in those patients.

Each patient was in sinus rhythm during all studies. Antiarrhythmic agents were stopped at least 5 half-lives before the studies. The signal-averaging, catheter, and intraoperative studies were performed within 3 to 5 days of one another.

All electrograms were classified as normal or fragmented (Fig. 2). An electrogram was considered normal if the duration was <60 ms and the peak to peak amplitude was >1 mV. (Sixty ms was used as a threshold since it was >2 standard deviations larger than the mean duration of 100 electrograms recorded over the normal left ventricle in pilot studies.) A fragmented electrogram had multiple components, a duration >60 ms, and a peak-to-peak amplitude typically <1 mV. The electrographic duration was measured from the beginning to the end of the rapidly moving components of the electrogram. The fragmented electrograms had a constant duration in this study; no examples of a Wenckebach conduction pattern were found.[5,6] The time of peak amplitude for the normal electrograms was considered to be the time of occurrence. The QRS onset was used as the reference time for all studies. The calibration of the oscillographic recorder was 1 mV/cm and 40

**TABLE II Fragmented Electrograms**

| | No VT | | VT | | |
|---|---|---|---|---|---|
| | Mean ± SD | Range | Mean ± SD | Range | p |
| Incidence/patient | | | | | |
| Endocardial sites | 2.0 ± 1.2 | 1–3 | 5.4 ± 2.1 | 3–9 | 0.008 |
| Total number of sites (endocardial and epicardial) | ... | ... | 6.1 ± 3.3 | 3–12 | ... |
| Timing from beginning of QRS (ms) | | | | | |
| Onset | 13.3 ± 7.9 | 0–24 | 30.2 ± 18.6 | 0–60 | 0.007 |
| End | 83.9 ± 6.3 | 78–96 | 120.2 ± 35.3 | 65–225 | 0.003 |
| Duration | 70.6 ± 11.1 | 62–88 | 90.0 ± 30.3 | 60–155 | 0.04 |
| End of latest electrogram in each patient | 87.3 ± 7.5 | 80–96 | 160.6 ± 43.3 | 95–225 | 0.002 |

The incidence and timing of the fragmented electrograms in patients with and without VT. In the "No VT" group the data are tabulated only from patients with fragmented electrograms. SD = standard deviation.

ms/cm. Electrograms were measured by observers who did not know the signal-averaged results. Statistical analysis was performed using 2 × 2 chi-square, RxC contingency table, and the *t* test (1-tail), as appropriate. Except as noted, all voltages were measured by the root mean square method. Results are presented as the mean ± standard deviation.

## Results

**Patients without VT:** Fragmented endocardial electrograms were found in 4 of the 6 patients with prior MI and were not found in the 5 patients without previous MI. The fragmented electrograms were located within areas showing wall motion abnormalities from the previous infarct. Table II summarizes the incidence and timing of the fragmented electrograms.

The mean time of activation for the normal endocardial electrograms was 23 ± 15 ms (range 0 to 54); the mean and median time of activation agreed within 0.7 ms (p = 0.18).

The filtered QRS complex from patients without VT was a symmetrical burst of high-frequency signal. No late potentials were found in these patients. The filtered QRS duration was 96 ± 8 ms, and the voltage in the last 40 ms was 51.5 ± 26.5 μV. Among patients without VT, there was no significant difference between patients with and without fragmented electrograms in filtered QRS duration (98 ± 6 versus 95 ± 9 ms, p = 0.23) or voltage in the last 40 ms (38.9 ± 12.5 versus 58.6 ± 80.4 μV, p = 0.13).

Figure 3 shows the time relation between the endocardial electrograms and the filtered QRS complex in patients with (Fig. 3A) and without (Fig. 3B) fragmented electrograms. Since the fragmented electrograms ended 84 ± 6 ms after QRS onset (Table II), they were contained within the high-amplitude portions of the filtered QRS complex.

**Patients with VT:** Fragmented electrograms were found in each patient with VT. Eighty-eight percent of the sites with fragmented electrograms were endocardial

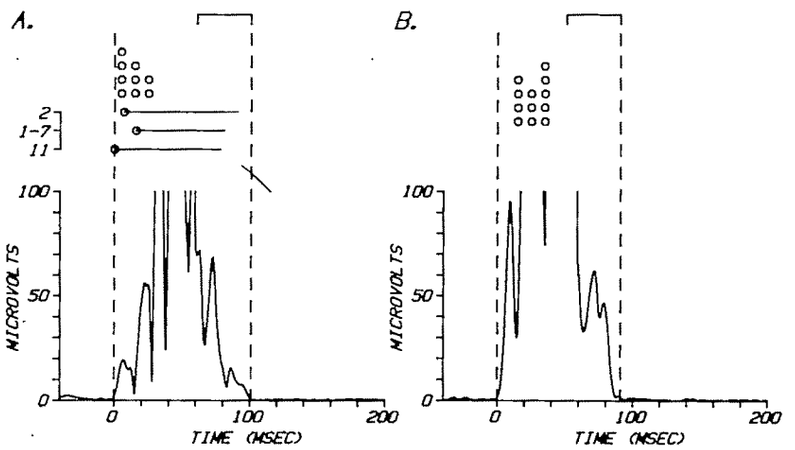



**FIGURE 3.** Patients 13 and 18. Examples of the time relations between the endocardial electrograms and the filtered QRS complex in patients with (**A**) and without (**B**) fragmented electrograms. Neither patient had VT. **Bottom,** filtered QRS complex; the **circles on top** indicate the timing of the endocardial electrograms. Normal electrograms are shown with an **isolated symbol.** Fragmented electrograms are depicted with a **line,** which indicates the duration of the electrogram. The **brackets** indicate the last 40 ms of the filtered QRS complex. The **numbers** indicate electrographic sites. The patient shown in **A** had 3 fragmented endocardial electrograms which ended 78, 81, and 91 ms after QRS onset.

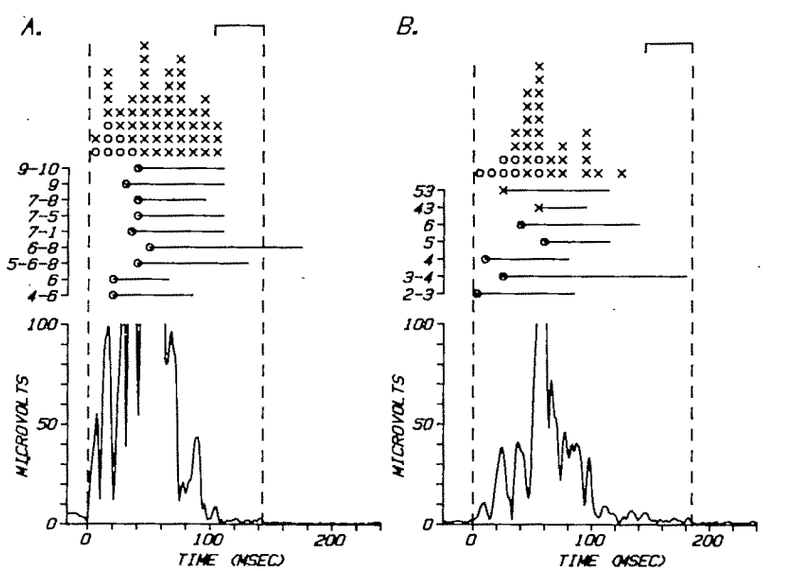



**FIGURE 4.** Patients 1 and 6. Examples of the time relation between the electrograms and the filtered QRS complex in 2 patients with VT. **Bottom,** filtered QRS complex. The **symbols on the top** indicate the timing of the electrograms. An **X** represents an epicardial electrogram and a **circle** represents an endocardial electrogram. Fragmented electrograms are indicated with a **line** which shows the timing and duration of the electrogram. The **brackets** indicate the last 40 ms of the filtered QRS complex. See text for details.

despite the fact that more epicardial than endocardial sites were sampled. Fragmented epicardial electrograms were found only in 2 patients at 2 and 4 sites, respectively. All fragmented electrograms were found within areas of previous infarct. They were found more frequently, began later, and ended later in patients with VT than in those with fragmented electrograms but without VT (Table II). The latest fragmented electrogram for each patient ended 161 ± 43 ms after QRS onset for the VT group, but only 87 ± 8 ms for the patients without VT ($p = 0.002$).

The time of activation for the normal endocardial electrogram was later in the VT group than in the group without VT (38 ± 30 versus 23 ± 15 ms, $p < 0.001$). If patients with intraventricular conduction delay or left bundle branch block were excluded, however, the time of endocardial activation was similar (26 ± 15 ms, range 0 to 48, $p = 0.15$). The latest normal electrograms (epicardial and endocardial) occurred 108 ± 25 ms after QRS onset in the VT patients. When patients with ventricular conduction delay were excluded, the latest normal electrogram occurred at 92 ± 9 ms.

The normal electrograms had a symmetrical time distribution; the median and mean time of activation agreed within 1.4 ± 5.5 ms ($p = 0.26$). The normal electrograms tended to cluster; within 40 ms of the latest normal electrogram, there were 18.8 ± 12.1 other sites showing normal configuration (37.2 ± 20.9% of all normal electrograms).

The filtered QRS complex differed in the patient with and without VT. The filtered QRS duration was longer (148 ± 29 ms versus 96 ± 8 ms, $p < 0.001$) and the voltage in the last 40 ms was lower (16.0 ± 20.4 versus 51.5 ± 26.5 μV, $p = 0.007$).

**VT patients with late potentials:** Six patients with VT had a distinctive, low-amplitude tail at the end of the filtered QRS complex; these patients met the criterion for VT we had developed earlier, that is, <25 μV of signal in the last 40 ms of the filtered QRS complex.[16] For these patients, the voltage during that time was 8.7 ± 7.2 μV and the filtered QRS duration was 154 ± 28 ms.

Figure 4 shows the time relation between the electrograms and the filtered QRS complex in 2 patients. In Figure 4A, the patient had fragmented activity at 9 endocardial sites. During the last 40 ms, there is a low amplitude of signal in the filtered QRS complex. During that time, 6 fragmented electrograms were present and only 3 normal electrograms occurred. For most of the 40 ms, the low-level body surface signal corresponded to 2 fragmented electrograms. Earlier in the QRS, when a large amplitude of high-frequency signal was present on the body surface, 59 normal electrograms were recorded. Some fragmented electrograms (for example, locations 4-6 and 6) had a brief duration and ended before all normal electrograms had occurred.

Figure 4B shows another example from a patient with a low-amplitude (3 μV) signal at the end of the filtered QRS complex. There were 7 fragmented electrograms (2 epicardial, 5 endocardial). During the last 40 ms of the filtered QRS complex, only 1 site was active and it showed fragmented activity. In contrast, 35 normal electrograms were found at an earlier time. Intraoperative right bundle branch block occurred in this patient and only the data from the left ventricle was analyzed.

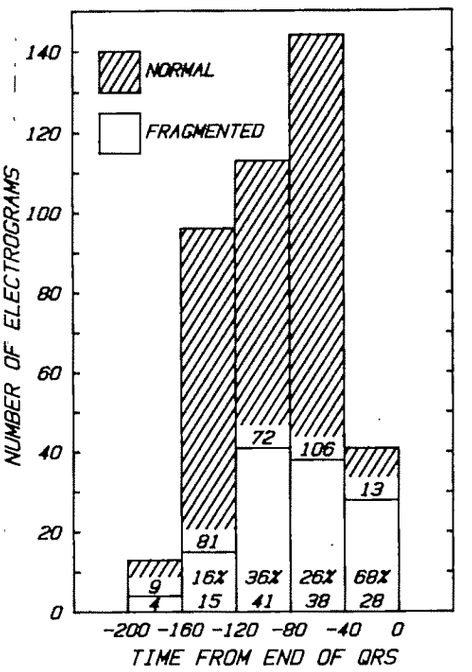



**FIGURE 5.** The number of normal and fragmented electrograms detected in various time segments of the filtered QRS complex in 6 VT patients with late potentials. The filtered QRS complex was divided into 40 ms segments, beginning at the end of the filtered QRS complex. The number of electrograms which were active in each time segment are indicated. The percentage of the total number of electrograms in each time segment which were fragmented is also shown.

In the 6 patients with late potentials, the latest fragmented electrograms lasted a mean of 54 ± 31 ms beyond the latest normal electrogram in each patient. There were 3.3 ± 2.9 fragmented electrograms/patient that persisted >20 ms beyond the latest normal electrogram. There was a high proportion of fragmented electrograms during the last 40 ms of the filtered QRS complex (Fig. 5). Relatively few (13) normal electrograms were active during that time; only 4.6% of the total number of normal electrograms occurred then. In the last 40 ms, 41 electrograms were active and 28 (68%) were fragmented. Earlier in the QRS, there were 309 electrograms detected and the proportion of fragmented electrograms in any 40 ms segment was lower (mean 27%, range 16 to 36, $p < 0.001$).

**VT patients without late potentials:** Two patients with VT did not have the low-amplitude signal at the end of the filtered QRS complex. One had left bundle branch block (Fig. 6A). The electrograms with normal configuration were delayed and obscured the signal from the fragmented electrograms. During the last 40 ms there were 4 fragmented and 10 normal electrograms. The body surface signal was 46 μV during that time. In addition, this patient did not have a peak of

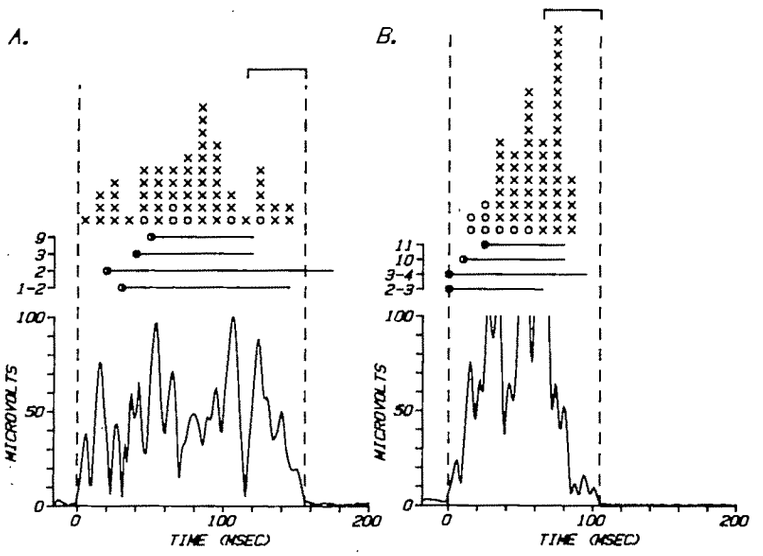



**FIGURE 6.** Patients 8 and 4. Time relation between the filtered QRS complex and electrograms in the 2 patients with VT who did not have late potentials. Symbols as in Figure 4. See text for details.

high-frequency signal in the first 100 ms of the filtered QRS complex; in contrast to all other patients, the high-frequency signal had a more uniform level over 156 ms.

Figure 6B shows the records from the other patient with VT who did not have a low-amplitude, late potential. The voltage during the last 40 ms was 59 $\mu$V. During that time there were 3 fragmented and 25 normal electrograms. The fragmented electrograms were brief and ended 80 ± 12 ms after QRS onset. The other patients with VT had longer fragmented electrograms that ended 122 ± 36 ms after QRS onset ($p = 0.01$).

The 2 VT patients without the late potentials had a low proportion of fragmented electrograms during the last 40 ms of the filtered QRS complex. In these patients, only 17% of the electrograms in the last 40 ms were fragmented (7 fragmented, 35 normal electrograms); in contrast, 68% of the electrograms in the last 40 ms were fragmented in the patients with the low-amplitude signal ($p < 0.001$). In the 2 patients without late potentials there was no significant difference in the proportion of fragmented electrograms active in each 40 ms segment of the QRS; a mean of 18% (range 13 to 24) of the electrograms in each segment were fragmented ($p = 0.59$).

In the results discussed so far, the normal electrograms were analyzed according to the time of their peak amplitude. Data were reanalyzed taking into consideration the total duration of the normal electrograms, which was 43 ± 6 ms. The VT patients with the late potentials had a high proportion of fragmented electrograms in the last 40 ms compared with the other segments of the QRS complex ($p < 0.001$). Similar results were found when only left ventricular epicardial sites were analyzed ($p < 0.001$).

For the patients with VT, the filtered QRS voltage at a particular time correlated with the number of sites with active electrograms at that time. The mean linear correlation coefficient was 0.80 (range 0.51 to 0.96), and the mean slope was 5.6 $\mu$V (range 3.2 to 9.4) per electrographic site. The body surface voltage associated with fragmented electrograms was estimated from 5 patients with VT who had a 20 to 60 ms segment of the filtered QRS complex during which normal electrograms were not present. The mean voltage was 2.0 ± 0.4 $\mu$V/site showing fragmented activity.

## Discussion

This study used 2 advanced signal processing techniques to record low-level potentials on the body surface: signal-averaging and a bidirectional high-pass filter. Signal-averaging reduces random noise, which arises primarily from muscle, and allows the detection of microvolt level signals which would otherwise be obscured by noise. The high-pass filter sharply attenuates low-frequency activity, but allows high-frequency potentials to pass without reduction. The filtering allows one to detect electrical activity arising from changes in conduction velocity or direction of activation,[26] and simultaneously suppresses the low-frequency activity that originates from the plateau phase of the action potentials. The filter we used had excellent attenuation of low-frequency events; in the S-T segment of all patients, there was no signal other than random noise, a mean of 0.6 $\mu$V. The filter operated in a bidirectional mode to eliminate filter ringing, an artifact which would mask a low-amplitude signal that occurred immediately after a larger signal, such as the QRS complex.[16]

In previous work, we demonstrated that 90% of patients with VT after MI had a distinctive low-amplitude, late potential which was continuous with the earlier portions of the QRS complex.[16,18,19] A similar potential was found in only 6% of patients without serious ventricular arrhythmias after MI. A low level of signal in the last 40 ms of the filtered QRS complex (<25 $\mu$V) iden-

tified patients with VT with 90% sensitivity and 94% specificity. Several groups of investigators have identified a similar low-amplitude, late potential in patients with VT.[11–15]

The purpose of this work was to identify the origin of the low-level, late potential by correlation with directly recorded epicardial and endocardial ventricular electrographic maps. In 6 patients with VT the late potential occurred at a time when a high proportion of active electrode sites showed fragmented activity. During the time of low-amplitude signal, 68% of the active electrograms were fragmented. In contrast, only 27% of active electrograms were fragmented earlier in the QRS complex (Fig. 5). The 2 patients with VT without late potentials did not have a high proportion of fragmented electrograms late in the QRS complex. No low-level, late potentials were found in 4 patients without VT who had fragmented electrograms after MI; the longest fragmented electrogram in those patients ended a mean of 87 ms after QRS onset, presumably during normal ventricular activation.

The condition necessary to detect slow ventricular activation on the body surface is that the disorganized and delayed activation must outlast normal ventricular activation. When fragmented electrograms were brief in duration, no distinctive signal was identified. Conversely, in the 6 VT patients with late potentials, the longest fragmented electrograms outlasted the latest normal electrogram by 54 ms.

This study offers insight on why a low-amplitude signal at the end of the filtered QRS complex identified patients with VT in our previous studies. First, the signal from delayed ventricular activity is low level. Only a few sites have fragmented electrographic activity late in the QRS complex; in the 6 VT patients with the late potentials a mean of only 3.3 sites lasted 20 ms beyond the latest normal electrogram. Each site with fragmented activity, moreover, was associated with a low-level signal on the body surface, estimated at 2 $\mu$V/site. Second, normal ventricular activation generates a high-level, symmetrical burst of high-frequency energy. This was apparent on examination of the filtered QRS complex from patients without VT (Fig. 1 and 3). The normal electrograms had a symmetrical time distribution; the mean and median times of activation agreed within 2 ms. In the patients with VT, the normal electrograms tended to cluster together in time as expected from the syncytial nature of myocardium; within the 40 ms preceding the latest normal electrogram, a mean of 19 sites with active normal electrograms was detected. As a consequence, normal ventricular activation causes a relatively high amplitude of high-frequency voltage on the body surface which ends abruptly, in contrast to the low-level signal that fragmented and delayed ventricular activation creates. The distinguishing criterion for detecting delayed and fragmented ventricular activation is a low-amplitude potential which persists at the end of the QRS complex. This study suggests that the low-amplitude signal represents disorganized and delayed activation within 1 or more protected sites and is in agreement with the findings of Fontaine,[11] Breithardt,[14] Rozanski[15] and their co-workers, who have reported examples of fragmented epicardial and endocardial electrograms which correlated in time with late potentials.

The 2 patients with VT who did not have the low-amplitude, late potential illustrate limitations of the signal-averaging technique. Patients with bundle branch block may have sufficient delay in epicardial activation that masks the fragmented electrical activity elsewhere in the heart. Also, some patients with VT may not have fragmented electrographic activity of sufficient duration to allow detection from the body surface during sinus rhythm (Fig. 6). In our previous studies,[16,18,19] we found the incidence of failure to detect delayed potentials among VT patients without bundle branch block to be 10%, possibly because of insufficient delay of ventricular activation. Rapid pacing or insertion of a premature beat may improve the sensitivity of the signal-averaging technique by prolonging the duration of delayed ventricular activity.[5,6,8]

Several technical difficulties in this study should be noted and require further investigation. First, the patients without VT did not have ventricular aneurysms, yet all but 1 of the patients with VT had an aneurysm. A more appropriate control group, and one more difficult to obtain, would be patients with ventricular aneurysms yet without ventricular arrhythmias. However, in previous studies late potentials were found in patients with VT but without ventricular aneurysms, and the voltage late in the filtered QRS complex was nearly identical in patients with VT despite the presence or absence of an aneurysm.[16] These findings suggest that the late potential is related to the VT and not to the ventricular aneurysm.

Second, standards should be developed to define the end points of normal and fragmented electrograms. At sufficiently high gain and with a low noise level, an electrode will record distant activity. With fragmented electrograms, the difficult of defining the end points increases. From our previous experience with ventricular mapping, we used the rapidly moving components of the electrograms to establish the end points; we recognize that this definition is somewhat arbitrary. Third, the epicardial electrodes we used had a smaller interelectrode distance (1.5 mm) than the catheter endocardial electrode (1 cm). Data from animal studies suggest that increasing the interelectrode distance does not significantly prolong the endocardial electrogram[27]; similar studies are needed in humans, especially in regions of myocardium with delayed and fragmented electrical activity.

Finally, since the signal-averaging and mapping studies were not simultaneous, it is not clear whether failure to detect some fragmented activation (as site 6-8, Fig. 4A) on the body surface represents a lack of sufficient sensitivity by the signal-averaging technique or a change in duration of the fragmented electrogram over time.

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## References


1. **Boineau JP, Cox JL.** Slow ventricular activation in acute myocardial infarction. A source of reentrant premature ventricular contractions. Circulation 1973;48:702–713.
2. **Waldo AL, Kaiser GA.** A study of ventricular arrhythmias associated with acute myocardial infarction in the canine heart. Circulation 1973;47: 1222–1228.
3. **Scherlag BJ, El-Sherif N, Hope RR, Lazzara R.** Characterization and localization of ventricular arrhythmias due to myocardial ischemia and infarction. Circ Res 1974;35:372–383.
4. **El-Sherif N, Scherlag BJ, Lazzara R.** Electrode catheter recordings during malignant ventricular arrhythmias following experimental acute myocardial ischemia. Circulation 1975;51:1003–1014.
5. **El-Sherif N, Scherlag BJ, Lazzara R, Hope RR.** Reentrant ventricular arrhythmias in the late myocardial infarction period. I. Conduction characteristics in the infarction zone. Circulation 1977;55:686–702.
6. **El-Sherif N, Hope RR, Scherlag BJ, Lazzara R.** Reentrant ventricular arrhythmias in the late myocardial infarction period. II. Patterns of initiation and termination of reentry. Circulation 1977;55:702–719.
7. **Myerburg RJ, Gelband H, Nilsson K, Sung RJ, Thurer RJ, Morales AR, Bassett AL.** Long-term electrophysiological abnormalities resulting from experimental myocardial infarction in cats. Circ Res 1977;41:73–84.
8. **Josephson ME, Horowitz LN, Farshidi A.** Continuous local electrical activity: a mechanism of recurrent ventricular tachycardia. Circulation 1978;57: 659–665.
9. **Spear JF, Horowitz LN, Hodess AB, MacVaugh H, Moore EN.** Cellular electrophysiology of human myocardial infarction. I. Abnormalities of cellular activation. Circulation 1979;59:247–256.
10. **Berbari EJ, Scherlag BJ, Hope RR, Lazzara R.** Recording from the body surface of arrhythmogenic ventricular activity during the S-T segment. Am J Cardiol 1978;41:697–702.
11. **Fontaine G, Guiraudon G, Frank R, Vedel J, Grosgogeat Y, Cabrol C, Facquet J.** Stimulation studies and epicardial mapping in ventricular tachycardia: study of mechanisms and selection for surgery. In: Kulbertus HE, ed. Reentrant Arrhythmias, Mechanisms and Treatment. Lancaster: MTP Press, 1977:333–350.
12. **Uther JB, Dennett CJ, Tan A.** The detection of delayed activation signals of low amplitude in the vectorcardiogram of patients with recurrent ventricular tachycardia by signal averaging. In: Sandoe E, Julian DG, Bell JW, eds. Management of Ventricular Tachycardia—Role of Mexiletine. Amsterdam: Excerpta Medica, 1978:80–82.
13. **Hombach V, Höpp H-W, Braun V, Behrenbeck DW, Tauchert M, Hilger HH.** Die Bedeutung von Nachpotentialen innerhalb des ST-Segmentes im Oberflächen—EKG bei Patienten mit koronarer Herzkrankheit. Dtsch Med Wochenschr 1980;105:1457–1462.
14. **Breithardt G, Becker G, Seipel L, Abendroth RR, Ostermeyer J.** Non-invasive detection of late potentials in man—a new marker for ventricular tachycardia. Eur Heart J 1981;2:1–11.
15. **Rozanski JJ, Mortara D, Myerburg RJ, Castellanos A.** Body surface detection of delayed depolarizations in patients with recurrent ventricular tachycardia and left ventricular aneurysm. Circulation 1981;63:1172–1178.
16. **Simson MB.** Identification of patients with ventricular tachycardia after myocardial infarction from signals in the terminal QRS complex. Circulation 1981;64:235–242.
17. **Simson MB, Euler D, Michelson EL, Falcone RA, Spear JF, Moore EN.** Detection of delayed ventricular activation on the body surface in dogs. Am J Physiol 1981;241(Heart Circ Physiol 10):H363–H369.
18. **Simson M, Spielman S, Horowitz L, Harken A, Josephson ME, Kastor J.** Surface ECG manifestations of ventricular tachycardia. In: Josephson ME, ed. Ventricular Tachycardia: Mechanisms and Management. Mt Kisco, NY: Futura, 1982, in press.
19. **Simson MB, Spielman SR, Horowitz LN, Harken AH, Josephson ME, Kastor JA.** Late potentials in man and cardiac arrhythmias. In: Hombach V, Hilger HH, eds. Signal Averaging Techniques in Clinical Cardiology. Stuttgart, New York: FK Schattauer Verlag, 1982, 253–264.
20. **Josephson ME, Seides SF.** Clinical Cardiac Electrophysiology: Techniques and Interpretations. Philadelphia: Lea & Febiger, 1979:247–280.
21. **Horowitz LN, Josephson ME, Farshidi A, Spielman SR, Michelson EL, Greenspan AM.** Recurrent sustained ventricular tachycardia. 3. Role of the electrophysiologic study in selection of antiarrhythmic regimens. Circulation 1978;58:986–997.
22. **Josephson ME, Harken AH, Horowitz LN.** Endocardial excision. A new surgical technique for the treatment of ventricular tachycardia. Circulation 1979;60:1430–1439.
23. **Horowitz LN, Josephson ME, Kastor JA, Harken AH.** Ventricular resection guided by epicardial and endocardial mapping for treatment of recurrent ventricular tachycardia. N Engl J Med 1980;302:589–593.
24. **Josephson ME, Horowitz LN, Farshidi A, Spear JF, Kastor JA, Moore EN.** Recurrent sustained ventricular tachycardia. 2. Endocardial mapping. Circulation 1978;57:440–447.
25. **Josephson ME, Horowitz LN, Spielman SR, Greenspan AM, VandePol C, Harken AH.** Comparison of endocardial catheter mapping with intraoperative mapping of ventricular tachycardia. Circulation 1980;61:395–404.
26. **Berbari EJ, Collins S, Salu Y, Arzbaecher R.** A computer model for stimulation of noninvasive His-Purkinje system recordings. In: Computers in Cardiology. Los Angeles: IEEE Computer Society, 1981:47–52.
27. **Durrer D, VanDer Tweel LH, Blickman JR.** Spread of activation in the left ventricular wall of the dog. III. Transmural and intramural analysis. Am Heart J 1954;48:13–35.

# Clinical Spectrum of Ventricular Tachycardia With Left Bundle Branch Morphology

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**Twenty-nine patients with apparent ventricular tachycardia (VT) of left bundle branch block (LBBB) morphology were evaluated. Tachycardia was associated with an organic basis in 24 of 29 patients: 7 had Mahaim fibers of the nodoventricular type, 7 had arrhythmogenic right ventricular dysplasia, 5 had coronary heart disease, 3 had biventricular cardiomyopathy, and 2 had associated congenital heart disease.**

**In many patients the underlying cardiac disease was not readily apparent. In the patients with a Mahaim fiber, the electrocardiogram taken during sinus rhythm was frequently normal. A reentry tachycardia with anterograde conduction over the nodoventricular fiber could mimic VT as diagnosed by the usual criteria; nodoventricular fibers were, therefore, often unsuspected before electrophysiologic evaluation. In patients with arrhythmogenic right ventricular dysplasia, cineangiography demonstrated abnormalities of the right ventricle, but only minor or no abnormalities of the left ventricle. Clinical and electrocardiographic features were not distinctive. Of the 29 patients, 22 had serious symptoms accompanying the tachyarrhythmia or had required cardioversion. Patients were followed up for an average of 20 months: 4 patients died. Thus, VT exhibiting an LBBB morphology is not uncommon and is frequently associated with organic heart disease, serious symptoms, and significant mortality. Right ventricular angiography and electrophysiologic study may clarify the diagnosis in these patients.**

Recurrent VT may be a manifestation of a variety of organic heart diseases with differing prognostic and therapeutic significance. It is often difficult to distinguish between the various causes based on clinical features alone. The QRS morphology of the VT has sometimes been assumed to convey useful diagnostic information by indicating the ventricle of origin[1–6]—tachycardia having an LBBB morphology originating from the right ventricle and tachycardia having a right bundle branch block (RBBB) morphology originating from the left ventricle. It was recently shown, however, that the assignment of the origin of the tachycardia on the basis of the bundle branch block morphology of the tachycardia may be misleading.[7,8] Nevertheless, it is frequently suggested that premature ventricular beats or VT with an LBBB morphology imply a benign prognosis and are often unassociated with organic heart disease.[2,6,9,10] These observations have not been confirmed by other investigators,[11,12] and the significance of VT with an LBBB morphology remains unknown. This report assesses the implications of a tachycardia exhibiting an LBBB morphology among patients referred to this institution for evaluation of recurrent VT.

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## Methods

Patients referred to Duke University Medical Center with presumed recurrent VT as defined by electrocardiographic or His bundle electrographic criteria were eligible for the study. Patients with intact atrioventricular accessory pathways were excluded. VT was diagnosed when a wide QRS tachycardia with either atrioventricular dissociation (on the surface electrocardiogram or documented by eosphageal recording), atrial capture beats, or fusion beats were identified. In equivocal cases, VT was diagnosed if the QRS complex during the tachycardia was not preceded by a His bundle deflection or was preceded by a His deflection at an H-V interval shorter than that seen during sinus rhythm.[13] At least 2 documented episodes of sustained VT (≥1 minute) were required for inclusion in this study. In most cases, the number of episodes far exceeded this minimum. Patients with myocardial infarction within the preceding 6 weeks, suspected

**TABLE I Clinical Features in 29 Patients With Tachycardia Exhibiting an LBBB Morphology**

| Case | Age (yr) & Sex | Cardiac Diagnosis | Presenting Symptoms | Duration of Symptoms | History of Cardioversion | Therapy | Follow-Up (mo) |
|---|---|---|---|---|---|---|---|
| | | | Patients With Nodoventricular Fibers | | | | |
| 1 | 15M | NVF, Ebstein's anomaly | Palpitations, presyncope | 4 yr | No | Quinidine | No recurrence (38) |
| 2 | 14M | NVF, S/P closure of ASD | Palpitations, CP | 3 days | Yes | Quinidine | No recurrence (21) |
| 3 | 4M | NVF | Palpitations | 4 days | No | Quinidine | Recurrence X1 (42) |
| 4 | 34F | NVF | Palpitations, syncope | 2 yr | Yes | Quinidine | No recurrence (32) |
| 5 | 18F | NVF, Ebstein's anomaly, S/P division of Kent bundle | Palpitations, presyncope | 1 mo | Yes | Digoxin + verapamil | No recurrence (48) |
| 6 | 20M | NVF, Ebstein's anomaly, S/P division of Kent bundle | Palpitations | 5 mo | Yes | None | No recurrence (42) |
| 7 | 34M | NVF | Palpitations | 6 yr | Yes | Verapamil | No recurrence (1) |
| | | | Patients With Arrhythmogenic Right Ventricular Dysplasia | | | | |
| 8 | 37M | ARVD, CREST syndrome | Presyncope, CP | 4 mo | Yes | Cryoablation of tachycardia origin (RVOT) | Recurrence X1 (42) |
| 9 | 13F | ARVD | Palpitations, seizures | 13 mo | Yes | Quinidine | Sudden death (19) |
| 10 | 69M | ARVD | Dizziness | 12 yr | Yes | EEV (posterior RV) | Recurrence X2 (9) |
| 11 | 41F | ARVD, MVP | Palpitations, syncope | 8 yr | No | Amiodarone | No recurrence (18) |
| 12 | 16M | ARVD | Syncope | 15 mo | No | Amiodarone | No recurrence (9) |
| 13 | 33M | ARVD | Palpitations, syncope | 7 mo | Yes | Quinidine | No recurrence (5) |
| 14 | 67F | ARVD | Palpitations, fatigue | 6 mo | Yes | PA | No recurrence (2) |
| | | | Patients With Coronary Artery Disease | | | | |
| 15 | 45M | CAD, LV aneurysm | Palpitations, VF | 8 mo | Yes | EEV (posterior LV) | No recurrence (16) |
| 16 | 52M | CAD, LV aneurysm | Palpitations, CP | 10 mo | Yes | Endocardial resection, aneurysmectomy (anterior LV) | No recurrence (12) |
| 17 | 67M | CAD, LV aneurysm | Seizures | 18 mo | Yes | EEV, aneurysmectomy, (posterior LV), CABG | Perioperative death (renal failure) |
| 18 | 57M | CAD, LV & RV aneurysm; CHF | Dizziness, presyncope | 27 mo | Yes | Tocainide + PA | Died (1) |
| 19 | 57M | CAD, LV aneurysm | Palpitations | 6 yr | Yes | Endocardial resection, aneurysmectomy, (posterior LV), CABG | No recurrence (2) |
| | | | Patients With Miscellaneous Causes | | | | |
| 20 | 29M | Cardiomyopathy | Palpitations, syncope, CPA | 8 yr | Yes | Disopyramide phosphate | Sudden death (25) |
| 21 | 16F | Cardiomyopathy | Palpitations, syncope | 5 yr | No | EEV, cryoablation of tachycardia origin (RVOT) | No recurrence (22) |
| 22 | 36M | Cardiomyopathy, MVP | Palpitations | 1 yr | No | Disopyramide phosphate and propranolol | No recurrence (21) |
| 23 | 20M | Ebstein's anomaly | Syncope, shock | 3 yr | Yes | Disopyramide phosphate | No recurrence (39) |
| 24 | 22M | Corrected tetralogy of Fallot | Dizziness, presyncope | 11 yr | Yes | Quinidine | No recurrence (16) |
| 25 | 50F | None | Weakness, dizziness, presyncope | 1 mo | No | Disopyramide phosphate | Recurrence X5 (33) |
| 26 | 52M | None | Palpitations, chest pain | 10 yr | No | Disopyramide phosphate | No recurrence (17) |
| 27 | 27M | None | Palpitations, CP | 2 yr | No | Tocainide | No recurrence (7) |
| 28 | 20F | None | Syncope | 6 yr | No | None | No recurrence (2) |
| 29 | 28M | None | Palpitations | 2 yr | No | Propranolol | No recurrence (2) |

ARVD = arrhythmogenic right ventricular dysplasia; ASD = atrial septal defect; CABG = coronary artery bypass graft; CAD = coronary artery disease; CP = chest pain; CPA = cardiopulmonary arrest; CREST = calcinosis, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia; EEV = encircling endocardial ventriculotomy; LV = left ventricle; MVP = mitral valve prolapse; NVF = nodoventricular fiber; PA = procainamide; RV = right ventricle; RVOT = right ventricular outflow tract; S/P = status post; VT = ventricular fibrillation.

drug toxicity, or an acute precipitating cause of VT were excluded. No patient exhibited a Q-T prolongation syndrome. Fifty patients who fulfilled these criteria and who underwent electrophysiologic study comprise the study population.

LBBB morphology was diagnosed when the QRS complex exceeded 120 ms and was predominantly negative in lead $V_1$ with a terminal S wave. RBBB morphology was diagnosed when there was a predominantly positive QRS complex in lead $V_1$ with a terminal R wave. Serious arrhythmias were defined by the occurrence of seizure, syncope, shock, or cardiac arrest in association with the tachycardia.

All patients were placed on continuous telemetry upon admission to the hospital. When appropriate, all cardioactive medications were discontinued before study. All patients had a history and physical examination, routine blood work, electrocardiogram, and chest x-ray before electrophysiologic study. Each patient underwent additional evaluation to determine the nature and extent of organic heart disease. The specific studies were dictated by the clinical circumstances but frequently included right or left heart catheterization, or both, and ventriculography, coronary angiography, 2-dimensional (2-D) echocardiography, and radionuclide angiography. M-mode and 2-D echocardiography were performed using standard techniques.[14,15] Single-pass and multigated radionuclide angiography were performed after the intravenous injection of 30 mCi of technetium-99m using standard techniques.[16]

All but 1 patient underwent electrophysiologic study by the catheter technique (43 patients) or intraoperative study (13 patients), or both, using techniques fully described elsewhere.[17,18] During the study in the electrophysiology laboratory, the right atrial catheter was advanced into the right ventricle for purposes of mapping during tachycardia or for programmed intracardiac stimulation from multiple sites (apex, high and low outflow tract, septum, and inflow tract) within the right ventricle. The protocol for inducing VT included the introduction of (1) progressively more premature single, then (2) double extrastimuli during ventricular pacing at 1 or more pacing rates, and (3) bursts of rapid pacing from the apex of the right ventricle, right ventricular outflow tract, or left ventricle. Termination of the tachycardia was attempted using single or double premature extrastimuli and rapid ventricular pacing. Left ventricular pacing was accomplished by way of either the distal electrode pair of the coronary sinus catheter or retrograde catheterization of the left ventricle from the right femoral artery. No serious complications were encountered.

## Results

Of our 50 patients (Fig. 1), 58% had VT exhibiting an LBBB morphology. No organic basis for the tachycardia was found in 5 of the 29 patients with LBBB morphology (a proportion similar to that found in patients with RBBB morphology, 3 of 18 patients). The other 24 patients with tachycardia having LBBB morphology had 1 of the following causes: Mahaim fiber of the nodoventricular type (7 patients), arrhythmogenic RV dysplasia (7 patients), coronary artery disease (5 patients), biventricular cardiomyopathy (3 patients), or congenital heart disease (2 patients) (Table I).

**Patients with nodoventricular Mahaim fibers:** Patients with a nodoventricular fiber tended to be younger than other patients with tachycardia exhibiting an LBBB morphology with a mean age of 20 years (range 4 to 34). Palpitations were the most common presenting symptom and serious symptoms were infrequent. One patient had had syncope during tachycardia and 5 patients had a history of cardioversion. Associated cardiac disease (Ebstein's anomaly, atrial septal defect, atrioventricular accessory pathway) was not uncommon.

During sinus rhythm, all patients with a nodoventricular fiber had a normal P-R interval. The configuration of the QRS complexes in sinus rhythm either showed varying degrees of LBBB morphology (5 patients) (Fig. 2) or was consistently normal (2 patients). Only a single morphology was observed during spontaneous tachycardia.

The presence of a nodoventricular fiber in these patients and its anterograde involvement in a reentry tachycardia was demonstrated by previously described

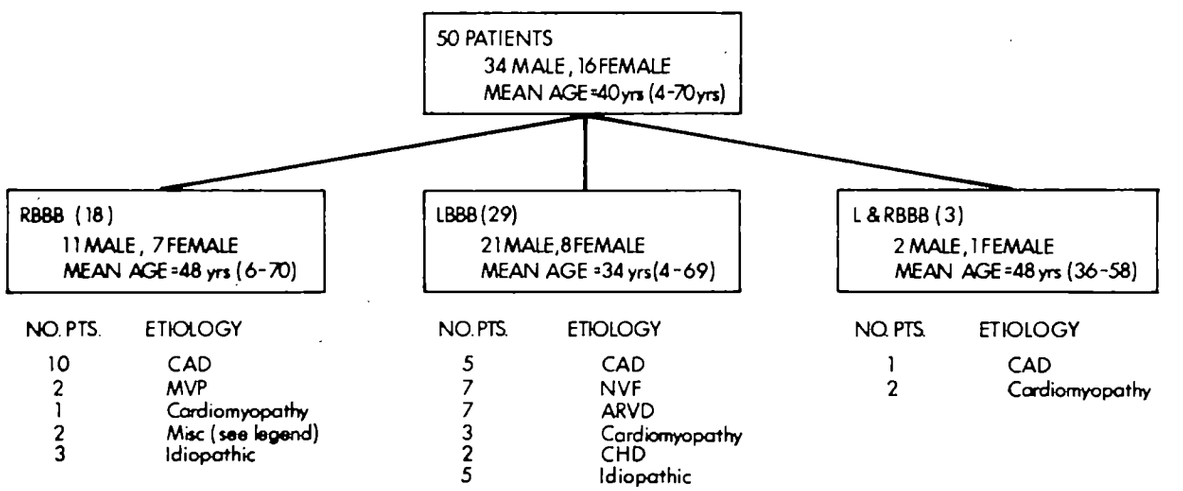



**FIGURE 1.** Tachycardia morphology and distribution of etiologies in 50 patients with recurrent VT. One patient with VT with an RBBB morphology had a left ventricular aneurysm of uncertain cause and another had a catecholamine-related tachycardia. ARVD = arrhythmogenic right ventricular dysplasia; CAD = coronary artery disease; CHD = congenital heart disease; MVP = mitral valve prolapse; NVF = nodoventricular fiber.

**TABLE II Electrocardiographic and Electrophysiologic Features of Patients With Tachycardia Exhibiting LBBB Morphology**

| | | Sinus Rhythm: 12-Lead ECG | | | Spontaneous Tachycardia, 12-Lead ECG | | | Electrophysiologic Study | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case | P-R | QRS | Axis | Comments | Morphologies (n) | Axis (°) | C-L (ms) | P-A (ms) | A-H (ms) | H-V (ms) | Inducible | Modes of Initiation | Termination by PS |
| 1 | 0.17 | 0.10–0.14 | 90° | QRSM variable IRBBB—LBBB | 1 | 60° | 210–380 | 60–65 | 60–110 | 0–55 | Yes | RV $S_2$ | Yes |
| 2 | 0.17 | 0.16 | −30° | RBBB—LBBB | 1 | −60° | 240–260 | 20 | 155–215 | 0–45 | Yes | RA pacing | Yes |
| 3 | 0.14 | 0.14 | +120° | RBBB | 1 | −45° | 250–300 | 25 | 55 | 35 | Yes | RV $S_2$ | Yes |
| 4 | 0.14 | 0.08–0.16 | −10° | N—LBBB | 1 | 0° | 290–400 | 45 | 60–85 | 15–45 | Yes | RV pacing RA pacing | Spontaneous |
| 5 | 0.16 | 0.08–0.16 | −30° | N—LBBB | 1 | 0° | 320 | 45 | 120 | 0–25 | Yes | RA $S_2$ | Spontaneous |
| 6 | 0.17 | 0.09–0.16 | −20° | LAE RBBB—LBBB | 1 | 0° | 400 | 30 | 140 | 0–55 | No | Spontaneous | . . . |
| 7 | 0.15 | 0.08 | 80° | Persistently N QRSM | 1 | −30° | 300–370 | 50 | 56 | 45 | Yes | RV $S_2$, RA, CS pacing | Yes |
| 8 | 0.18 | 0.08 | −20° | Low voltage $T\downarrow V_1$–$V_6$ | 1 | −30° | 215–430 | Paced | 180 | 50 | No | Spontaneous | No, incessant |
| 9 | 0.16 | 0.09 | 70° | $S_{I,II,III}$ IRBBB, $T\downarrow V_1$–$V_3$ | 1 | −30° | 215–230 | 40 | 40 | 50 | Yes | RVOT $S_3$ | Spontaneous |
| 10 | 0.24 | 0.10 | 30° | Low voltage, IVCD, $T\downarrow V_1$–$V_6$, $\epsilon$ potential | 1 | −45° | 360–520 | 40 | 140 | 60 | Yes | RVA pacing | Yes |
| 11 | 0.14 | 0.09 | 45° | $T\downarrow V_1$–$V_2$ | 1 | 110° | 280–340 | 40 | 33 | 40 | No | Spontaneous | No |
| 12 | 0.18 | 0.08 | 10° | $T\downarrow V_1$–$V_4$ | 2 | +110°, −60° | 250–300 | 50 | 48 | 43 | Yes | RVA $S_3$ RVOT $S_2$ | Spontaneous |
| 13 | 0.18 | 0.08 | 45° | Low voltage, $T\downarrow V_1$–$V_5$ | 2 | −30°, −90° | 270 | Not performed | | | | | |
| 14 | 0.16 | 0.10 | 90° | Low voltage, IRBBB, $T\downarrow$ | 1 | −60° | 325–430 | Paced | 150 | 45 | Yes | RVA pacing | Yes |
| 15 | 0.18 | 0.10 | 60° | Inferior MI, low voltage, $T\downarrow V_1$–$V_5$ | 1 | −60° | 240 | 42 | 68 | 44 | Yes | LV pacing | Yes |
| 16 | 0.18 | 0.12 | −120° | Anterolateral MI, persistent S-T abnormality | 2 | −80°, +120° | 220–420 | 42 | 57 | 52 | Yes | RVA pacing | Yes |
| 17 | 0.17 | 0.08 | −30° | Diaphragmatic MI | 1 | −80° | 300 | * | * | 40 | No | Spontaneous | No |
| 18 | 0.16 | 0.11 | 60° | Diaphragmatic MI, persistent S-T abnormality | 2 | −90°, 30° | 230–470 | 55 | 45 | 55 | Yes | RVA $S_3$ | Yes |
| 19 | 0.19 | 0.11 | −30° | Diaphragmatic lateral MI, persistent S-T abnormality | 1 | −70° | 480 | 35 | 85 | 58 | Yes | RVA $S_2$ | Yes |
| 20 | 0.14 | 0.08 | 60° | Low voltage $T\downarrow V_1$–$V_4$ | 2 | 70°, 90° | 270–360 | 40 | 55 | 45 | Yes | RVA $S_3$ | No |
| 21 | 0.13 | 0.08 | 80° | $T\downarrow V_1$–$V_3$ | 1 | 80° | 300–400 | 45 | 40 | 44 | Yes | RVA $S_3$ | Yes |
| 22 | 0.18 | 0.10 | 90° | IRBBB | 1 | 90° | 250 | 52 | 70 | 66 | No | . . . | No |
| 23 | 0.23 | 0.18 | −45° | Low voltage, RBBB | 1 | −30° | 320 | 75 | 85–90 | 65 | Yes | RVA $S_3$ | Spontaneous |
| 24 | 0.17 | 0.18 | −60° | RBBB | 1 | −90° | 215–270 | 45 | 40 | 50 | Yes | RVOT pacing RVA $S_3$ | Yes |
| 25 | 0.12 | 0.08 | 70° | $T\downarrow V_1$–$V_2$ | 2 | 80°, 100° | 390–430 | 42 | 82 | 48 | Yes | RVA $S_3$† | Spontaneous |
| 26 | 0.16 | 0.09 | 20° | N | 1 | 100° | NA | 50 | 60 | 43 | No | Spontaneous | No |
| 27 | 0.16 | 0.08 | 75° | Low voltage | 1 | 80° | 280–430 | 52 | 50 | 45 | Yes | RVA $S_2$ | Yes |
| 28 | 0.14 | 0.09 | 80° | N | 1 | 45° | 420–480 | 35 | 55 | 50 | No | Spontaneous | No |
| 29 | 0.16 | 0.06 | 60° | N | 1 | 110° | 300–335 | 55 | 75 | 60 | No | Spontaneous | No |

* Underlying rhythm was atrial flutter-fibrillation. † During isoproterenol infusion.

CL = cycle length; CS = coronary sinus; ECG = electrocardiogram; $\epsilon$ = epsilon potential; IRBBB = incomplete right bundle branch block; IVCD = intraventricular conduction delay; LAE = left atrial enlargement; LV = left ventricle; MI = myocardial infarction; N = normal; NA = not available; PS = programmed stimulation; QRSM = QRS morphology; RA = right atrium; RV = right ventricle; RVA = right ventricular apex; RVOT = right ventricular outflow tract.

electrophysiologic criteria.[19] Tachycardia using the nodoventricular fiber in the anterograde direction exhibited features suggestive of VT including the following: wide QRS tachycardia with LBBB morphology (7 patients), absence of a His deflection preceding the QRS complexes during tachycardia (7 patients), and ventriculoatrial dissociation during tachycardia (3 patients). Tachycardia could be frequently induced or terminated by premature atrial stimuli or rapid atrial pacing (Table II).

Six patients remain well and free of sustained symptomatic tachycardia on medical therapy (mean follow-up 30 ± 17 months). One patient, a 4-year-old boy, had been treated with quinidine, initially with a dose that was therapeutic. During his growth this dose became inadequate and he developed recurrent tachycardia. Since his dosage was adjusted, he has had no tachycardia.

**Patients with arrhythmogenic right ventricular dysplasia:** Seven patients were felt to have arrhythmogenic right ventricular dysplasia.[20] Four patients had had serious symptoms in association with their arrhythmia and 5 patients had required multiple cardioversions. Five patients had symptoms predominantly or exclusively associated with exercise or activity.

Associated cardiac disease was unusual. There was no obvious familial association but 1 patient had a family history of sudden death and another had a sibling with exercise-induced VT. Patients with arrhythmogenic right ventricular dysplasia had no distinctive physical findings, although 1 patient presented with right ventricular failure. Chest x-rays were typically normal and electrocardiographic features during sinus rhythm were nonspecific (Fig. 3, top left): low voltage in the limb leads (4 patients), T-wave inversion in the right precordial leads (7 patients), nonspecific intra-

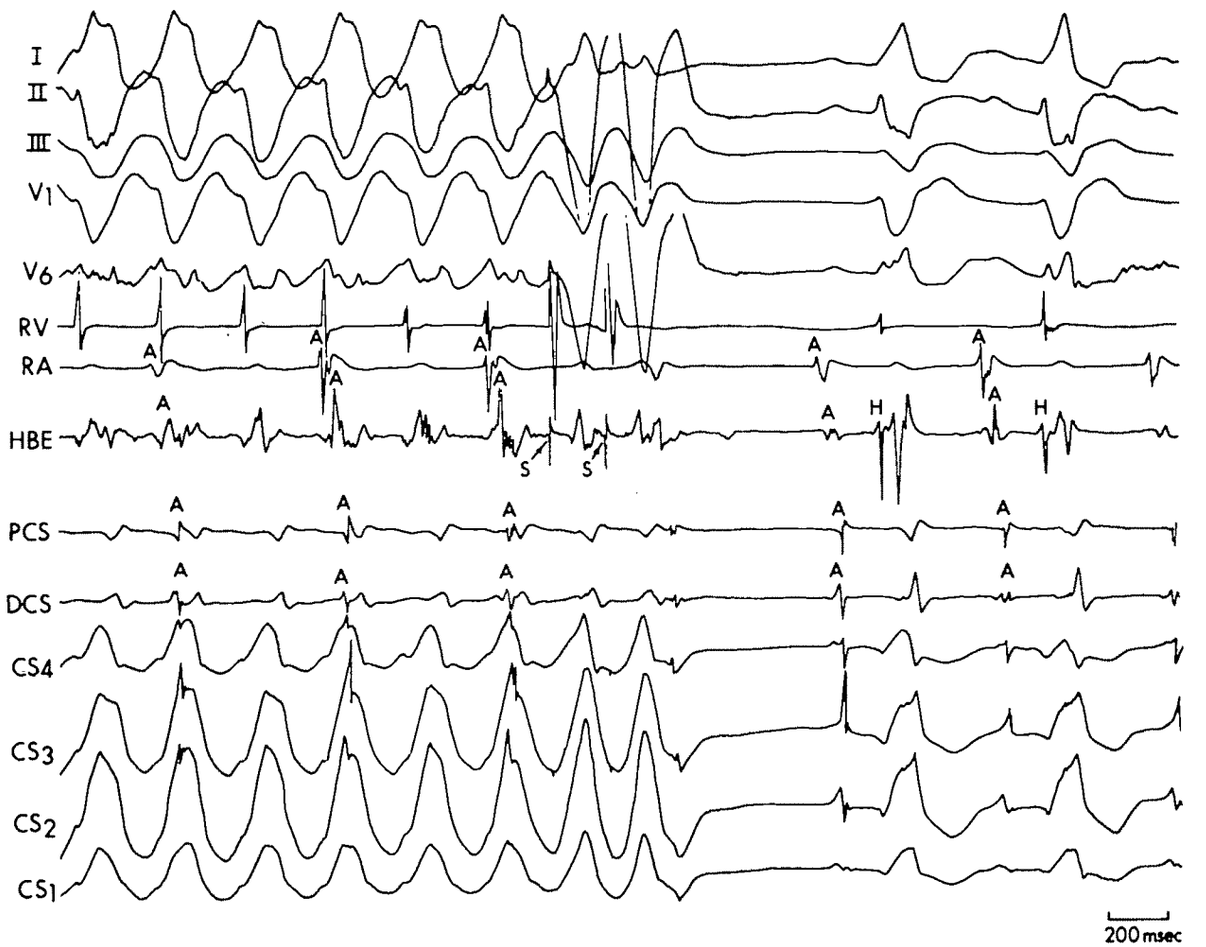



**FIGURE 2.** Patient 2. Termination of reciprocating tachycardia in a patient with a nodoventricular fiber. Recordings from **top** to **bottom** include standard electrocardiographic leads I, II, III, $V_1$, and $V_6$; bipolar electrograms recorded from the right ventricular apex (RV), the right atrium (RA), the region of the His bundle (HBE), the proximal coronary sinus (PCS), and the distal coronary sinus (DCS); and unipolar electrograms recorded from the proximal ($CS_4$) to the distal ($CS_1$) coronary sinus. Initially, tachycardia with an LBBB morphology is present. No His electrogram is visible before the QRS complexes and there is complete ventriculoatrial dissociation. After 7 beats of tachycardia, 2 successive ventricular premature depolarizations are introduced, resulting in conversion to sinus rhythm. The morphologies of the ventricular complexes in sinus rhythm are similar to those during the tachycardia and show varying degrees of LBBB aberration; in addition, the His deflection occurs after the onset of the surface QRS complex.

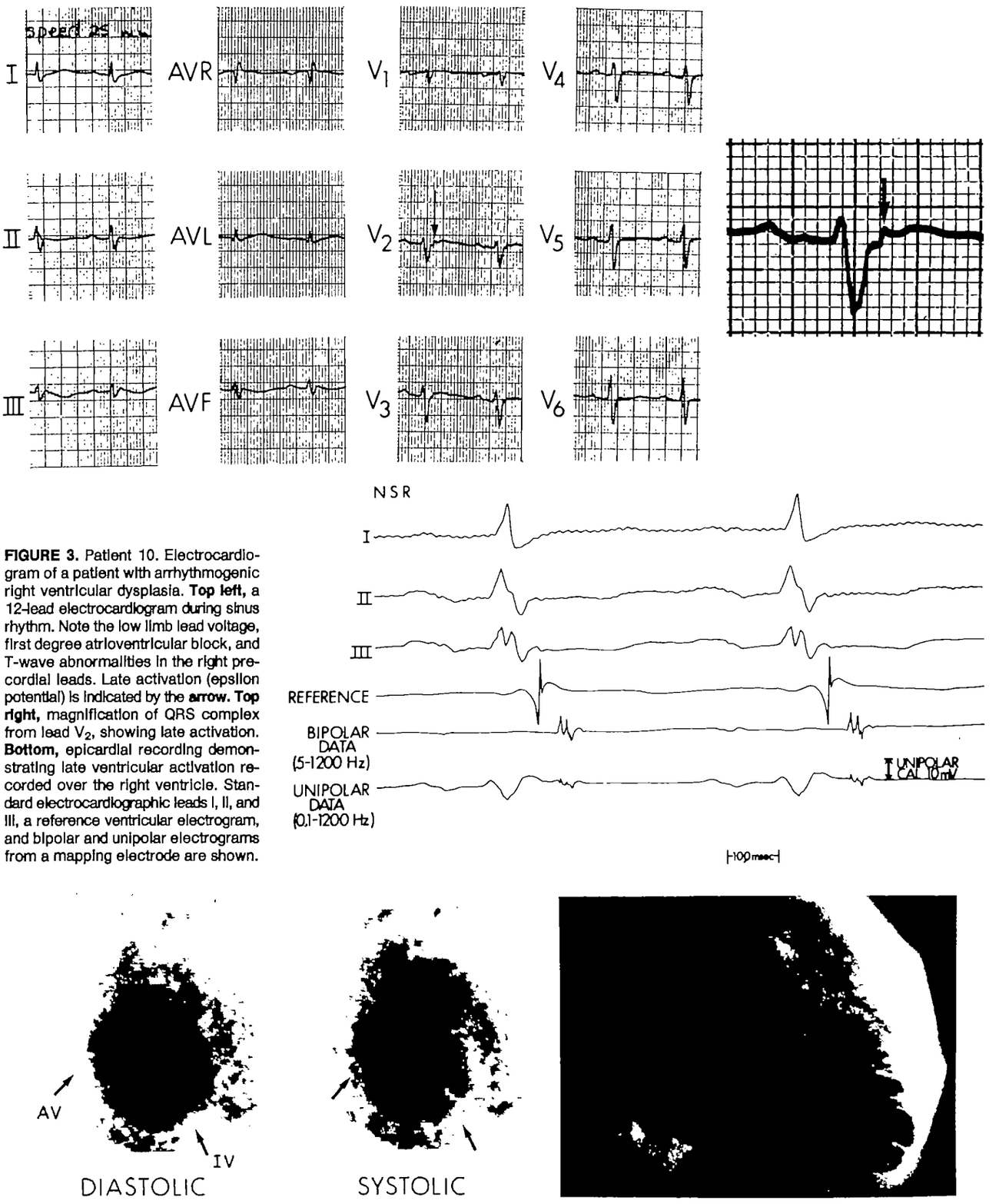



**FIGURE 3.** Patient 10. Electrocardiogram of a patient with arrhythmogenic right ventricular dysplasia. **Top left,** a 12-lead electrocardiogram during sinus rhythm. Note the low limb lead voltage, first degree atrioventricular block, and T-wave abnormalities in the right precordial leads. Late activation (epsilon potential) is indicated by the **arrow. Top right,** magnification of QRS complex from lead $V_2$, showing late activation. **Bottom,** epicardial recording demonstrating late ventricular activation recorded over the right ventricle. Standard electrocardiographic leads I, II, and III, a reference ventricular electrogram, and bipolar and unipolar electrograms from a mapping electrode are shown.




**FIGURE 4.** Patient 12. Comparison of radionuclide angiograms and a cineangrogram in a patient with arrhythmogenic right ventricular dysplasia. **Left,** multigated radionuclide angiograms taken in the left anterior oblique view with 45° of caudal inclination of the camera, end-diastolic and end-systolic frames. The **arrows** indicate the plane of the interventricular septum (IV) and the atrioventricular groove (AV). The right ventricle is markedly enlarged and hypokinetic (ejection fraction 15%). The left ventricle is normal in size and function (ejection fraction 74%). **Right,** cineanglogram, posteroanterior view. The right ventricle is enlarged and hypokinetic, and there are akinetic segments of the apex, diaphragmatic surface, and outflow tract. Delay is evident in the emptying of the right ventricle along the inferior border, with stagnation of contrast material.

ventricular conduction delay (4 patients), and first-degree block (1 patient). The electrical axis was normal in all patients. Only 1 patient showed evidence of delayed depolarization (epsilon potential)[21] on the standard electrocardiogram (Fig. 3).

Despite the lack of characteristic clinical features, noninvasive evaluation frequently suggested right ventricular abnormalities in these patients. In 5 of the 6 patients who had echocardiographic studies (Table III), the right ventricular chamber appeared enlarged and hypokinetic. The left ventricles appeared normal in all patients. Only 1 patient, who only had an M-mode study, had a normal echocardiogram.

Dramatic right ventricular enlargement and hypokinesia were seen in the 3 patients who underwent radionuclide study (Fig. 4, left). Right ventricular ejection fractions were estimated at <30% for the 3 patients who had left ventricular ejection fractions of 58, 74, and 70%, respectively. In 1 patient, focal right ventricular wall motion abnormalities were also detected by radionuclide angiography.

With right ventricular angiography, all of these patients demonstrated global dysfunction and enlargement of the right ventricle in addition to localized right ventricular dyskinesia or diverticula of the right ventricular wall (Fig. 4). Localized abnormalities of the right ventricular wall were frequently multiple. Despite the angiographic abnormalities, right-sided hemodynamic function was typically normal. Only 2 patients had modest elevation of the right ventricular end-diastolic pressure (16 mm Hg in both).

Findings on left ventricular angiography were normal in 4 patients, with 3 having only minor wall motion abnormalities of the left ventricle. Left ventricular end-diastolic pressure was normal in all patients and none had significant coronary artery disease.

All but 1 patient with arrhythmogenic right ventricular dysplasia underwent electrophysiologic study. Initiation of VT by programmed right ventricular stimulation was possible in 4 of the 6 and could be terminated by right ventricular pacing in both patients in which it was sustained.

Endocardial and intraoperative mapping during VT localized the site of earliest ventricular activation to the right ventricle in all 6 patients. In the 2 patients who underwent intraoperative mapping, late activation (Fig. 3, bottom) and low amplitude, fragmented potentials were present over extensive portions of the right ventricle. Activation of the left ventricle appeared normal.

Five patients were treated medically and 2 underwent surgery: 1 patient underwent cryoablation of an ectopic focus,[22] and in the other a large portion of the right ventricle was isolated by an encircling endocardial ventriculotomy.[23] One patient (Patient 9) treated with quinidine died suddenly 19 months after evaluation,

**TABLE III Angiographic, Echocardiographic, and Radionuclide Angiographic Findings in Patients With Arrhythmogenic Right Ventricular Dysplasia**

| | Angiography | | | | Echocardiography | | |
|---|---|---|---|---|---|---|---|
| Case | RV Enlargement and Global Dysfunction | Local RV Dyskinesia | RV Diverticulum | LV Abnormalities (EF) | M-Mode | 2-Dimensional | Radionuclide Angiography |
| 8 | Yes | Yes | ... | None (44%) | Not performed | Not performed | Not performed |
| 9 | Yes | Yes | ... | None (52%) | Enlarged RV | Enlarged RV, paradoxical septal motion, normal LV | Not performed |
| 10 | Yes | Yes | Apex, INF, DIAPH | Apical dyskinesia (58%) | Enlarged & hypokinetic RV, paradoxical septal motion | Enlarged & hypokinetic RV; paradoxical septal motion | Hypokinetic RV (EF 34%) |
| 11 | Yes | ... | | None | MVP, normal RV, normal LV | Not performed | Not performed |
| 12 | Yes | Yes | INF (multiple) | None (74%) | Enlarged RV | Enlarged & hypokinetic RV, normal septal motion | Enlarged & hypokinetic RV (EF 15%), with inferospical dyskinesia, normal LV |
| 13 | Yes | Yes | | Anterior hypokinesia (57%) | Enlarged RV | Not performed | Not performed |
| 14 | Yes | Yes | INF, DIAPH | 1(+) MR, apical dyskinesia (70%) | Enlarged RV | Enlarged & hypokinetic RV, paradoxical septal motion, pericardial effusion, normal LV | Enlarged & hypokinetic RV (EF 19%), with akinesia of anterior, apical, & inferior wall |

DIAPH = diaphragmatic surface; EF = ejection fraction; INF = infundibulum; LV = left ventricle; MR = mitral regurgitation; MVP = mitral valve prolapse; RV = right ventricle.

although she was shown to have therapeutic serum quinidine levels at the time of death. The remaining 6 patients were alive and well at follow-up (mean 14 months, range 2 to 42.)

**Patients with coronary artery disease:** Five male patients (45 to 67 years of age, mean 56) had coronary artery disease. Two patients had had serious symptoms associated with VT and all had required multiple cardioversions. Angiography confirmed the presence of a left ventricular aneurysm in all patients.

The electrocardiogram indicated prior myocardial infarction in all 5 patients and 3 showed persistent S-T segment elevation, suggesting the presence of a ventricular aneurysm.

Four of the 5 patients had inducible sustained VT. Intraoperative mapping showed that VT originated in the interventricular septum bordering the aneurysm in 4 patients. The fifth patient underwent catheter endocardial mapping which was consistent with a left ventricular origin of the tachycardia.

Four patients were treated surgically. Two underwent an encircling endocardial ventriculotomy as described by Guiraudon et al[24] and 2 underwent endocardial resection. There was 1 perioperative death. Three patients were alive and without clinical recurrence 2, 12, and 16 months postoperatively. One patient with congestive failure and progressive glomerulonephritis was treated medically and died within 1 month of evaluation.

**Patients with biventricular cardiomyopathy:** Three patients were found to have a biventricular cardiomyopathy. Symptoms in these patients were primarily related to episodes of VT. Two of the 3 had had syncope. Symptoms of left ventricular failure were not prominent in any of the 3. All 3 patients underwent cineangiography of the right ventricle and had localized right ventricular contraction abnormalities, but no patient was observed to have sacculations or diverticula of the right ventricle. Two patients had normal coronary angiograms; the third patient, a 16-year-old girl, did not undergo coronary angiography.

Endocardial mapping during tachycardia demonstrated ventricular activation to be earliest in the right ventricle in 2 patients. One patient (Patient 21) was also mapped intraoperatively. The earliest area of activation was located in the right ventricular outflow tract.

One patient underwent surgical cryoablation of the site of origin of the VT with additional encircling transmural ventriculotomy. She remains well and free of arrhythmia 22 months after surgery. One medically treated patient had progressively more frequent episodes of recurrent VT despite aggressive antiarrhythmic therapy and died suddenly 25 months after initial evaluation. The other medically treated patient was alive and well at follow-up.

**Patients with congenital heart disease:** Two male patients had congenital heart disease; 1 had Ebstein's anomaly and the other had undergone complete surgical repair of tetralogy of Fallot 15 years previously. Neither had significant hemodynamic abnormalities. The patient with Ebstein's anomaly had had syncope and hypotension during VT. Both had required cardioversion.

Both patients had VT that could be induced. Earliest activation was recorded from the right ventricle in both patients. Both patients have been free of sustained recurrent tachycardia on medical therapy alone, at 16 and 39 months after evaluation.

**Patients without organic heart disease:** In 5 patients, 3 male and 2 female (20 to 52 years old, mean 35), no cause of tachycardia could be demonstrated. Only 1 of these 5 patients had had serious symptoms in association with the tachycardia; none had required cardioversion. All 5 patients had normal left ventriculograms, no significant coronary artery disease, and right ventriculograms that were considered normal.

VT could be induced in only 2 of the 5 patients. Limited endocardial activation mapping was carried out in 3 patients during tachycardia and in 1 patient during a period when frequent premature ventricular contractions occurred. Earliest ventricular activation occurred in the right ventricle in 3 patients and in the region of the His bundle catheter in 1 patient.

All 5 patients have received medical therapy. Mean follow-up has been 12 months (range 2 to 33). Four patients have had no sustained tachycardia. One patient has had a recurrence of VT about every 6 months.

## Discussion

The present study describes the findings in 29 patients with tachycardia exhibiting exclusively an LBBB morphology. More than 80% had an associated cardiac abnormality. This finding differs from those in other studies[9,10] in which idiopathic ventricular tachycardia was more common in patients exhibiting LBBB configuration than in patients whose VT had RBBB morphology. The reason for this difference is uncertain, but no cases of arrhythmogenic right ventricular dysplasia or nodoventricular fibers were reported in the other series. Since both may be mistaken for idiopathic VT in the absence of right ventriculography or electrophysiologic study, the difference may be related to the nature of the diagnostic evaluation in previously reported series. We routinely performed right heart angiography and complete electrophysiologic study in these patients. Alternatively, the discrepancy may be due to differences in case selection. Our referral population tends to select patients with uncertain cause and management difficulty. Thus, the proportion of patients with arrhythmogenic right ventricular dysplasia and nodoventricular fibers in the present study may be high and not representative for an unselected population of patients with VT having LBBB morphology.

Patients with nodoventricular fibers were included in this study because the reentry tachycardia mimicked VT. Indeed, these patients were often referred with a presumptive diagnosis of VT. The presence of LBBB morphology, indicating preexcitation of the right ventricle, was observed intermittently during sinus rhythm in 5 of 7 and consistently during tachycardia in 7 of 7 patients. No patient with a nodoventricular fiber preexciting the left ventricle has been seen in over 400 cases of preexcitation studied in this laboratory. Thus, the presence of a Mahaim fiber should be considered and excluded in the setting of a tachycardia having LBBB morphology, especially if the QRS complexes

during sinus rhythm show varying degrees of apparent LBBB aberration.

Arrhythmogenic right ventricular dysplasia was diagnosed in 7 patients. This cardiomyopathy primarily involves the right ventricle and was first characterized by Fontaine et al.[25] In their studies as well as in the present study, the disorder exhibited no distinctive clinical or electrocardiographic characteristics. The lack of characteristic clinical features and the presence of normal chest x-rays and left ventricular angiograms suggested an idiopathic VT in the absence of any further evaluation. The diagnosis can be made by right ventricular angiography. Echocardiography and radionuclide angiography were also seen to be sensitive in detecting isolated abnormalities of the right ventricle. These techniques may be useful for noninvasive screening and follow-up of these patients.

Diagnosis of the underlying disease in patients manifesting tachycardia with an LBBB morphology has prognostic and therapeutic implications. Patients with nodoventricular fibers were usually without serious symptoms, had a relatively benign course, and were responsive to medical management. In contrast, the diagnosis of arrhythmogenic right ventricular dysplasia may be associated with serious symptoms and sudden death. The severity and frequency of symptoms in patients with arrhythmogenic right ventricular dysplasia varied widely, but there was no apparent relation between the severity of the arrhythmia and the degree of angiographic abnormality. The course of the process was also variable and no patient with a clearly progressive course has been identified. However, the observation that all of these patients have had serious associated symptoms or cardioversion and the sudden death of a 14-year-old child 19 months after diagnosis indicated that this disorder is not benign.

Most of our patients with arrhythmogenic right ventricular dysplasia have been managed medically. The potential for surgical therapy in medically refractory persons with this condition was confirmed in 2 of our patients.[26] In 1, VT with a different morphology reemerged 23 months after successful cryoablation surgery. Thus, it is possible that a new focus of VT may appear after successful surgical therapy.

Patients with coronary artery disease and biventricular cardiomyopathy had, as expected, significant mortality. Patients without apparent organic heart disease had a good prognosis and rarely had serious associated symptoms.

We conclude that for the referred population of patients with recurrent symptomatic VT, tachycardia originating from the right ventricle is not uncommon and is usually associated with organic heart disease. Prognosis depends on the underlying organic disease but serious symptoms occur often and characterization of right ventricular tachycardia as benign are unjustified. Electrophysiologic studies and right ventricular cineangiography are helpful in the complete evaluation of these patients.

## Addendum

Since submission of this report, 2 of our medically treated patients with arrhythmogenic RV dysplasia have had surgical exclusion of the entire free wall of the right ventricle, with good results.

## References


1. **Bisteni A, Sodi-Pallares D, Medrano GA, Prieggi F.** A new approach for the recognition of ventricular premature beats. Am J Cardiol 1960;5: 358–369.
2. **Manning GW, Ahuja SP, Gutierrez MR.** Electrocardiographic differentiation between ventricular ectopic beats from subjects with normal and diseased hearts. Acta Cardiol 1968;23:462–470.
3. **Rosenbaum MB.** Classification of ventricular extrasystoles according to form. J Electrocardiol 1969;2:289–297.
4. **Castellanos A Jr, Ortiz JM, Pastis N, Castillo C.** The electrocardiogram in patients with pacemakers. Prog Cardiovasc Dis 1979;13:190–209.
5. **Scherf D, Schott A.** The localization of the site of origin and the spread of extrasystoles. In: Extrasystoles and Allied Arrhythmias. 2nd ed. Chicago: Year Book Medical, 1973:529–559.
6. **Lewis S, Kanakis C, Rosen KM, Denes P.** Significance of site of origin of premature ventricular contractions. Am Heart J 1979;97:159–164.
7. **Josephson ME, Horowitz LN, Farshidi A, Spielman SR, Michelson EL, Greenspan AM.** Recurrent sustained ventricular tachycardia. 4. Pleomorphism. Circulation 1979;59:459–468.
8. **Josephson ME, Horowitz LN, Farshidi A, Spear JF, Kastor JA, Moore EN.** Recurrent sustained ventricular tachycardia. 2. Endocardial mapping. Circulation 1978;57:440–447.
9. **Pietras RJ, Mautner R, Denes P, Wu D, Dhingra R, Towne W, Rosen KM.** Chronic recurrent right and left ventricular tachycardia. Comparison of clinical, hemodynamic and angiographic findings. Am J Cardiol 1977;40: 32–37.
10. **Chapman JH, Schrank JP, Crampton RS.** Idiopathic ventricular tachycardia. An intracardiac electrical, hemodynamic and angiographic assessment of six patients. Am J Med 1975;59:470–480.
11. **Bodenheimer MM, Banka VS, Helfant RH.** Relation between the site of origin of ventricular premature complexes and the presence and severity of coronary artery disease. Am J Cardiol 1977;40:865–869.
12. **Kaplinsky E, Ogawa S, Kmetzo J, Dreifus LS.** Origin of so-called right and left ventricular arrhythmias in acute myocardial ischemia. Am J Cardiol 1978;42:774–780.
13. **Puech P.** Ectopic ventricular rhythms: ventricular tachycardia and His bundle recordings. In: Narula O, ed. His Bundle Electrocardiography and Clinical Electrophysiology. Philadelphia: FA Davis, 1975:243–260.
14. **Matsumoto M, Matsuo H.** Echocardiography for the evaluation of the tricuspid valve, right ventricle, and atrium. Prog Cardiovasc Dis 1978;21: 1–41.
15. **Kisslo J, Von Ramm OT, Thurstone FL.** Cardiac imaging using a phased array ultrasound system. II. Clinical technique and application. Circulation 1976;53:262–269.
16. **Leiti GP, Buchanan JW, Wagner HN.** Monitoring cardiac function with nuclear techniques. Am J Cardiol 1980;46:1125–1132.
17. **Gallagher JJ, Pritchett ELC, Sealy WC, Kasell J, Wallace AG.** The preexcitation syndromes. Prog Cardiovasc Dis 1978;20:285–327.
18. **Gallagher JJ, Oldham HN, Wallace AG, Peter RH, Kasell J.** Ventricular aneurysm with ventricular tachycardia. Report of a case with epicardial mapping and successful resection. Am J Cardiol 1975;35:696–700.
19. **Gallagher JJ, Benson DW Jr, Kasell JH, Smith WM, Sterba R, Grant AO.** Role of Mahaim fibers in cardiac arrhythmias in man. Circulation 1981; 64:176–189.
20. **Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malerque C, Grosgogeat Y.** Right ventricular dysplasia: a report of 24 adult cases. Circulation 1982;65:384–398.
21. **Fontaine G, Guiraudon G, Frank R.** Intramyocardial conduction defects in patients prone to chronic ventricular tachycardia. I. The post-excitation syndrome in sinus rhythm. In: Sandoe E, Julian DG, Bell JW, eds. Management of Ventricular Tachycardia. Role of Mexiletine. Amsterdam: Excerpta Medica, 1978:39–55.
22. **Gallagher JJ, Anderson RW, Kasell JH, Rice JR, Pritchett ELC, Gault JH, Harrison L, Wallace AG.** Cryoablation of drug-resistant ventricular tachycardia in a patient with a variant of scleroderma. Circulation 1978;57: 190–197.
23. **Gallagher JJ, Kasell JH, Cox JL, Smith WM, Ideker RE, Smith WM.** Techniques of intraoperative electrophysiologic mapping. Am J Cardiol 1982;49:221–240.
24. **Guiraudon G, Fontaine G, Frank R, Escande G, Etievent P, Carbrol C.** Encircling endocardial ventriculotomy: a new surgical treatment for life threatening ventricular tachycardia resistant to medical treatment following myocardial infarction. Ann Thorac Surg 1978;26:438–444.
25. **Fontaine G, Guiraudon G, Frank R, Cabrol C, Grosgogeat Y.** Arrhythmogenic right ventricular dysplasia. A previously unrecognized syndrome (abstr). Circulation 1979;52:Suppl II:II–65.
26. **Guiraudon G, Fontaine G, Frank R, Leandri R, Barra J, Cabrol C.** Surgical treatment of ventricular tachycardia guided by ventricular mapping in 23 patients without coronary artery disease. Ann Thorac Surg 1981;32: 439–450.

# Electrophysiologic Studies in Atrial Fibrillation

## Slow Conduction of Premature Impulses: A Possible Manifestation of the Background for Reentry

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**Extrastimulus-induced intraatrial conduction delays were measured in 12 patients with documented episodes of atrial fibrillation (AF) by recording atrial electrograms at the high right atrium, His bundle region, and coronary sinus. Seventeen patients with and without heart disease, but without atrial arrhythmias served as the control group. During baseline-paced atrial rhythms, a conduction delay zone could be delineated, near the atrial effective refractory period, during which all extrastimuli produced conduction delays. When compared at the same paced cycle lengths (500 to 650 ms), the patients with AF had shorter atrial effective refractory periods (mean ± standard deviation 206 ± 24.1 versus 233 ± 28.2 in control patients, $p < 0.02$), wider conduction delay zones (79 ± 21.7 ms versus 52 ± 21 in control patients, $p < 0.01$), and longer conduction delays both to the His bundle region (64 ± 18.3 ms versus 35 ± 21.7 in control patients, $p < 0.005$) and the coronary sinus (76 ± 18.9 ms versus 35 ± 16.1 in control patients, $p < 0.001$). Repetitive atrial responses were recorded in 6 patients with AF and in 9 control subjects. Sinus nodal function abnormalities were detected in 6 of the patients with fibrillation.**

**Patients with AF had a higher tendency than control subjects to develop slow intraatrial conduction, as well as shorter effective refractory periods. Since both features would favor reentry, they may be the electrophysiologic manifestations of the abnormalities making these patients prone to atrial reentrant arrhythmias. Repetitive atrial responses were of no predictive value. Sinus nodal dysfunction was frequently found, but was not essential for the occurrence of AF.**

The sustained electrical activity that characterizes flutter and fibrillation has been the object of continuous interest and research. The self-sustaining character of these arrhythmias has been explained mainly through reentrant mechanisms,[1,2] although a role of abnormal automaticity in its precipitation and maintenance has been suggested.[3–5]

Animal experiments have repeatedly confirmed the possibility of sustaining atrial flutter through a reentrant mechanism; in all of these experiments a conduction disturbance was essential in the mechanism. In some cases, conduction was disturbed by anatomic lesions,[6–8] in others by stimulation during in complete recovery of excitability of the myocardium.[8–10] Differences in the timing of recovery of excitability of adjacent areas were shown to cause unidirectional block, setting the grounds for a continuous circular movements of the propagated impulse.

AF has also been explained as an alteration of impulse conduction. Further dispersion of the recovery of excitability, creating more marked desynchronization of adjacent areas of myocardium, would break the activation fronts into multiple wavelets that could perpetuate themselves as continuous irregular atrial activation, given a large enough mass of tissue and a short enough refractory period.[1,2,8] The continuous and erratic spread of excitation in multiple crisscrossing patterns would be the basis for further dispersion of the recovery of excitability, and thus should tend to sustain

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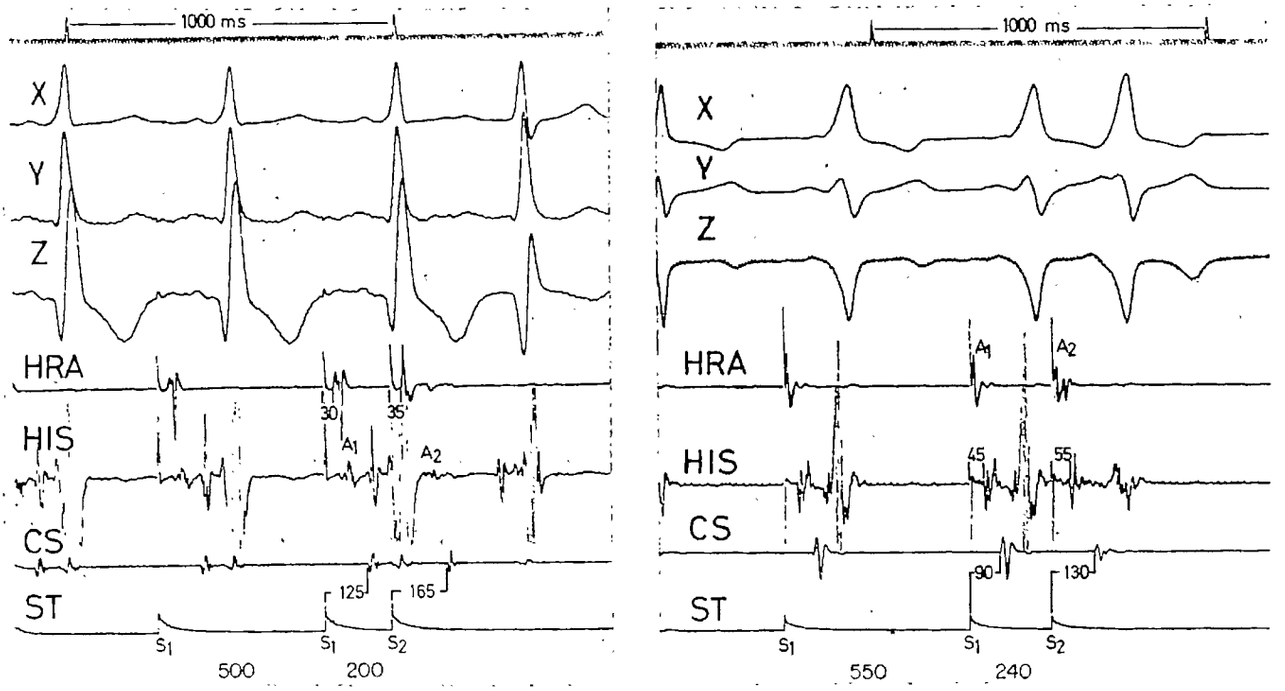



**FIGURE 1.** Effect of early extrastimuli on intraatrial conduction. Measurements of $S_1$-$A_1$ and $S_2$-$A_2$ intervals are shown. **Left panel,** an extrastimulus with a 200 ms $S_1$-$S_2$ interval, over a basic paced cycle length of 500 ms, prolongs intraatrial conduction from 30 to 35 ms in the high right atrium (HRA) and from 125 to 165 ms in the coronary sinus electrogram (CS). The atrial deflection of the His bundle electrogram (HBE) becomes slurred and of low amplitude, and no reliable measurement can be made of the $S_2$-$A_2$ interval here. ST = stimulator output. **Right panel,** the basic cycle length is 550 ms. An extrastimulus with an $S_1$-$S_2$ interval of 240 ms increases conduction time to the HIS and the CS, and the HRA $A_2$ shows a "double" deflection. All values in milliseconds.

the arrhythmia. On the other hand, a prolongation of the refractory period tended to terminate the arrhythmia, through a progressive synchronization of the activation of adjacent areas of muscle.[1,2,8–10]

The onset of clinical human flutter and fibrillation may also be related to slow conduction of impulses through partly recovered myocardium. Rapid stimulation of the myocardium, or rapid repetitive firing at a point of stimulation, may induce enough conduction delay and dispersion of the recovery of excitability to precipitate sustained flutter or fibrillation.[11,12]

The role of normal pacemaker function in the induction and maintenance of AF is probably complex. AF is common in the sick sinus syndrome,[13,14] and pathologic examination of the sinus node in patients with AF shows a high incidence of abnormalities.[15,16] It has been postulated that bradycardia may induce an increase in the dispersion of excitability recovery and thus facilitate reentrant arrhythmias,[16,17] and that AF may be a manifestation of sinus nodal dysfunction. On the other hand, it has been shown that experimental AF is easier to sustain if normal pacemaker function continues.[18]

The application of clinical electrophysiologic techniques to the study of atrial flutter and fibrillation has not clearly defined the features that may characterize a propensity to develop these arrhythmias spontaneously. AF can be produced in normal subjects by atrial stimulation, but usually as a short-lived nonsustained episode.[19] Repetitive atrial responses may also be induced by atrial extrastimuli; their appearance has been considered an expression of "atrial vulnerability," and even a sign of a predisposition to atrial flutter or fibrillation.[20,21] However other clinical and experimental evidence supports the concept that repetitive atrial responses are a nonspecific phenomenon.[8,9,22,23]

The atrial effective refractory period has been measured by several investigators in patients with atrial flutter or fibrillation; while some describe a tendency to short values,[20] others have found no significant deviations.[12,24,25] The degree of dispersion of the recovery of excitability has been explored by measuring atrial effective refractory periods in different points of the right atrium[20] and in both atria,[25] but no significant results have been obtained in atrial flutter or fibrillation. The work of Simpson et al[26] (published only in abstract form) suggests that slow conduction of premature impulses in patients with prolonged P-wave duration may be related to the pathogenesis of AF; however, a direct relation was not shown in their results.

With this background in mind, our study was prospectively designed to analyze the electrophysiologic properties of the atrium and sinus node in patients with documented episodes of AF. Specifically, we addressed the following questions: (1) What are the features of intraatrial conduction during premature stimulation? (2) What is the duration of the atrial refractory period? (3) What is the significance of repetitive responses? (4) What is the role of sinus nodal dysfunction?

## Methods

**Patient population:** The study group consisted of 12 patients with AF. The arrhythmias were paroxysmal in all but Patient 4, who was studied after cardioversion of fibrillation that was sustained for several months. Ages ranged from 25 to 72 years (mean ± standard deviation 55.5 ± 12.7). Associated arrhythmias included sinus bradycardia or sinus arrest in 3 and reentrant tachycardias related to the Wolff-Parkinson-White syndrome in 2. Associated cardiovascular diseases were hypertension (2 patients), coronary artery disease with angina (1 patient), hypertrophic obstructive cardiomyopathy (1 patient), and chronic obstructive pulmonary disease (1 patient). Two (Patients 6 and 8) had mild elevations of thyroid hormone levels in the serum.

The control group consisted of 17 patients with and without organic heart disease or associated arrhythmias, but without a history of atrial flutter or fibrillation. Their ages ranged from 19 to 73 years (mean 49 ± 18). Associated rhythm abnormalities were sinus bradycardia in 6, manifest or concealed Wolff-Parkinson-White syndrome with reentrant atrioventricular tachycardia in 2, ventricular tachycardia in 3, and reentrant nodal tachycardia in 1. One patient had hypertrophic cardiomyopathy, 3 had coronary artery disease, and 1 had an atrial septal defect. Only 2 of the control patients were normal subjects.

**Electrophysiologic studies:** Informed consent was obtained from the patients for the performance of the studies. All cardioactive medications were discontinued at least 3 days before the procedure. The patients were fasting and lightly sedated with oral diazepam. Under local anesthesia, quadripolar catheter-electrodes with a 1-cm interelectrode distance were advanced to the right atrial appendage from the femoral vein, and to the middle or distal coronary sinus from the arm. Stimulation of the right atrium was performed through the distal pair of electrodes in the right atrial catheter. Bipolar recordings were obtained from the high right atrium through the proximal pair of electrodes of the same catheter, and from the left atrium through the distal pair of the coronary sinus catheter. A His bundle electrogram was recorded with the 2 distal electrodes of a tripolar catheter-electrode, or with a bipolar catheter electrode; in either case interelectrode distance was 1 cm. Stimulation was performed with square impulses 2 ms in duration, and intensity twice threshold, delivered by a programmable stimulator (Medtronic 5325).

The intracardiac signals were filtered to record frequencies of 40 to 500 Hz. Recordings were made on a photographic (DR-12, Electronics for Medicine) or ink-jet (Elema) recorder, at a speed of 100 mm/s with simultaneous inscription of leads X, Y, and Z of the orthogonal Frank system.

**Measurements and terms:** The P wave was measured from the simultaneous, high gain X, Y, and Z leads recorded at 100 mm/s. Intervals to and from the intracardiac potentials were taken at their onset, marked by the first sharp deflection taking off from the baseline. This was usually easy to recognize in the coronary sinus and high right atrial electrograms; however, after the application of early extrastimuli the atrial deflection of the His bundle electrogram was occasionally so slurred as to make it difficult to recognize its onset, and in these cases the measurement was omitted (Fig. 1, left panel). When premature stimulation resulted in a split or double atrial deflection, measurements were taken to the onset of the first part of the deflection (Fig. 1, right panel). The difficulty in locating the intrinsecoid deflection after some extrastimuli was the main reason to use the onset of the electrograms for timing, even though this may have underestimated intraatrial conduction time by recording some distant electrical activity.

$A_1$ and $S_1$ refer to the atrial deflection and the driving stimulus of the basic rhythm. $S_2$ and $A_2$ refer to the extrastimulus and the atrial deflection resulting from it, when the basic rhythm is paced. S refers to an extrastimulus delivered on a spontaneous atrial rhythm. The *atrial effective refractory period* is the longest $A_1$-S or $S_1$-$S_2$ interval not resulting in capture by S or $S_2$. *Atrial conduction delay* was the increase in S-$A_2$ or $S_2$-$A_2$ observed with early premature beats, when compared with late premature beats. *Conduction delay zone* was the range of extrastimuli producing atrial conduction delay in any of the sites explored. *Atrial repetitive responses* were defined as the appearance of 2 or more atrial complexes at intervals shorter than 300 ms in all atrial electrograms, in response to 1 extrastimulus.

*Sinus nodal recovery time* was measured after atrial pacing during 1 minute at cycle lengths of 600, 460, and 375 ms, the longest value being reported. A corrected recovery time longer than 525 ms was considered abnormal.[27] *Secondary pauses*

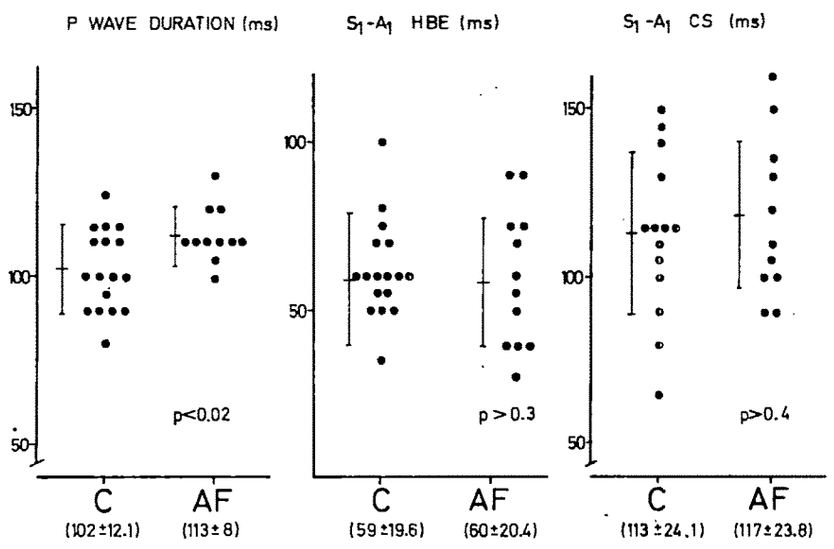



**FIGURE 2.** Graphic representation of P-wave duration and basal conduction time of the atrial stimuli ($S_1$-$A_1$) to the His bundle electrogram (HBE) and the coronary sinus (CS) electrogram. The **vertical bars** represent mean ± 1 standard deviation. AF = patients with atrial fibrillation; C = control group. Values in milliseconds.

were defined as those occurring after the second beat after recovery, and having a duration at least 40% longer than the basic cycle length.[28] *Sinoatrial conduction time* was estimated by Strauss's method, and a noncorrected value of 260 ms or longer was considered abnormal.[29]

The results are expressed as the mean ± 1 standard deviation. The statistical significance of the differences was analyzed by Student's *t* test for unpaired values.

## Results

The electrophysiologic findings are summarized in Table I.

**Intraatrial conduction:** P-wave duration was significantly longer in the study group (113 ± 8 ms) than in control subjects (102 ± 12.1, $p < 0.02$), but the 2 groups overlapped to a large extent (Fig. 2). Intraatrial conduction of nonpremature stimuli ($S_1$-$A_1$ interval) to the His bundle region and to the coronary sinus was not different in either group (Fig. 2). This interval was the same as that for the extrastimuli (S-$A_2$ or $S_2$-$A_2$) during most of the cardiac cycle. However, S-$A_2$ and $S_2$-$A_2$ prolongation tended to occur when the atrial effective refractory period was approached (Fig. 3), defining a conduction delay zone. In 2 patients of the study group (Patients 6 and 8), shortening of the S-$A_2$ or $S_2$-$A_2$ occurred in some recording sites, even though other sites might have shown a conduction delay for the same extrastimulus (Fig. 3 and 4).

During sinus rhythm, the conduction delay zone was almost always very short or undectable, and the atrial conduction delays were minimal to all recording sites (Fig. 3, 5). However, during atrial paced rhythms, both atrial conduction delays and conduction delay zones increased markedly and could be easily measured (Fig. 3). Minimal changes in rate by atrial pacing caused marked increases in atrial conduction delays and conduction delay zone duration, while further rate increases produced generally fewer changes, and in variable directions (Fig. 5). The degree of atrial conduction delay to the various recording sites was quite different (Fig. 3, Table I).

For the comparison between both groups we used only the results obtained at paced cycle lengths of 500 to 650 ms. The patients with AF had wider conduction

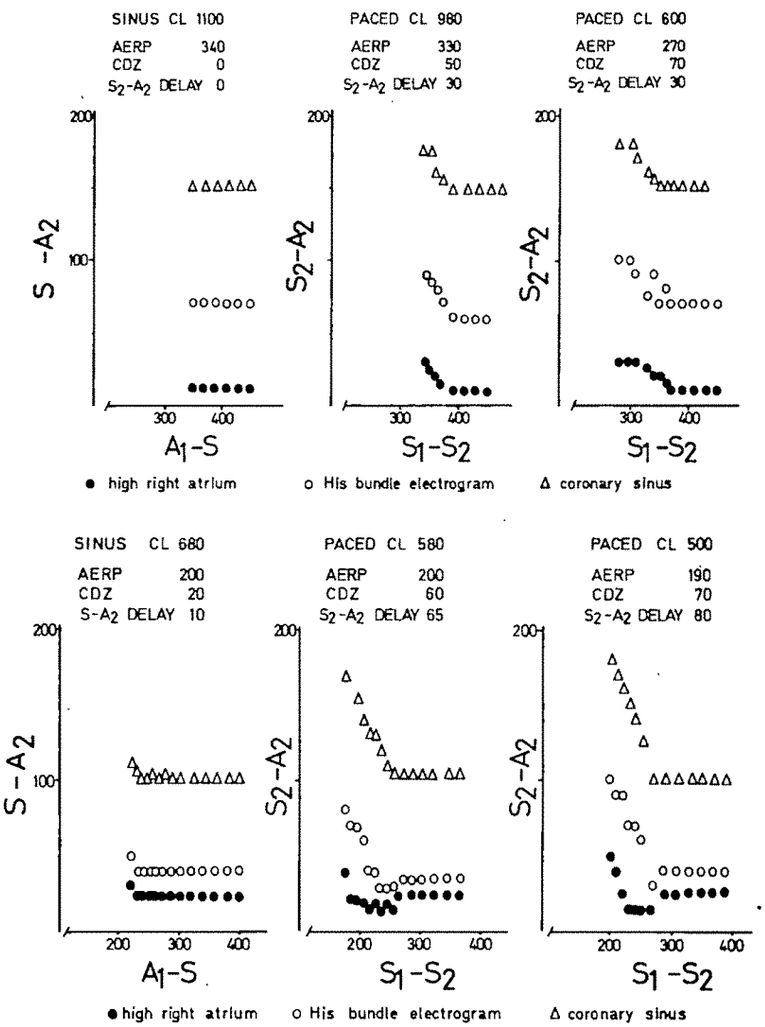



**FIGURE 3.** Graphic representation of the changes in $S_2$-$A_2$ with increasing prematurity of $S_2$. **Top panel,** Patient 8 of the control group. Basal intraatrial conduction is long, but extrastimulus-induced atrial conduction delay is small. **Bottom panel,** Case 5 of the study group. Despite a much shorter intraatrial conduction time basally, extrastimulus-induced conduction delays are much longer. This patient also showed some shortening of the $S_2$-$A_2$ intervals to the high right atrium and the His bundle electrograms that were simultaneous with delays to the coronary sinus electrogram. AERP = atrial effective refractory period; CDZ = conduction delay zone; CL = cycle length; $S_2$-$A_2$ delay = atrial conduction delay. Values in milliseconds.

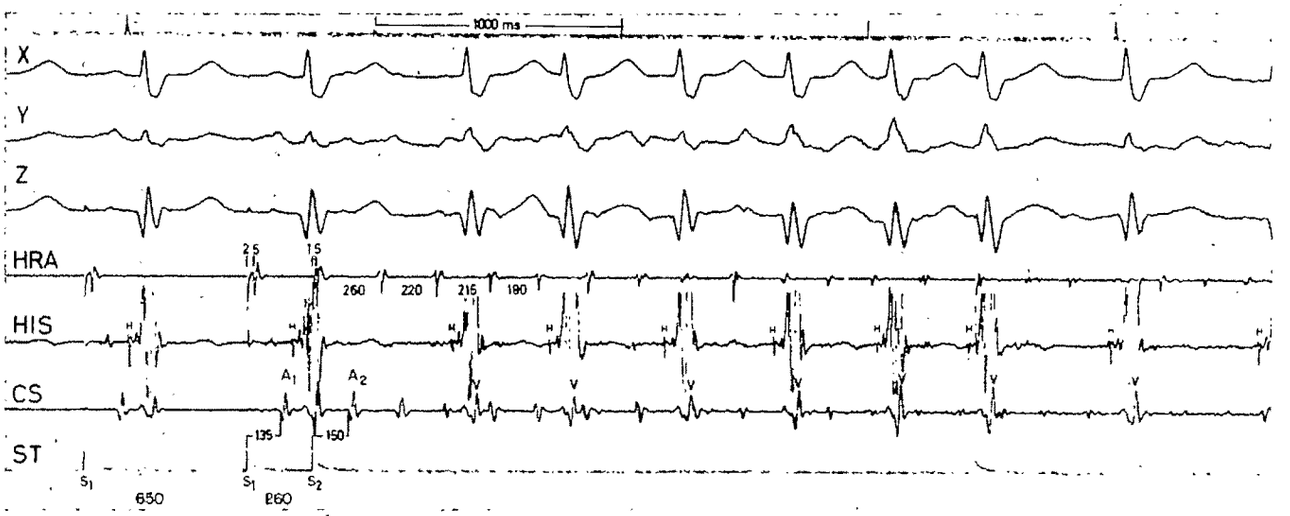



**FIGURE 4.** Precipitation of AF with 1 extrastimulus in Patient 7 of the study group. $S_2$ produces a conduction delay to the coronary sinus (CS) and slight shortening of conduction time to the high right atrium (HRA). $S_2$-$A_2$ is not measurable to the His bundle electrogram (HBE). Multiple atrial responses follow, with irregular intervals of <300 ms. The arrhythmia was sustained and was terminated by direct-current cardioversion 20 minutes later. Values in milliseconds.

delay zones (79 ± 21.7 ms versus 52 ± 21 in control patients, $p < 0.01$) (Fig. 6), and longer maximal conduction delays, both to the His bundle electrogram (64 ± 18.3 ms versus 35 ± 21.7 in control patients, $p < 0.005$) and to the coronary sinus (76 ± 18.9 ms versus 35 ± 16.1 in control patients, $p < 0.001$) (Fig. 7). The correlation of P-wave duration with the maximal atrial conduction delay observed was weak ($r = 0.3$).

**Atrial effective refractory period:** At the same paced cycle lengths of 500 to 650 ms, the atrial effective refractory period was shorter in the patients with AF (206 ± 24.1 ms than in the control subjects (233 ± 28.2 ms, $p < 0.02$) (Fig. 6). The difference was still significant when the comparison was made at cycle lengths of 500 to 600 ms (both spontaneous and paced): study group, 209 ± 20.9 ms, versus control group, 238 ± 26.7 ($p < 0.02$).

**Repetitive atrial responses:** Repetitive responses were observed mainly during the conduction delay zone, at paced cycle lengths of 800 to 400 ms. Only 1 patient (Patient 8, study group) developed repetitive responses on a basic sinus rhythm, during a "superconduction" zone, in which the $S$-$A_2$ interval decreased to a variable extent in all 3 electrograms. In the study group, 6 of 10 patients studied at paced basic cycle lengths of 500 to 650 ms developed repetitive responses. This incidence was similar to that in the control group at the same cycle lengths (8 of 14 patients).

Repetitive responses led to AF in 2 patients (Patients 8 and 11 of the study group). The stimulus leading to AF in Patient 8 showed shortened conduction time to the high right atrium, and prolonged conduction time to the His bundle and coronary sinus electrograms (Fig. 4).

**Sinus nodal function in patients with AF:** Corrected sinus nodal recovery time was prolonged over 525 ms in 3 patients, and another patient had secondary sinus pauses. Sinoatrial conduction time was longer than 260 ms in 4 patients. A total of 6 patients (50%) had abnormal sinus nodal function by these parameters. The dysfunction was clinically significant in 2 patients with bradycardia-related syncope or near-syncope (Patients 10 and 12) and in Patient 11, who developed sinus arrest after cardioversion.

## Discussion

The study of intraatrial conduction of premature stimuli in this group of patients with AF showed a marked tendency to slow propagation, both in terms of an increase in conduction delay in several directions, and of a wider time zone during which the early premature impulses were slowly conducted. The overlap with the control group might have been reduced if these later patients had been normal; however, variation in electrophysiologic features might be expected in patients with a history of AF, given the importance of functional neurologic factors[30,31] as well as the various underlying anatomic substrates.[13]

The correlation of basal intraatrial conduction, as expressed by P-wave duration, with extrastimulus-induced conduction delays was weak. The slow conduction of early extrastimuli may be a manifestation of conduction during partial recovery of myocardial excitability,[32] and the increased conduction delays of our patients with fibrillation could be a manifestation of abnormal cellular electrophysiology, as it may be found in diseased atrial muscle.[33] On the other hand, increased P-wave duration may be a reflection of atrial enlargement or disruption of the internodal and interatrial tracts,[34,35] or both.

Conduction of nonpremature stimuli did not differ in our patients with AF and the control subjects. Since these stimuli were applied at the right atrial appendage,

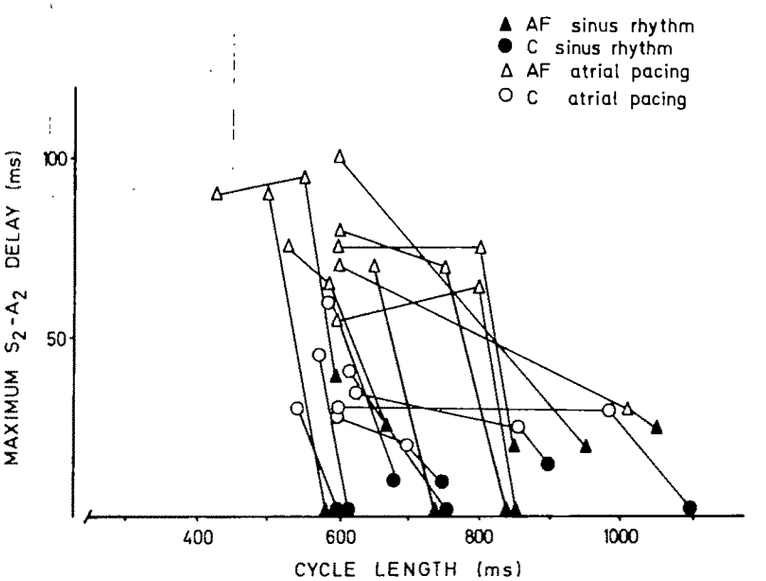



**FIGURE 5.** Graphic representation of the changes in maximal atrial conduction delay measured to any atrial site (maximal $S_2$-$A_2$ delay) produced by changes in cycle length by atrial pacing. Only the patients studied at least 1 cycle length close to the sinus cycle length are represented. The **solid lines** link the findings for the same patient at various cycle lengths. AF = atrial fibrillation group; C = control group. Values in milliseconds.

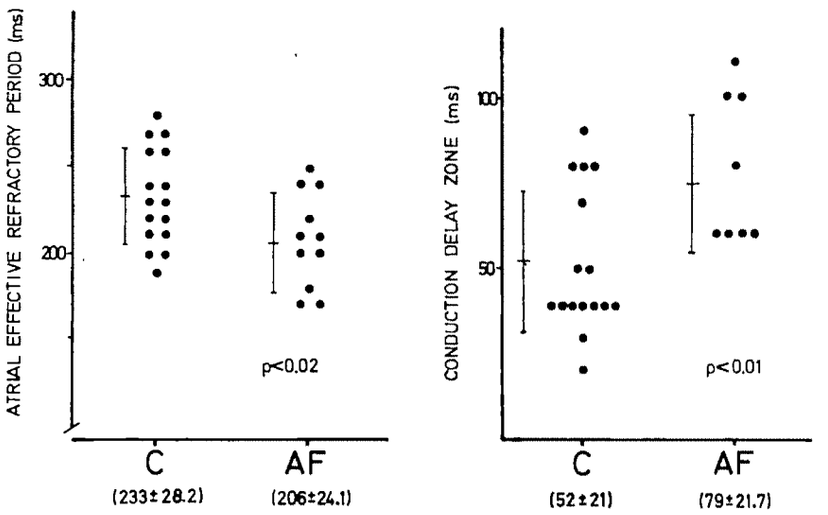



**FIGURE 6.** Graphic representation of atrial effective refractory periods and length of conduction delay zones in the atrial fibrillation (AF) and control (C) groups. Only the values for patients tested at paced basic cycle lengths between 500 and 650 ms are compared. The **vertical bars** represent the mean ± 1 standard deviation. Values in milliseconds.

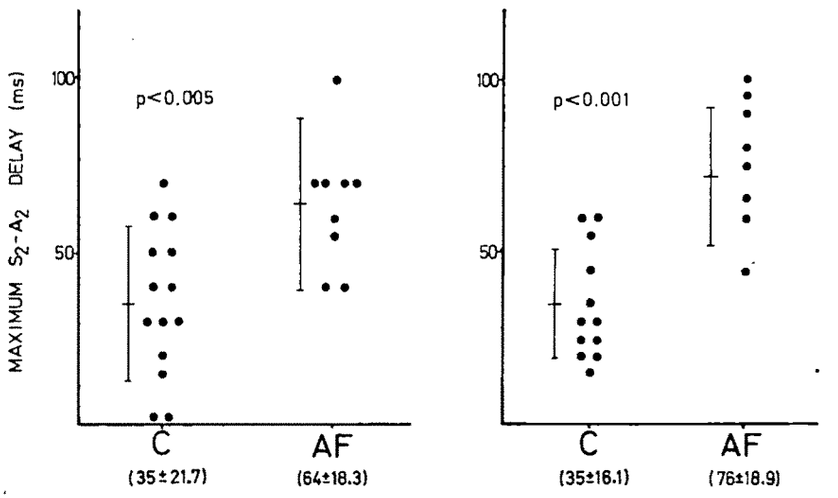



**FIGURE 7.** Graphic representation of the maximal conduction delays measured to the His bundle electrogram (**left**) and the coronary sinus (**right**) in the atrial fibrillation (AF) and control (C) groups. Only values during basic paced cycle lengths between 500 and 650 ms are shown. The **vertical bars** represent the mean ± 1 standard deviation.

**TABLE I Summary of the Electrophysiologic Findings**

| Case | P Wave | SNRT | SACT | Basic Cycle | AERP | CDZ | HRA $S_1$-$A_1$ | HRA CD | HIS $S_1$-$A_1$ | HIS CD | CS $S_1$-$A_1$ | CS CD | RR | FA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Group (Patients With Atrial Fibrillation)** | | | | | | | | | | | | | | |
| 1 | 120 | 340 | 290 | **860** | 300 | 0 | 25 | 0 | 75 | 0 | 135 | 0 | − | − |
| | | | | 800 | 250 | 80 | | 15 | | 65 | | 45 | − | − |
| | | | | 600 | 240 | 80 | | 15 | | 55 | | 45 | − | − |
| 2 | 110 | 250 | 180 | **600** | 190 | 50 | 10 | 0 | 40 | 20 | 90 | 40 | − | − |
| | | | | 550 | 170 | 100 | | 20 | | 70 | | 95 | + | − |
| | | | | 400 | 160 | 100 | | 20 | | 70 | | 90 | + | − |
| 3 | 110 | 580 | 370 | **900** | 330 | 10 | 35 | 5 | 75 | 10 | 120 | 0 | − | − |
| 4 | 110 | 500 | 180 | **750** | 250 | 40 | 30 | 10 | 55 | 10 | 90 | 10 | − | − |
| 5 | 105 | 230 | 215 | **680** | 200 | 20 | 25 | 0 | 40 | 10 | 105 | 10 | − | − |
| | | | | 580 | 200 | 60 | | 15* | | 40 | | 65 | + | − |
| | | | | 500 | 190 | 70 | | 25 | | 60 | | 80 | + | − |
| 6 | 100 | 195 | 140 | **570** | 180 | 60 | 10 | 30 | 30 | 65 | 100 | 40 | − | − |
| | | | | 540 | 170 | 100 | | 35 | | 60 | | 90 | − | − |
| | | | | 400 | 150 | 110 | | 45 | | 105 | | 105 | − | − |
| 7 | 120 | 340 | 330 | **720** | 210 | 0 | 30 | −20* | 90 | −50 | 130 | −20 | + | − |
| | | | | 650 | 210 | ≥50 | | 10 | | 70 | | 60 | + | + |
| 8 | 110 | 440 | 125 | **850** | 240 | 10 | 20 | 20 | 50 | 20 | 110 | 15 | − | − |
| | | | | 800 | 230 | 70 | | 20 | | 70 | | 75 | + | − |
| | | | | 600 | 200 | 60 | | 20 | | 70 | | 75 | + | − |
| 9 | 110 | 400 | 180 | **860** | 250 | 0 | 20 | 0 | 40 | 0 | 100 | 0 | − | − |
| | | | | 750 | 240 | 60 | | 15 | | 40 | | 70 | − | − |
| | | | | 600 | 220 | 60 | | 10 | | 40 | | 80 | − | − |
| 10 | 110 | 550 | 210 | **1,050** | 300 | 10 | 15 | 25 | 70 | 20 | − | − | − | − |
| | | | | 750 | 240 | 60 | | 15 | | 40 | | 70 | − | − |
| | | | | 600 | 220 | 60 | | 10 | | 40 | | 80 | − | − |
| 11 | 120 | <7,000 | − | 600 | <210 | − | 3− | ≥5 | 90 | ≥40 | 150 | ≥10 | + | + |
| 12 | 130 | SP | 300 | **950** | 310 | 30 | 20 | 20 | 60 | 20 | 160 | 20 | − | − |
| | | | | 600 | 210 | 110 | | 30 | | 100 | | 100 | + | − |
| **Control Group** | | | | | | | | | | | | | | |
| 1 | 115 | 120 | 220 | **600** | 270 | 10 | 25 | 10 | 55 | 0 | 110 | 0 | − | − |
| | | | | 540 | 210 | 30 | | 10 | | − | | 30 | − | − |
| 2 | 115 | 500 | 330 | **850** | 270 | 40 | 20 | 25 | 100 | 40 | − | − | − | − |
| | | | | 600 | 230 | 90 | | 30 | | 70 | | − | + | − |
| 3 | 110 | 600 | 260 | **1,000** | 300 | 10 | 20 | 5 | 80 | 0 | 130 | 0 | − | − |
| | | | | 600 | 240 | 50 | | 10 | | − | | 20 | − | − |
| 4 | 110 | 180 | 120 | **690** | 220 | 20 | 20 | 10 | 50 | 20 | 80 | − | − | − |
| | | | | 500 | 190 | 80 | | 10 | | 50 | | − | + | − |
| 5 | 100 | 580 | 180 | **920** | 280 | 20 | 20 | 10 | 70 | 15 | 140 | 10 | − | − |
| | | | | 600 | 240 | 40 | | 10 | | 15 | | 25 | + | − |
| 6 | 80 | 190 | 140 | **540** | 200 | 0 | 20 | 0 | 35 | 0 | 90 | 0 | − | − |
| | | | | 400 | 180 | 50 | | 20 | | 55 | | 50 | − | − |
| 7 | 100 | 360 | 160 | **900** | 320 | 20 | 15 | 5 | 60 | 5 | 115 | 15 | − | − |
| | | | | 860 | 300 | 40 | | 5 | | 20 | | 25 | − | − |
| | | | | 600 | 260 | 40 | | 15 | | 30 | | 35 | + | − |
| 8 | 90 | 540 | 150 | **1,100** | 340 | 0 | 10 | 0 | 70 | 0 | 150 | 0 | − | − |
| | | | | 980 | 330 | 50 | | 20 | | 30 | | 30 | + | − |
| | | | | 600 | 270 | 70 | | 20 | | 30 | | 30 | − | − |
| 9 | 100 | 340 | 200 | **750** | 250 | 20 | 20 | 15 | 50 | 10 | 115 | 10 | − | − |
| | | | | 700 | 240 | 20 | | 15 | | 20 | | 10 | − | − |
| | | | | 600 | 230 | 40 | | 20 | | 30 | | 15 | − | − |
| 10 | 90 | − | − | 650 | 270 | 50 | 25 | 25 | 60 | 40 | − | − | − | − |
| 11 | 125 | 520 | 200 | **880** | 370 | 30 | 30 | 10 | 55 | 0 | − | − | − | − |
| | | | | 600 | 280 | 40 | | 20 | | 0 | − | − | − | − |
| 12 | 115 | 320 | 260 | **870** | 220 | 70 | 15 | 0 | 50 | 25 | 65 | 30 | − | − |
| | | | | 600 | 210 | 80 | | 40 | | 50 | | 60 | − | − |
| 13 | 90 | 300 | − | 600 | 220 | 80 | 20 | 20 | 60 | 60 | 100 | 55 | + | − |
| 14 | 90 | 400 | − | **620** | 260 | 20 | 25 | 15 | 60 | 0 | 145 | 0 | − | − |
| | | | | 600 | 220 | 40 | | 45 | | 60 | | 45 | + | − |
| 15 | 110 | 440 | 170 | **850** | 340 | 0 | 25 | 0 | 75 | 0 | 105 | 0 | − | − |
| | | | | 600 | 260 | 20 | | 0 | | 0 | | 25 | − | − |
| 16 | 95 | 165 | 140 | **750** | 250 | 0 | 30 | 0 | 60 | 0 | 115 | 0 | − | − |
| | | | | 600 | 200 | 40 | | 5 | | 40 | | 20 | + | − |
| 17 | 100 | 180 | 150 | **680** | 230 | 10 | 30 | 5 | 60 | 0 | 115 | 10 | − | − |
| | | | | 580 | 200 | 40 | | 10 | | 20 | | 60 | + | − |

AERP = atrial effective refractory period; AF = appearance of atrial fibrillation after 1 extrastimulus; CD = extrastimulus-induced atrial conduction delay; CDZ = conduction delay zone; CS = coronary sinus electrogram; HIS = His bundle electrogram; HRA = high right atrial electrogram; RR = atrial repetitive responses; SACT = sinoatrial conduction time (not corrected); SNRT = corrected sinus nodal recovery time; SP = secondary sinus pauses.

* Patients with supernormal conduction (see text for explanation).

Cycle lengths in boldface type represent sinus rhythm. <, >, ≥ indicate that the exact value could not be determined because of the appearance of atrial fibrillation. In the case of SNRT, it indicates that the pause was interrupted by pacing.

they were probably not conducted through the preferential atrial pathways; this may explain the apparent discrepancy with the prolongation of intraatrial conduction time found by others during sinus rhythm.[12,24]

The remarkable enhancement of atrial conduction delays by paced cycle lengths, without apparent close relation to rate, is an interesting phenomenon. Since both the stimuli pacing the basic rhythm and the extrastimulus were applied at the same point, the former ($S_1$) may have influenced the spread of the latter ($S_2$) by altering local activation sequences, perhaps promoting slow activation fronts,[32] that may increase local dispersion of recovery, and favor slow circuitous spread of $S_2$.[2,4,9,10] Studies of atrial conduction with extrastimuli applied to areas other than the one used to pace the basic rhythm may help clarify this point in the future.

Without intracellular recordings at the site of stimulation, it is difficult to rule out that the $S_2$-$A_2$ delays are caused by latency resulting from local tissue polarization by stimuli applied during the "absolute" refractory period.[36] However, several observations in our patients make this explanation very unlikely: (1) Latency would tend to produce equal delays to all sites, unless a change in excitation spread patterns also resulted. (2) Since latency depends mostly on stimulus intensity and duration,[36] similar delays should have been present in sinus and paced rhythms. (3) In case the $S_2$-$A_2$ delays were due to latency, the difference in the S-$A_2$ interval (during sinus rhythm) and the $S_2$-$A_2$ interval (during paced rhythm) at similar rates should be accompanied by a similar shortening of the effective atrial refractory period.[36] The pattern of $S_2$-$A_2$ delay in our patients did not fulfill any of these conditions.

The patients with AF also had a shorter atrial effective refractory period, and this should also favor reentry.[2] Similar findings were reported by Luck[20] in patients with atrial fibrillation and the sick sinus syndrome, but could not be confirmed by Bauernfeind[25] in patients with the Wolff-Parkinson-White syndrome. It is possible that different selected groups of patients may show variations in the electrophysiologic mechanisms underlying AF.

The incidence of repetitive atrial responses was similar in our patients with atrial flutter or fibrillation and the control subjects, indicating that this response is not a reliable index of a tendency to develop atrial arrhythmias spontaneously. Repetitive atrial responses have been used by some as an index of atrial vulnerability, this term often being used to imply a tendency towards atrial arrhythmias.[20,21] Our results coincide with other observations[22,23] in that atrial repetitive responses are a nonspecific finding. Animal studies show that the mechanism of these responses is local reentry around the point of stimulation, different in pattern from flutter or fibrillation circuits.[8–10] Notwithstanding, repetitive responses may create conditions favorable for the development of flutter or fibrillation[8–10]; this was the case in our experience and that of others.[11,12] We believe that the term atrial vulnerability should be used with caution in reference to the appearance of repetitive atrial responses. It is possible that the appearance of sustained flutter or fibrillation with a single extrastimulus may be a more specific sign of a tendency to spontaneously develop these arrhythmias[12]; however, no satisfactory conclusion appears possible with the information presently available.

The observations on supernormal conduction in 2 of the patients with AF merit some comment. Although supernormal intraatrial conduction may be a common phenomenon during premature stimulation,[37] it is conceivable that a combination of depressed conduction in some directions with enhanced conduction in others (as observed in some of our cases) may increase dispersion of the recovery of excitability, and facilitate arrhythmias of reentrant origin. A larger number of observations should be necessary to understand the role of supernormal conduction in atrial arrhythmogenesis.

The prevalence of clinically apparent or subclinical sinus nodal dysfunction was high in the patients with AF, but 50% of the patients had normal sinus function tests; sinus nodal dysfunction did not appear to be a necessary association for the development of fibrillation in the atria. The incidence of sinus nodal dysfunction in patients with AF will be markedly influenced by the patient selection protocol, and may be quite different among different series.

Some limitations of this study should be considered. Both the study and control groups included patients with a variety of clinical and electrophysiologic abnormalities, and this may have influenced the results in unpredictable ways. For this reason our results should be considered suggestive, and further studies in more homogeneous groups of patients appear necessary to better test their significance. Notwithstanding, certain observations were quite remarkable for such apparently mixed groups. For instance, the little superposition observed in the extrastimulus-induced conduction delays rarely reached 60 ms in the control group, while in most patients in the study group it surpassed that figure.

The rates at which our patients were tested were not completely uniform, due to the partly retrospective nature of the study. There was, however, no significant difference between the mean test cycle lengths in the AF cases (591 ± 32.2 ms) and in the control subjects (592 ± 32 ms; difference not significant). We preferred to include a larger number of observations, because our results suggested that it was mainly the fact that the basic cycle was paced, and not so much the pacing rate, which affected intraatrial conduction of the extrastimuli.

Not enough emphasis has been placed on the study of intraatrial conduction under premature stimulation in clinical electrophysiologic studies. Our observations suggest that intraatrial conduction of extrastimuli may be an important index of abnormal atrial electrophysiology, and a better knowledge of its changes in disease states may help us understand the pathogenesis of certain atrial arrhythmias.

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## References

1. **Moe GK.** On the multiple wavelet hypothesis of atrial fibrillation. Arch Int Pharmacodyn Ther 1962;140:183–188.
2. **Moe GK, Rheinboit WC, Abildskov IA.** A computer model of atrial fibrillation. Am Heart J 1964;67:200–220.
3. **Scherf D.** The atrial arrhythmias. N Engl J Med 1955;252:928–933.
4. **Moe GK, Harris AS, Wiggers CJ.** Analysis of the initiation of fibrillation by electrocardiographic studies. Am J Physiol 1941;134:473–492.
5. **Cranefield PF.** Ventricular fibrillation. N Engl J Med 1973;189:732–736.
6. **Rosenblueth A, Garcia Ramos J.** Estudios sobre el flutter y la fibrilación. II. La influencia de los obstáculos artificiales en el flutter auricular experimental. Arch Inst Cardiol Mex 1947;17:1–19.
7. **Rosenblueth A, Garcia Ramos J.** Estudios sobre el flutter y la fibrilación. IV. La naturaleza del flutter auticular y de la actividad lenta autosostenida del músculo auricular aislado. Arch Inst. Cardiol Mex 1947;17:441–457.
8. **Boineau JP, Shuessler RB, Mooney CR, Miller CB, Wylds AC, Hudson RD, Borremans JM, Brockus CW.** Natural and evoked atrial flutter due to circus movement in dogs. Role of abnormal atrial pathways, slow conduction, nonuniform refractory period distribution and premature beats. Am J Cardiol 1980;45:1167–1181.
9. **Allessie MA, Bonke FIM, Schopman FJG.** Circus movement in rabbit atrial muscle as a mechanism of tachycardia. II. The role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes. Circ Res 1976;39:168–177.
10. **Allessie MA, Bonke FIM, Schopman FJG.** Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstable. Circ Res 1977;41:9–18.
11. **Bennett MA, Pentecost BL.** The pattern of onset and spontaneous cessation of atrial fibrillation in man. Circulation 1970;41:981–988.
12. **Watson R, Josephson ME.** Atrial flutter. I. Electrophysiologic substrates and modes of initiation and termination. Am J Cardiol 1980; 45:732–741.
13. **Mosa AJ, Davis RJ.** Brady-tachy syndrome. Prog Cardiovasc Dis 1974; 16:439–454.
14. **Rubenstein JJ, Schulman CL, Yurchak PM, DeSanctis R.** Clinical spectrum of the sick sinus syndrome. Circulation 1972;46:5–13.
15. **Sims BA.** Pathogenesis of atrial arrhythmias. Br Heart J 1972;34:336–340.
16. **Davies MJ, Pommerance A.** Pathology of atrial fibrillation in man. Br Heart J 1972;34:520–525.
17. **Han J, Millet D, Shizzonitti B, Moe GK.** Temporal dispersion of excitability in atrium and ventricle as a function of heart rate. Am Heart J 1966;71: 481–487.
18. **Nadeau RA, Roberge FA, Billette J.** The role of the sinus node in the mechanism of cholinergic atrial fibrillation. Circ Res 1970;27:129–138.
19. **Haft JI, Lau SH, Stein E, Kosowsky BD, Damato AN.** Atrial fibrillation produced by atrial stimulation. Circulation 1968;37:70–74.
20. **Luck JC, Engel TR.** Dispersion of atrial refractoriness in patients with sinus node dysfunction. Circulation 1979;60:404–412.
21. **Engel TR, Gonzalez A del C.** Effects of digitalis on atrial vulnerability. Am J Cardiol 1978;42:570–576.
22. **Wyndham CRC, Amat-y-Leon F, Wu D, Denes P, Dhingra R, Simpson R, Rosen KM.** Effects of cycle length on atrial vulnerability. Circulation 1977;55:260–267.
23. **Goodman DJ, Rossen RM, Rider AK, Harrison DC.** The effect of cycle length on cardiac refractory periods in the denervated human heart. Am Heart J 1976;91:332–338.
24. **Leier CV, Meacham JA, Schaal SF.** Prolonged atrial conduction. A major predisposing factor for the development of atrial flutter. Circulation 1978;57:213–216.
25. **Bauernfeind RA, Wyndham CR, Swiryn SP, Pallieo EV, Strasberg B, Lam W, Westveer D, Rosen KM.** Paroxysmal atrial fibrillation in the Wolff-Parkinson-White syndrome. Am J Cardiol 1981;47:562–569.
26. **Simpson RJ, Foster JR, Gettes LS.** Atrial excitability and conduction in patients prone to atrial fibrillation (abstr). Am J Cardiol 1981;47:496.
27. **Narula OS,Samet P, Javier RP.** Significance of the sinus node recovery time. Circulation 1972;45:140–158.
28. **Strauss HC, Bigger JT, Saroff AL, Giardina EGV.** Electrophysiologic evaluation of sinus node function in patients with sinus node dysfunction. Circulation 1976;53:763–776.
29. **Reiffel JA, Bigger JT, Cramer M, Reid DS.** Ability of Holter electrocardiographic recording and atrial stimulation to detect sinus nodal dysfunction in symptomatic and asymptomatic patients with sinus bradycardia. Am J Cardiol 1977;40:189–194.
30. **Alessi R, Nusynowitz M, Abildskov JA, Moe GK.** Nonuniform distribution of vagal effects on the atrial refractory period. Am J Physiol 1958;194: 406–410.
31. **Coumel P, Leclercq J-F, Attuel P, Lavallee J-P, Flammang D.** Autonomic influences in the genesis of atrial arrhythmias: atrial flutter and fibrillation of vagal origin. In: Narula OS, ed. Cardiac Arrhythmias. Electrophysiology, Diagnosis, and Management. Baltimore: Williams & Wilkins, 1979:243–255.
32. **Spach MS, Miller WT, Geselowitz DB, Barr RC, Kootsey JM, Johnson EA.** The discontinuous nature of propagation in normal canine cardiac muscle. Evidence for recurrent discontinuities of intracellular resistance that affect the membrane currents. Circ Res 1981;48:39–54.
33. **Trautwein W, Kassebaun DG, Nelson RM, Hecht HH.** Electrophysiologic study of human heart muscle. Circ Res 1962;10:306–312.
34. **Demoulin JC, Kulbertus HE.** Pathological correlates of atrial arrhythmias. In: Kulbertus HE, ed. Re-entrant Arrhythmias. Mechanisms and Treatment. Lancaster: MTP Press, 1977:99–113.
35. **James TN, Sherf L.** Specialized tissues and preferential conduction in the atria of the heart. Am J Cardiol 1971;28:414–427.
36. **Orias O, Brooks CMcC, Suckling EE, Gilbert JL, Siebens AA.** Excitability of the mammalian ventricle throughout the cardiac cycle. Am J Physiol 1950;163:272–282.
37. **Agha AS, Castillo CA, Castellanos A, Myerburg RJ, Tessler MP.** Supernormal conduction in the human atria. Circulation 1972;46:522–527.

# Problems in Health Data Analysis: The Maryland Permanent Pacemaker Experience In 1979 and 1980

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**In a recent report the Maryland statewide health data base, which is derived from "face sheet" data, was used to determine the appropriateness of permanent pacemaker insertion. In the present study the same indications were utilized and both the complete medical records and the face sheet were reviewed for those patients who had been classified as having permanent pacemakers inserted for inappropriate or questionable reasons. In 32 hospitals, 75% of the records were reviewed (610 of 817 patients). Although coded as having received permanent pacemakers, 16% had received temporary pacemakers, battery change, and the like. Diagnoses justifying permanent pacemaker insertion had been omitted in 53% of the face sheets, and coding errors were found in 39%. Although none of the 610 medical records reviewed had a valid indication for permanent pacemaker insertion listed on the face sheet, complete medical record review demonstrated valid indications in 95%. Inherent difficulties arise in attempting to list rigid indications for permanent pacemaker insertion. The face sheet does not provide adequate data for assessing the appropriateness of permanent pacemaker insertion.**

In Maryland, the availability of a computerized statewide health data system has afforded an opportunity for the analysis of many items present on the "face sheet" of the medical record. These include entries which by law are reported to the Maryland Health Services Cost Review Commission including day of admission, day of discharge, length of stay, discharge status, demographic data, date of birth, age, sex, coding of all diagnoses, coding of all procedures, and financial classification. In addition, the statewide data include financial information derived from billing data. Specific items excluded from the report to the statewide data system are the name of the patient and the name of the physician. The individual hospitals assign code numbers to both the patients and the physicians, and these data are only available to the hospital originating the information. The availability of such data provides excellent possibilities for the analysis and correlation of many important factors relating to health care delivery, including cost, quality measures, mortality, procedures, and hospital funding.

In a recent Health Research report,[1] *face sheet data* were utilized to determine whether permanent pacemakers had been inserted for appropriate reasons in Maryland during 1979 and 1980. After reviewing data from 2,222 permanent pacemaker insertions, it was concluded that 23% were unnecessary and an additional 13% were questionable. In the present study, both the complete medical records and the face sheet information were reviewed. The same indications for permanent pacemaker insertions were utilized in both studies in an effort to determine the validity of using only face sheet data for the determination of appropriateness of procedures. Additional consideration was given to the general problem of trying to establish guidelines for pacemaker insertion.

## Methods

With the cooperation of the Baltimore City Professional Standards Review Organization, the Maryland statewide data base for 1979 and 1980 was utilized to obtain the listing of all diagnoses for patients who had received permanent pacemakers during that time. The following procedure codes (ICD-9-CM)[2] were used:

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**TABLE I Diagnoses Justifying Implantation of Permanent Pacemakers Judged Appropriate by the Health Research Group, and the ICD-9-CM Codes**

| | | |
|---|---|---|
| 426.0 | Atrioventricular block, complete | |
| | Third degree atrioventricular block | |
| 426.12 | Mobitz (type) II atrioventricular block | |
| | Incomplete atrioventricular block: | |
| | Mobitz (type) II | |
| | Second degree, Mobitz (type) II | |
| 426.54 | Trifascicular block | |
| 426.6 | Other heart block | |
| | Intraventricular block: | Sinoatrial block |
| | Not otherwise specified: | Sinoauricular block |
| | Diffuse | |
| | Myofibrillar | |
| 426.9 | Conduction disorder, unspecified | |
| | Heart block, not otherwise specified | Stokes-Adams syndrome |
| 427.81 | Sinoatrial node dysfunction | |
| | Sinus bradycardia: | Syndrome: |
| | Persistent | Sick sinus |
| | Severe | tachycardia-bradycardia |
| 780.2 | Snycope and collapse | |
| | Blackout | Vasovagal attack |
| | Fainting | |

**TABLE II Diagnoses Which Are Questionable and May Justify Implantation of a Permanent Pacemaker Under Appropriate Circumstances, as Based on the Health Research Group Report**

| | |
|---|---|
| 426.3 | Other left bundle branch block |
| | Left bundle branch block: |
| | Not otherwise specified |
| | Anterior fascicular with posterior fascicular |
| | Complete |
| | Main stem |
| 426.50 | Bundle branch block, unspecified |
| 426.51 | Right bundle branch block and left posterior fascicular block |
| 426.52 | Right bundle branch block and left anterior fascicular block |
| 426.53 | Other bilateral bundle branch block |
| | Bifascicular block not otherwise specified |
| | Bilateral bundle branch block not otherwise specified |
| | Right bundle branch block with left bundle branch block (incomplete) (main stem) |
| 426.89 | Other |
| | Dissociation: |
| | Atrioventricular |
| | Interference |
| | Isorhythmic |
| | Nonparoxysmal atrioventricular nodal tachycardia |
| 427.1 | Paroxysmal ventricular tachycardia |
| | Ventricular tachycardia (paroxysmal) |
| 427.9 | Cardiac dysrhythmia, unspecified |
| | Arrhythmia (cardiac) not otherwise specified |
| 746.86 | Congenital heart block |
| | Complete or incomplete atrioventricular block |

37.73 Insertion of permanent pacemaker into atrium, transvenous route

37.74 Insertion of permanent pacemaker into ventricle, transvenous route

37.75 Insertion of permanent cardiac pacemaker into unspecified site, transvenous route

37.76 Insertion of permanent pacemaker into epicardium
Implantation of electrode into myocardium by:
sternotomy
thoracotomy

37.77 Insertion of permanent cardiac pacemaker, unspecified approach
Implantation of permanent cardiac pacemaker, not otherwise specified

These procedures exclude the insertion of temporary pacemakers; replacement of battery, electrode, or pulse generators; mechanical complications; fitting and adjustment of cardiac pacemakers; and other codes relating to pacemakers. In addition, the diagnoses for patients identified by procedure code 37.70 (insertion of cardiac pacemaker not otherwise specified) were reviewed but not included in this report.

To compare this study with the Health Research report, which had been based only on face sheet information, we used the same indications as they did for permanent pacemaker insertions. These are listed as justifying implantation of a permanent pacemaker ("appropriate") (Table I), or as having ". . . proper indications under appropriate circumstances but which, by themselves, cannot be used as justifications for pacing" ("questionable") (Table II).

The participating Maryland hospitals were contacted and an explanatory letter sent to the head of cardiology. In addition, a release form was included and was to be signed by the Chief Executive Officer or his representative in each hospital. This form was addressed to the Information Service Center of the Staff of the Maryland Health Services Cost Review Commission, and authorized the release to the Quality Assurance Chairman of the requesting hospital the chart numbers of patients who had had permanent pacemakers implanted. The participating hospitals were then provided with a detailed computer printout for each of their patients whose record had been *coded* in the statewide data base as having received a permanent pacemaker, and for patients who had been *coded* as *not* having a diagnosis which justified the implantation of a permanent pacemaker—that is, both the unnecessary and questionable groups. These printouts are confidential data as they identify the patient by a medical record number.

In each hospital this printout was sent to the Quality Assurance Chairman and reviews of the medical record were undertaken, usually by members of the Quality Assurance committees. In several instances, members of the Utilization Review committees, teams of cardiologists, or heads of the

**TABLE III Summary of the Charting Problems Encountered in the Detailed Review of 610 Medical Records**

| | n | % |
|---|---|---|
| A. Diagnosis Errors on Face Sheet | | |
| 1. Omission in recording diagnosis or diagnosis | 323 | 53.0 |
| 2. Vague diagnosis subject to misinterpretation by coder | 123 | 20.2 |
| 3. Other | 31 | 5.1 |
| B. Operation (Pacemaker Insertion) | | |
| 1. Omission in recording operation | 34 | 5.6 |
| 2. Vague description of operation | 14 | 2.3 |
| 3. Other | 2 | 0.3 |
| C. Coding Errors | | |
| 1. Misinterpretation errors | | |
| a. Vague or unclear diagnosis operation miscoded by coder | 60 | 9.8 |
| b. Diagnosis/operation affected by other diagnosis and miscoded | 4 | 0.7 |
| 2. Wrong diagnosis coded | 68 | 11.1 |
| 3. Wrong procedure coded | 81 | 13.3 |
| 4. Other coding error | 23 | 3.8 |
| D. Other Errors | 31 | 5.1 |

departments of medicine in their respective hospitals performed the reviews. A standard form was developed and provided for the detailed analysis of each medical record. Instructions were given for the diagnoses and codes to be copied from the face sheet, as were the procedures and their codes. The medical record review was then performed and additional diagnoses or procedures relating to pacemakers were listed. It was requested that the sources for these data be listed: consultation notes, operative notes, progress notes, electrocardiograms, and so on. In addition, the reviewer was asked (1) to indicate whether a permanent pacemaker was inserted; (2) to indicate whether a temporary pacemaker was inserted; (3) to indicate whether the pacemaker insertion was considered justified; and (4) to categorize any errors in charting utilizing a standard code for error types. A space for additional comments was provided.

The hospitals returned the completed forms and these were reviewed in detail. All codes for both diagnoses and procedures were verified, and all comments, information, and judgments on justification and classification of coding errors were reviewed. These were tabulated and provide the basis for this report.

## Results

The total number of permanent pacemakers implanted was found to be 2,182 for 1979 and 1980 in the present study, compared with the total of 2,222 in the Health Research report, a difference of <2%, employing the same indications. The number of pacemaker insertions in the unnecessary or questionable groups was 801 patients in our study, compared with 817 in the Health Research report, a difference of 2%. A total of 610 patient medical records (75% of the total of 817) have been reviewed in 32 of the 52 hospitals in Maryland, and these comprise the data for the present analysis. In 8 hospitals, there were either no insertions of new pacemakers or no record of any patient receiving a permanent pacemaker without having appropriate indications. Of the remaining 12 hospitals, 4 had only 1 to 3 inappropriate permanent pacemakers in 1979 and 1980 according to face sheet data. The remaining hospitals have not yet responded. In some hospitals included in this study, some charts were not available at the time of medical record review.

The Health Research report stated that all 801 patients included in their study had received permanent pacemakers. This statement was based on face sheet data recorded in the statewide data system. Detailed medical record analysis, however, showed that only 514 (84%) had actually had permanent pacemakers inserted. Thirteen (2%) of the patients previously classified as having had permanent pacemakers inserted had received replacement of battery units; 59 patients (10%) had received temporary pacemakers; and 24 patients (4%) were admitted with a *history* of a pacemaker having been inserted in the past but were not admitted for new pacemaker implants.

Recording problems were reviewed in detail, and 323 (53%) of the medical records reviewed revealed a significant omission on the face sheet in the recording of the appropriate diagnosis justifying the insertion of the pacemaker (Table III). Detailed medical record review in these patients demonstrated an appropriate diagnosis utilizing the same criteria as in the Health Research report (Table I). In 123 patient records (20%), the diagnosis listed on the face sheet was so vague that it was subject to misinterpretation by the coder. In 60 (10%) of the medical records, the diagnosis or operation was vague or unclear and was misinterpreted by the coder. Diagnoses were miscoded in the face sheets in 68 patients (11%) and procedures were miscoded in 81 patients (13%). Other coding or recording errors occurred 139 times (23%). Five examples are provided in Tables IV to VIII, which present diagnoses and procedures with

**TABLE IV Example A**

| | |
|---|---|
| I. Diagnosis—Face Sheet | |
| 1. Lymphoma—histocytic | 200.08 |
| 2. | 426.10* |
| II. Procedure—Face Sheet | |
| 1. Excision mass, left neck & right inguinal area | 86.3 |
| 2. Temporary transvenous pacemaker | 37.75* |
| 3. Permanent pacemaker | 37.72 |
| 4. Temporary transvenous pacemaker removed | 37.86 |
| III. Chart Review | |
| 1. Complete atrioventricular block | 426.0 |

* The only diagnosis listed on the face sheet was lymphoma. The coder assigned a code to the diagnosis and on review also assigned code 426.10. In ICD-9-CM, this code is atrioventricular block, unspecified. This diagnosis does not justify the implantation of a permanent pacemaker. However, complete atrioventricular block, 426.0, is a justifiable diagnosis. In addition, 37.75 is the code for a permanent pacemaker.

**TABLE V Example B**

| | |
|---|---|
| 1. Diagnosis—Face Sheet | |
| 1. Cardiac arrhythmia, treated | 427.9* |
| 2. Severe degenerative arthritis | 715.96 |
| 3. Osteoarthritis, right knee | 736.41 |
| 4. Genu valgus deformity | 733.00 |
| 5. Generalized osteoporosis | 997.4 |
| II. Procedures—Face Sheet | |
| 1. Temporary pacemaker | 37.74* |
| 2. Permanent pacemaker | 37.72 |
| III. Chart Review | |
| 1. Sick sinus syndrome | 427.81 |

* The coder assigned 427.9 to cardiac arrhythmia. In ICD-9-CM, this code is for cardiac dysrhthmia, unspecified. The specific diagnosis on chart review was sick sinus syndrome, 427.81, a justifiable diagnosis for permanent pacemaker insertion. In addition, 37.74 is the code for a permanent pacemaker.

**TABLE VI Example C**

| | |
|---|---|
| 1. Diagnosis—Face Sheet | |
| 1. Acute transmural myocardial infarction with pericarditis | 410.0 |
| 2. Cardiac failure secondary to ventricular tachycardia and ventricular fibrillation | 420.90 |
| 3. Secondary to digitalis (?) | 428.0 |
| 4. | 427.41 |
| 5. | 427.1 |
| 6. | 427.89 |
| II. Procedures—Face Sheet | |
| 1. Temporary pacemaker | 37.74* |
| III. Chart Review | |
| 1. No permanent pacemaker | |

* On chart review, this patient had a temporary pacemaker, not a permanent pacemaker. Code 37.74 is for a permanent pacemaker.

**TABLE VII Example D**

| | |
|---|---|
| I. Diagnosis—Face Sheet | |
| 1. Renal failure | 585 |
| 2. Hypertension | 401.9 |
| II. Procedures—Face Sheet | |
| 1. Temporary pacemaker | 37.72* |
| 2. Permanent pacemaker | 37.74 |
| III. Chart Review | |
| 1. Sinus arrest | 426.6 |
| 2. Sick sinus syndrome | 427.81 |

On chart review, diagnoses justifying the insertion of a permanent pacemaker were documented. In addition, 37.72 is the code for a permanent, not a temporary pacemaker.

**TABLE VIII Example E**

| | |
|---|---|
| 1. Diagnosis—Face Sheet | |
| 1. Aortic stenosis | 424.1 |
| II. Procedures—Face Sheet | |
| 1. Aortic valve replacement | 35.22 |
| 2. Insertion of permanent pacemaker | 37.75 |
| III. Chart Review | |
| 1. Complete heart block | 426.0 |

This patient had complete heart block after open heart surgery for aortic valve replacement. This required the insertion of a permanent pacemaker. Only aortic stenosis had been recorded and not complete heart block, 426.0.

the codes as copied from the face sheet of the medical records. On chart review, the additional diagnoses were listed and coded. Errors in diagnosis, coding, and in omission are documented.

After medical record analysis, 31 patients (5%) in the present study were found *not* to have the indications listed in the Health Research report which would justify the insertion of a permanent pacemaker (Table IX). If the same percentage were to apply to the total 817 patients in the "unnecessary or questionable category," this would represent a total of 42 patients or 2% of the total of 2,182 patients who received pacemakers in Maryland in 1979 and 1980, again utilizing the same criteria as in the Health Research report. However, among other indications, ventricular overdrive is a valid reason for pacemaker insertion and was not so listed in the Health Research report. Eight patients had a permanent pacemaker inserted in Maryland for this diagnosis. Inclusion of this group as justifiable reduces the unnecessary or questionable percentage to 4% of the 610 medical records reviewed. This would reduce the number which might be considered unnecessary or questionable to 1.4% of the total of 2,182 pacemakers inserted.

**TABLE IX The 31 Questionable or Unnecessary Pacemaker Implants* Encountered in Review of the Medical Records of 610 Patients**

| |
|---|
| 8 Ventricular overdrive |
| 3 Bifascicular block (1 acute myocardial infarction) |
| 1 Wenckebach, 1st and 2nd degree |
| 1 RBBB with second degree atriventricular block |
| 1 RBBB and atrial fibrillation with acute myocardial infarction |
| 1 RBBB with acute myocardial infarction |
| 1 LBBB with acute myocardial infarction |
| 1 LBBB and second degree atrioventricular block with acute myocardial infarction |
| 1 Mobitz I with acute myocardial infarction |
| 1 Mobitz I |
| 5 Unclear indications stated (2nd degree atrioventricular block; nonconducted premature atrial contractions) |
| 5 Not justified on chart review |
| 1 Postural hypotension and sinus bradycardia |
| 1 To permit use of beta blocking agent |

* Utilizing the same criteria as in the Health Research Report.

In a few instances, the hospital reviewers commented that the pacemaker insertion was judged appropriate although the criteria enumerated in the Health Research report were not present. The authors, however, included all of these cases as being inappropriate for the purpose of this report and in order to make a direct comparison of face sheet data with complete medical record review.

## Discussion

Although the event which precipitated this study was the release of the Health Research report, there have been serious concerns about conclusions based on data sources similar to those employed in that report. The flow of information from which these data were derived is generally as follows. When a patient is discharged from the hospital, the face sheet of the chart is filled out with the diagnoses and procedures and other information not relevant to this discussion. These entries may be made by the cardiologist or by the attending physician on a different service. These diagnoses and procedures frequently include only some of the important ones which characterize the hospitalization of the patient. The terms used to describe the disease of the patient are often only generally stated, and frequently emphasize the disease (for example, acute myocardial infarction) and less often the manifestations of the disease (chest pain, type of disturbance in rhythm, and so on). The patient record is then sent to the medical record department, where medical record technicians, clerks, or coding personnel assign codes as listed in ICD-9-CM to each diagnosis and procedure. In some hospitals, record personnel are specially trained to review the medical records in detail and to assign the codes for any additional diagnoses and procedures not listed on the face sheet. In other hospitals this function is not performed. These assigned codes are then transcribed to abstract forms, batched, and keyed into an external or internal data system. Regular reports are then provided to the participating hospital, and the data tapes are ultimately forwarded to the Maryland Health Services Cost Review Commission together with financial or billing data. These data are then made available for specific types of analyses once all confidential data have been removed. Thus, physician names or patient chart numbers are not generally available except to the individual hospital itself.

It is this statewide data system based on face sheet information that may be the basis for hospital funding, research, quality care studies, and other investigations. Several hospitals estimate that ≥15% of all patient records reaching the record department have no diagnosis or procedure listed at the time of patient dis-

charge. Record department personnel frequently assign code numbers after review of these medical records in the absence of a completed face sheet. Some hospitals assign a code number representing "undiagnosed disease, not specified as to site or system involved." These codes are then changed at a later date when final disease and operation data become available. Frequently, the patient records arrive in the medical record department before the operative notes or the discharge summaries have been completed. These data are therefore not available when the information on the face sheet is coded. In some hospitals, it was found that a copy of the face sheet is sent to the billing department immediately upon discharge, and codes are then assigned by billing personnel for insurance purposes. The record room department staff codes the face sheet attached to the medical record, resulting at times in different codes being assigned to the same patient. It is probable that there is a disparity between the statewide data coding and the coding provided by billing departments to insurance carriers.

Accreditation of hospitals by the Joint Commission on Accreditation of Hospitals requires that there be a Quality Assurance Committee and Program in each hospital.[3] These groups of physicians and allied health personnel maintain ongoing programs to assure quality care. Periodically, review of various medical problems are undertaken: that is, focused reviews. The local Professional Standards Review Organization, on review of the data from each hospital, may require hospital Utilization Review Committees or Quality Assurance Committees to perform selected focused review. The face sheet information is utilized on the basis of the following principle: "Face Sheet Discharge Data Are Only Indicators That Direct One To Review The Medical Record."

Physicians concentrate their documentation in the patient medical record. It is in the main body of the medical record that the admission history and physical examination, progress notes, record of treatment, plans for therapy, consultation notes, laboratory reports, nurses' notes, operative notes, and discharge summaries are found. The face sheet is *not* the focus of attention since the important details are in the body of the medical record and the face sheet is often a form to be quickly completed in order to sign the patient out of the hospital. Although the face sheet data may be utilized for the purpose of abstracting discharge data, for quality control, hospital funding, cost-effectiveness, and research, care should be exercised whenever such data are employed for these purposes. In some hospitals, the face sheet serves as the discharge summary. No final judgment can be made on medical diagnoses, procedures, or operations, severity of illness, mortality data, morbidity data, appropriate lengths of stay or other factors without a detailed review of the patient medical record.

The accuracy of the coding of the face sheet diagnoses and procedures is best when these are essentially simple and straightforward, and not subject to misinterpretation. They are more difficult when the diagnoses and procedures are complex, vague, and technical and when fine distinctions must be made between almost-identical terminology. Selected reviews by the Baltimore City Professional Standards Review Organization have revealed coding error rates of 5 to 24% for several hospitals in Baltimore City in the designation of a diagnosis to the wrong diagnostic related group. There is no standard "face sheet" in Maryland.

Physicians, with rare exception, are not familiar with the ICD-9-CM code system nor with its utilization in the medical record department for the statewide discharge data base. The physician may not use the appropriate nomenclature for diagnosis of the patient's disease, and may not use nomenclature precise enough to exclude erroneous ICD-9-CM codes from being assigned to the diagnoses listed. The physician may not include all of the manifestations of the disease. The coding may involve highly technical terminology, not familiar to the coding personnel or easily located in the code book.

Cardiac arrhythmias probably represent the one discipline of cardiology which is most technical in its terminology. In completing the face sheet, the physician may not mention the specific arrhythmia, or may state it vaguely or use an ambiguous term subject to misinterpretation. The coding personnel are then faced with making distinctions in this selection in order to assign a specific 4- or 5-digit code.

The present study was specifically directed at determining the relation between the codes as derived from the face sheet and the entire medical record contents themselves in an effort to determine whether the "justifying diagnosis" was clearly documented in the body of the medical record but not on the face sheet. The study participants in each hospital copied the face sheet diagnoses and procedures (including codes), and then reviewed the entire medical record for additional diagnoses or procedures. The hospitals which participated included university hospitals, teaching hospitals, and community hospitals from throughout the state and involved medical record department personnel, quality assurance personnel, utilization review staffs, cardiologists, and others. With few exceptions a distinct uniformity in the findings was observed in each hospital.

Specific problems encountered in review of the face sheet included the following, as determined from the medical record review: (1) omission of the diagnosis which justified the pacemaker insertion; (2) lack of specificity in listing the arrhythmia diagnosis; (3) coding problems due to nonspecific diagnosis being listed; (4) correct diagnosis listed but wrong code number assigned; (5) compound diagnosis for which the coder assigned a code to only part of the diagnosis and omitted the secondary codes; (6) failure of the physician to designate the type of pacemaker correctly; (7) pacemaker listed correctly but coded incorrectly; (8) sixth diagnosis that justified a pacemaker, but only 5 diagnoses entered into the available computer system.

As noted, 31 patients were not found to have the appropriate diagnosis for permanent pacemaker insertion according to the indications listed in the Health Research report. These indications were accepted only for the purpose of this study in order to permit a direct comparison of face sheet data with complete medical record review. More widely accepted indications, how-

ever, would further reduce the number of insertions listed as inappropriate in the present report. Permanent pacemakers were inserted in 8 patients for ventricular overdrive and their charts clearly justified these decisions. In 7 other patients, permanent pacemakers were inserted for bifascicular blocks or for the new onset of intraventricular conduction defects in the presence of acute myocardial infarction. These indications, as well as the insertion of a permanent pacemaker for postural hypotension with bradycardia, and to permit the use of beta blockers in the presence of bradycardia, are controversial but may be acceptable judgment decisions by the consulting physician.

Indications for cardiac pacemaking have been widely reported.[4–10] In general, pacing is appropriate for the control of symptomatic bradyarrhythmias, particularly bradyarrhythmias unresponsive to medical management. Pacemaker technology has expanded indications for permanent pacing. Synchronized (demand) capability, and physiologic (atrioventricular sequential) modes have extended pacer treatment to complex brady- and tachyarrhythmias. Even after 25 years of clinical use, however, we do not know in all cases just when to prescribe a permanent pacemaker.[11] Controversy is unresolved in new onset bundle branch block in the setting of ischemic heart disease,[8] in bifascicular and trifascicular block,[9] and in intermittent and undocumented symptomatic low cardiac output syndromes.[4]

Electrophysiologic testing with His bundle recordings and rapid pacing or drug-induced stress assessment of the conducting system is of proven value in some but not all uncertain pacemaker candidates. Often physiologic assessment is impractical. Moreover, the propriety of the practice in which only 1 or 2 pacemakers per year is inserted in some hospitals is unresolved. In 1 report, retrospective peer review was apparently successful in reducing the number of permanent pacemaker insertions.[12] Peer review as generally practiced in many Maryland hospitals offers the best assurance for appropriate utilization.

**Acknowledgment:** This study was carried out under the aegis of the Maryland Society of Cardiology Ad Hoc Committee on Permanent Pacemakers (Stephen C. Achuff, MD, Dean R. Taylor, MD, Donald H. Dembo, MD, and Leonard Scherlis, MD, Chairman). The Baltimore City Professional Standards Review Organization was instrumental in making this study possible. Appreciation is extended to each of the 32 hospitals whose medical staff, medical record department personnel, and review groups performed all of the detailed medical record reviews. Particular appreciation is extended to Suzanne Murphy for her advice. We also thank Shirley Heath, who helped coordinate this study and prepare the final report.

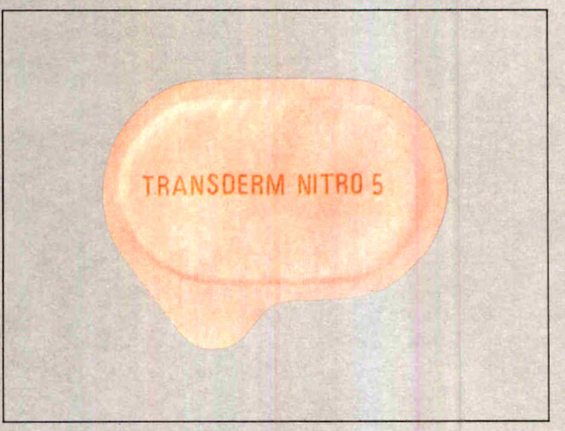
## References

1. **Greenberg A, Kowey PR, Bergmann E, Wolfe SM.** Permanent pacemakers in Maryland. Report by Health Research Group, 2000 P Street, NW, Washington, DC 20036, July 7, 1982.
2. International Classification of Diseases. 9th revision. Clinical Modification. Commission on Professional and Hospital Activities, 1968 Green Road, Ann Arbor, Michigan 48105. 1979.
3. Accreditation Manual for Hospitals. Joint Commission on Accreditation of Hospitals, 875 North Michigan Avenue, Chicago, Illinois 60611. 1982.
4. **Braunwald E.** Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia: WB Saunders, 1980:745–746.
5. **Hurst JW.** Update V: The Heart. McGraw-Hill, 1981;131–157.
6. **Del Negro AA, Fletcher RD.** Indications for and use of artificial cardiac pacemakers. Part I. Curr Probl Cardiol 1978;3.
7. **Del Negro AA, Fletcher RD.** Indications for and use of artificial cardiac pacemakers. Part II. Curr Probl Cardiol 1978;8.
8. **Hindman MC, Wagner GS, JaRo M, Atkins JM, Scheinman MM, DeSanctis RW, Hutter AH Jr, Yeatman L, Rubenfire M, Pujura C, Rubin M, Morris JJ.** The clinical significance of bundle branch block complicating acute myocardial infarction. 1. Clinical characteristics, hospital mortality, and one-year follow-up. Circulation 1978;58:679–688.
9. **McAnulty JH, Rahimtoola SH, Murphy E, DeMots H, Ritzman L, Kanarek PE, Kaufman S.** Natural history of "high-risk" bundle branch block. Final report of a prospective study. N Engl J Med 1982;307:137–143.
10. **Parsonnet V.** The proliferation of cardiac pacing: medical, technical, and socioeconomic dilemmas. Circulation 1982;65:841–845.
11. **Kastor JA.** Preventive pacemaking. Editorial. N Engl J Med 1982;307: 180–181.
12. **Chokshi AB, Friedman HS, Malach M, Vasavada BC, Bleicher SJ.** Impact of peer review in reduction of permanent pacemaker implantations. JAMA 1981;248:754–757.

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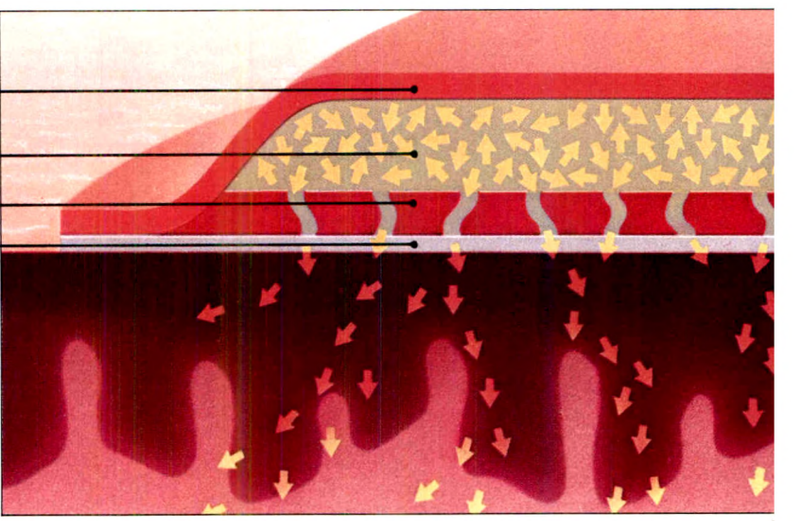
### Magnified cross section of Transderm-Nitro system

**impermeable water-resistant backing layer**

**nitroglycerin reservoir**

**rate-controlling membrane**

**hypoallergenic contact adhesive**
Contains an initial dose of medication to saturate skin-binding sites so that absorption begins immediately



# Precision dosage system assures 24-hour angina protection

### Steady, sustained 24-hour nitroglycerin levels

Constant protection against angina attacks assured by uninterrupted plasma concentrations of nitroglycerin: Transderm-Nitro 5 rated to release 5 mg/24 hours; Transderm-Nitro 10 rated to release 10 mg/24 hours.

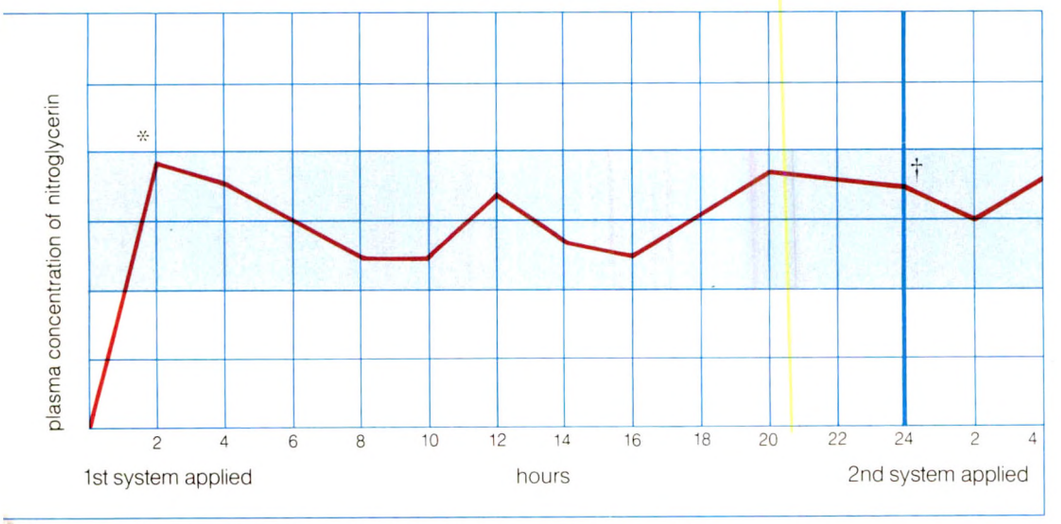
Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

### System is simple and easy to use

- Every 24 hours the old system is removed and the new one applied.
- Therapeutic effect can be anticipated 30 minutes after application and maintained for 30 minutes following removal.
- Can be applied anywhere on the body except the distal extremities.

### An advance beyond tablets and ointments

- 24-hour sustained therapeutic blood levels of nitroglycerin
- Precise dosage control
- Ease of administration...avoids mess and inconvenience of ointments
- Once-a-day dosage to enhance compliance
- May be worn while swimming, bathing and showering




*First measurement in this study was taken at 2 hours. However, a therapeutic effect can be anticipated 30 minutes after application of the system, and will be maintained for 30 minutes after its removal.

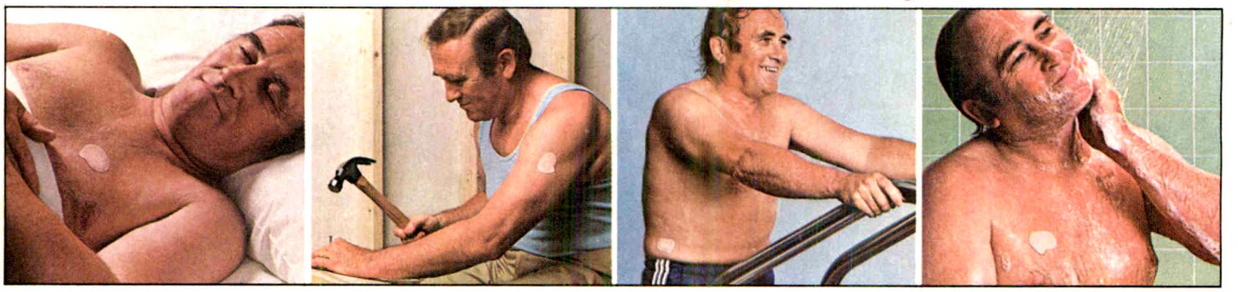
†After 24 hours, system is removed and a new one is applied to another site. Renewal of the system does not result in any significant alteration in the plasma levels, as long as the change is made without delay.

CIBA

*For full details, please see the prescribing information on the next page.*

# Transderm®-Nitro nitroglycerin

## Once-a-day, 24-hour protection against angina attacks



System can be applied anywhere except distal extremities. Doesn't compromise daily activities.

**Transderm®-Nitro**
(nitroglycerin)
**Transdermal Therapeutic System**

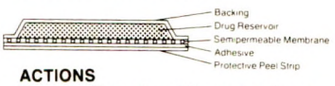
### DESCRIPTION

Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semipermeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 10 and 20 $cm^2$ respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system; 0.5 mg nitroglycerin is delivered *in vivo* for every $cm^2$ of system size.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface toward the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene/vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:




### ACTIONS

When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitrogiycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

### INDICATIONS AND USAGE

Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

### CONTRAINDICATIONS

Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

### WARNINGS

In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

### PRECAUTIONS

Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

### ADVERSE REACTIONS

Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

### DOSAGE AND ADMINISTRATION

Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

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# Cellular Electrophysiologic Abnormalities of Diseased Human Ventricular Myocardium

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**Using standard microelectrode techniques, the cellular electrophysiologic features of ventricular myocardium resected from 8 patients with refractory arrhythmias were studied in vitro. Action potentials from damaged myocardium compared with normal myocardium had reduced resting membrane potential, amplitude, and maximal upstroke velocity. Tetrodotoxin, but not verapamil, suppressed 3 action potentials with resting potentials of −60 to −64 mV and $V_{max}$ <70 V/s. Verapamil, but not tetrodotoxin, suppressed 4 action potentials with resting potentials of −44 to −57 mV and $V_{max}$ <20 V/s. Unidirectional block, Wenckebach block, and summation occurred in damaged zones. Exit block from and frequency-dependent entrance block into an ectopic focus were noted. Subthreshold responses in the focal area induced by action potentials in the surrounding myocardium and by subthreshold current pulses injected through the recording microelectrode altered the spontaneous discharge rate of the focus, as previously described for modulated parasystole. Pulses early in the spontaneous cycle delayed the next expected discharge, and later pulses accelerated the subsequent discharge. Pulses injected at the singular point completely suppressed automaticity (annihilation). Tetrodotoxin and verapamil suppressed automaticity in some fibers. Single action potentials induced in quiescent fibers triggered and terminated sustained rhythmic activity. These data suggest that depressed fast responses, slow responses, and subthreshold potentials can generate and modulate ectopic activity in damaged human ventricle and that fast- and slow-channel blocking agents and single premature stimuli can terminate such activity.**

Diverse cellular electrophysiologic phenomena have been found in resected human ventricular tissue studied in vitro.[1–5] Some of these phenomena such as slow conduction, decreased excitability, and various forms of abnormal automaticity may contribute to the development of arrhythmias in diseased human ventricles. However, few studies of human ventricular preparations have been reported, and it is likely that many abnormal cellular electrical properties of these tissues have not been identified. For example, slow-channel blocking agents, but not tetrodotoxin, depress the action potential upstroke of depolarized human ventricular cells.[1,2,5] These observations differ from those in studies of ischemic or hypoxic canine[6–8] and hamster[9] myocardium, in which lidocaine and tetrodotoxin suppressed abnormal action potentials but verapamil and D600, its methoxy derivative, did not. In view of these conflicting findings, further studies of depressed fast responses and slow responses in human ventricle appear warranted. In addition, aspects of modulated pacemaker activity as suggested by experiments in normal cardiac tissues subjected to abnormal environments[10–13] have not been examined in diseased human ventricle. These phenomena include phase resetting and annihilation by subthreshold and regenerative action potentials and modulation of reflected and parasystolic excitation patterns. Low-amplitude potentials that reach threshold may also trigger sustained rhythmic activity,[14–16] an event that has not been fully investigated in the human ventricle.[3,4]

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Because cardiac arrhythmias may be due to disorders of impulse formation, impulse propagation, or a combination of both mechanisms, we investigated aspects of abnormal automaticity and conduction in resected human ventricle that have not previously been examined in detail. The purpose of these studies was to test the hypotheses that (1) both slow responses and depressed fast responses exist in diseased human ventricle and can participate in abnormal conduction and pacemaker activity; (2) subthreshold potentials can also contribute to abnormal automaticity and conduction, as predicted by experimental models of oscillatory activity[10,17] and Wenckebach periodicity[18,19]; and (3) subthreshold afterdepolarizations may reach threshold after an appropriate stimulus and trigger sustained rhythmic activity.

## Methods

Seventeen ventricular preparations obtained from 8 patients, 7 men and 1 woman aged 52 to 73 years (Table I), were studied. Seven patients had ischemic heart disease associated with various degrees of heart failure, whereas 1 patient had no evidence of organic heart disease and was characterized as having primary electrical disease. All patients had recurrent ventricular tachycardia resistant to treatment with multiple standard and investigational antiarrhythmic agents. Left ventricular aneurysmectomy and endocardial resection was performed in the 7 patients with ischemic heart disease, and right ventricular myocardial resection was performed in the 1 patient with primary electrical disease. Areas were selected for resection on the basis of the site of earliest myocardial activation during ventricular tachycardia initiated at operation by programmed electrical stimulation. Myocardial activation sequences were determined using epicardial and endocardial mapping with a ring electrode and reference electrodes sewn to the right and left ventricular epicardium.[20]

The patient with primary electrical disease continued to have recurrent ventricular tachycardia after surgery, whereas 6 of the 7 other patients had no episodes of symptomatic or sustained ventricular tachycardia during follow-up periods of 5 to 38 months (Table I). One patient did not have ventricular tachycardia after surgery, but died 6 days postoperatively because of the low cardiac output syndrome. Cardiac glycosides were discontinued 1 day before surgery in all patients. Antiarrhythmic agents were discontinued 1 to 7 days before surgery in 6 patients. One patient (Patient 5) received amiodarone the day before surgery and was assumed to have therapeutic levels of the drug at operation. Patient 7 was administered procainamide at surgery to facilitate the induction of ventricular tachycardia. All patients were anesthetized with morphine and nitrous oxide during surgery.

At surgery the pieces of resected myocardium were placed immediately in Tyrode's solution (22° to 24°C) previously bubbled with 95% oxygen and 5% carbon dioxide and taken from the operating room to the cellular electrophysiology laboratory. The composition of the Tyrode's solution (m*M*) was: $MgCl_2$, 0.5; $NaH_2PO_4$, 0.9; $CaCl_2$, 2.7; NaCl, 137.0; $NaHCO_3$, 12.0; KCl, 4.0; glucose, 5.0. The pieces were then transferred to a tissue bath and superfused at a rate of 5 ml/min with oxygenated Tyrode's solution maintained at 37° ± 0.5°C, pH 7.35 ± 0.05, and $pO_2$ >400 mm Hg.

The preparations were allowed to beat spontaneously or were driven at a basic cycle length of 1,000 ms in the tissue bath for at least 30 minutes before study. Stimuli were rectangular pulses 2 ms in duration and an intensity twice diastolic threshold delivered through bipolar Teflon®-coated stainless steel electrodes. Transmembrane potentials were recorded with glass microelectrodes filled with 3 *M* KCl (DC resistance, 5 to 30 mΩ) coupled to silver-silver chloride wires leading to high impedance, capacitance-neutralizing amplifiers (model 701 or 707, W-P Instruments). The amplifiers were equipped with rapid switching systems that permitted the delivery of depolarizing and hyperpolarizing current pulses through the recording microelectrode. After delivery of the pulse, the amplifier reverted to the recording mode and the resulting voltage deflection was monitored. Electronic differentiation was used to obtain the first time derivative of the action potential upstroke. The recordings were displayed on a memory oscilloscope (Tektronix D15), photographed with a Polaroid® camera (C-59), and recorded on magnetic tape (Hewlett-Packard model 3960).

Recordings were obtained from abnormal and normal cells on the endocardial surface in 5 preparations and from the mid-myocardial surface in the remaining 8. Typical dimensions of the preparations were 5 cm long × 2.5 cm wide × 5 mm thick. The terms *abnormal* and *normal* are based on cellular electrophysiologic characteristics only. Cells were considered normal when their action potential characteristics fell within the range of values previously reported for presumably normal human ventricle.[1,3] Cells having action potential characteristics that fell outside this range were considered abnormal. However, the data reported in previous studies were obtained

**TABLE I Clinical Data on the 8 Patients Studied**

| Patient | Age (yr) & Sex | Diagnosis | Medications* | Area Resected | Follow-Up |
|---|---|---|---|---|---|
| 1 | 56M | PED | Aprindine | RV free wall, endo | VT, encainide (43 mo) |
| 2 | 52M | IHD | Digoxin, aprindine | LV endo of anterior wall at junction with septum | No VT, quinidine (38 mo) |
| 3 | 71M | IHD | Encainide, amiodarone, digoxin | LV endo at distal septum at junction with free wall | No VT (15 mo) |
| 4 | 62M | IHD | Digoxin, mexiletine, amiodarone, encainide | Widespread LV endo resection | No VT (11 mo) |
| 5 | 73M | IHD | Digoxin, quinidine, amiodarone† | Widespread LV endo resection | Died 6 days po due to LV failure; no VT |
| 6 | 70F | IHD RVD | Digoxin, quinidine | Large LV endo scar | No VT (7 mo) |
| 7 | 68M | IHD | Quinidine, digoxin, procainamide‡ | Large LV endo scar | No VT (8 mo) |
| 8 | 50M | IHD | Digoxin, lidocaine | LV endo near apex | No VT (5 mo) |

* Cardioactive drugs given 1 to 7 days before surgery. † Discontinued 1 day before surgery. ‡ Given at surgery.
Endo = endocardium; IHD = ischemic heart disease; LV = left ventricular; PED = primary electrical disease; po = postoperatively; RV = right ventricular; RVD = rheumatic valvular disease; VT = ventricular tachycardia.

from human hearts with some form of myocardial disease. Furthermore, because of similar action potential characteristics of human ventricular muscle and Purkinje tissue, we were unable to determine whether normal action potentials represented healthy ventricular muscle cells or slightly depressed Purkinje cells. Normal action potentials in this study were recorded from cells surrounding the aneurysm or necrotic areas or from islands of normal myocardium interspersed with areas of focal necrosis. Areas of the preparations that appeared to have been crushed during resection were excised and no data were collected from areas of myocardium near the cut edges of the specimens.

To determine whether the fast or the slow inward current mediated the upstrokes of abnormal cells, 7 cells with resting membrane potentials <−65 mV and maximal upstroke velocities <70 V/s were superfused first with Tyrode's solution containing tetrodotoxin ($5 \times 10^{-6}$ *M*) for 15 minutes followed by 30 minutes of washout and then with racemic verapamil ($2 \times 10^{-6}$ *M*) for 30 minutes. Verapamil was not given first to any of the preparations because its effects are not completely reversible in vitro.[21] Statistical analysis was performed using Student's *t* test for unpaired data.

## Results

**Action potential characteristics:** The action potential characteristics of abnormal ventricular myocardium were compared with those of apparently normal myocardium (Table II). Action potentials from abnormal cells usually had reduced resting membrane potential, action potential amplitude and duration, and maximal upstroke velocity of phase zero. However, in 2 cells from Patient 5 and 2 cells from Patient 6, variable amplitude action potentials were elicited from resting membrane potentials of −70 to −79 mV. The amplitudes and upstroke velocities of these action potentials depended on stimulus intensity, frequency, and polarity. In the example shown in Figure 1, bipolar cathodal stimulation consistently produced action potentials with amplitudes of approximately 91 mV (superimposed action potentials labelled 1 and 2). Anodal pulses elicited lower amplitude action potentials whose upstrokes were increasingly delayed in onset and reduced in amplitude (action potentials 3 to 11), until only a subthreshold depolarization was produced (labelled 12). The next stimulus after the subthreshold depolarization produced an action potential with a relatively large amplitude (action potential 13) and the sequence of progressive action potential depression was repeated (not shown). Data for the variable amplitude action potentials were not included in Table II.

**TABLE II Action Potential Characteristics**

| | RP (mV) | APA (mV) | APD50 (ms) | APD90 (ms) | $\dot{V}_{max}$ (V/s) |
|---|---|---|---|---|---|
| Normal | −81.0 | 109.7 | 249.3 | 378.3 | 219.0 |
| (n = 10) | ±1.2 | ±1.4 | ±15.2 | ±23.4 | ±23.5 |
| Abnormal | −60.8* | 75.5* | 112.2* | 206.3* | 45.8* |
| (n = 14) | ±1.7 | ±3.0 | ±15.9 | ±27.6 | ±9.1 |

* Statistically significantly different from normal to $p < 0.05$. Data are given as mean ± standard error of the mean.

APA = action potential amplitude; APD50 = action potential duration at 50% of repolarization; APD90 = action potential duration at 90% of repolarization; RP = resting potential; $\dot{V}_{max}$ = maximal action potential upstroke velocity.

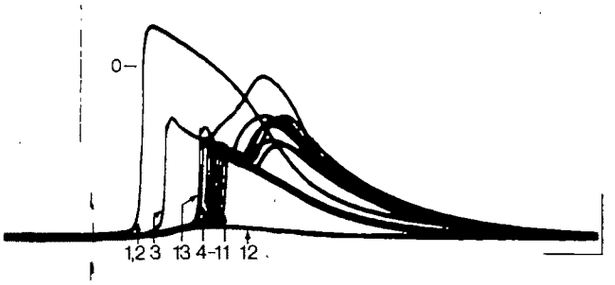



**FIGURE 1.** Consecutive superimposed recordings of variable amplitude action potentials in a human ventricular cell during stimulation at a basic cycle length of 1,000 ms. Action potentials and subthreshold responses are numbered sequentially in the order in which they occurred. Stimulus duration and intensity were constant at 2 ms and 100 V, respectively. The maximal diastolic potential was −75 mV. Vertical calibration, 25 mV. Horizontal calibration, 50 ms. Data obtained from Patient 6. See text for discussion.

**Conduction disturbances:** *Stimulus-dependent block:* Abnormal action potentials, as characterized in Table II, were associated with slow conduction and variable degrees of conduction block. Conduction across some areas of abnormal myocardium was facilitated by increasing the stimulus intensity, duration, or cycle length. An example of the dependence of conduction on stimulus frequency is shown in Figure 2. In this preparation microelectrode recordings were obtained from cells on opposite sides of an area of depressed conduction. One-to-one conduction across the depressed segment occurred at basic cycle lengths >1,100 ms (not shown), but 2:1 and higher degrees of block developed

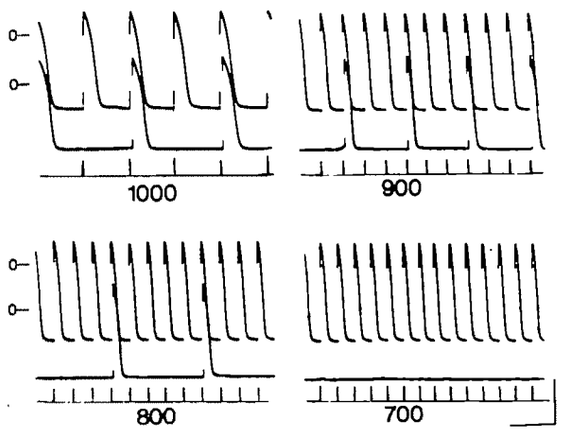



**FIGURE 2.** Increased degree of conduction block in diseased human ventricle with increasing stimulus frequency. Two microelectrode recordings were obtained from relatively normal cells on opposite sides of an area of abnormal cells approximately 14 mm wide. A bipolar stimulating electrode was placed in 1 of the normal areas. In each panel the upper action potentials were recorded near the stimulating electrode and the lower action potentials were recorded on the opposite side of the abnormal area. The bottom recording is the stimulus interval, which is given in milliseconds below each panel. The stimulus polarity, duration, and intensity were constant throughout at cathodal, 2 ms, and 10 V, respectively. Vertical calibration, 50 mV. Horizontal calibration, 1 second for a stimulus interval of 1,000 ms and 2 seconds for the rest. Data obtained from Patient 1. See text for discussion.

as the basic cycle length was shortened from 1,000 to 800 ms. Complete block occurred at a basic cycle length of 700 ms.

A similar relation between stimulus frequency and conduction was seen in another preparation (Fig. 3). However, in this preparation, 1:1 conduction across an area of abnormal cells occurred at shorter cycle lengths when the stimulating site was on one side of the abnormal area (X2) rather than the other (X1). As plotted in Figure 3, stimulation at site X1 during control produced 1:1 responses at the recording site near the stimulating electrode (the proximal site) and at a recording site on the opposite side of the preparation (the distal site) at a cycle length of 1,300 ms. Thus, the ratio of the distal response (DR) to the proximal response (PR) was 1.0. Two-to-one block developed at a cycle length of 1,200 ms, producing a DR/PR ratio of 0.5, and complete block occurred at a cycle length of 400 ms. One-to-one conduction occurred at a cycle length of 1,000 ms during control stimulation of site X2, with complete block at the distal recording site at a cycle length of 700 ms.

After control measurements, the preparation was exposed to isoproterenol ($10^{-7}$ *M*) for 10 minutes in an attempt to facilitate conduction.[22] After isoproterenol the cycle length at which 1:1 conduction occurred during pacing at site X1 shortened from 1,300 to 600 ms and complete block was not produced even at a cycle length of 400 ms (the proximal site did not respond 1:1 when the cycle length was shortened further). The cycle lengths at which 1:1 conduction and complete block were produced during stimulation at site X2 also were reduced after isoproterenol exposure, but to a lesser extent. Thus, isoproterenol effectively reversed the direction of block at some pacing cycle lengths.

*Summation:* The site of stimulation also could affect the configuration of action potentials in abnormal cells. In the preparation shown in Figure 4, stimulation of a relatively normal area of myocardium (X1) or an abnormal area (X2) produced a normal action potential near X1 and a slowly rising action potential ($V_{max}$ <10 V/s) near X2. Simultaneous stimulation of X1 and X2 also produced a normal action potential near X1, but markedly altered the action potential near X2. The maximal upstroke velocity of the abnormal cell was increased to approximately 40 V/s and there was less delay between the onset of the stimulus and the maximal action potential amplitude.

**Entrance and exit block:** In 2 preparations, a spontaneously discharging ectopic focus could be captured by action potentials elicited in the surrounding myocardium (Figs. 5 and 6). Stimulating the area surrounding 1 focus at a cycle length >1,200 ms resulted in 1:1 capture of the ectopic area with some delay (Fig. 5A). However, conduction into the focus from the stimulus site was unidirectional, because spontaneous action potentials generated by the focus did not produce an active response in the surrounding myocardium (Fig. 5B). Shortening the pacing cycle length from 1,200 to 400 ms produced increasing degrees of entrance block into the ectopic focus, and the coupling interval changed from 1:1 to 4:3, 3:2, 2:1, 3:1, and 4:1 (Fig. 6). At cycle lengths of 1,100, 1,000, and 800 ms, activation of the ectopic area showed Wenckebach-like characteristics, that is, activation times increased progressively before

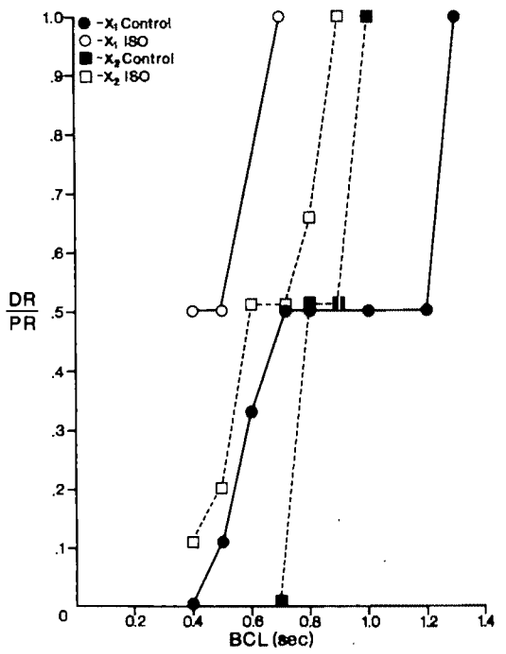



**FIGURE 3.** Dependence of conduction on pacing site and frequency in diseased human ventricle before and after exposure to isoproterenol (ISO) ($10^{-7}$ *M* for 10 minutes). Bipolar stimulating electrodes and recording microelectrodes were placed in relatively normal myocardium on opposite sides of an area of abnormal myocardium approximately 10 mm wide. Site X1 (**circles**) or site X2 (**squares**) was stimulated during control (**black symbols**) and after exposure to ISO (**white symbols**). Responses at the microelectrode site near the respective stimulating electrode (the proximal response [PR]) and on the opposite side of the depressed area (the distal response [DR]) were monitored. The ratio DR/PR is displayed as a function of the pacing basic cycle length (BCL) in milliseconds. Stimulus polarity, duration, and intensity were constant throughout at cathodal, 2 ms, and 20 V, respectively. Data obtained from Patient 1. See text for discussion.

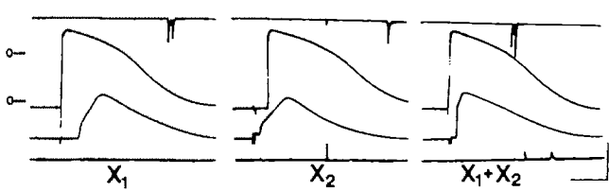



**FIGURE 4.** Summation in diseased human ventricle. Bipolar stimulating electrodes and recording microelectrodes were placed at a site along the border between an area of abnormal myocardium and relatively normal myocardium (X1) and at a site within the abnormal area (X2). The recordings shown are, **from top to bottom**, upstroke velocity of the border zone cell, action potential of the border zone cell, action potential of the abnormal zone cell, and upstroke velocity of the abnormal zone cell. Cycle length = 1,000 ms and stimulus intensity = 100 V. Stimulus duration = 3 ms for X1 and 6 ms for X2. Vertical calibration, 200 V/s for the top and bottom recordings and 50 mV for the middle recordings. Horizontal calibration, 10 ms for the top and bottom recordings and 100 ms for the middle recordings. Data obtained from Patient 3. See text for discussion.

block and activation times after the blocked action potential were relatively short. However, at cycle lengths of 900, 600, and 400 ms, the interval between complexes in the normal zone and in the ectopic zone were constant before and after block.

**Depressed fast responses and slow responses:** Tetrodotoxin had little effect on the action potentials of 4 cells with resting membrane potentials ranging from −44 to −57 mV and maximal upstroke velocities <20 V/s. In these cells, verapamil markedly reduced the amplitude and rate of rise of the action potential upstroke. An example of the effects of tetrodotoxin and verapamil on action potentials in a relatively normal cell and an abnormal cell is shown in Figure 7, A and B. Tetrodotoxin produced activation delay and intermittent conduction block in the normal zone but had little effect on the action potential of the abnormal cell. Verapamil reduced the action potential amplitude of the abnormal cell without affecting its resting membrane potential and slightly reduced action potential amplitude and maximal upstroke velocity in the normal cell. In 3 other cells with resting membrane potentials of −60 to −64 mV and maximal upstroke velocities <70 V/s, tetrodotoxin markedly reduced action potential amplitude and maximal upstroke velocity (Fig. 7C), whereas verapamil only slightly reduced action potential amplitude (not shown).

**Automaticity:** *Triggered activity:* Six of the resected pieces were discharging spontaneously at the time of study. Maximal diastolic potentials of automatic cells ranged from −72 to −33 mV, and spontaneous activity arose from early and delayed afterdepolarizations and from gradual diastolic depolarization. Sustained rhythmic activity could be triggered by single stimulated action potentials or by short trains of stimulation in 2 preparations. An example of the latter phenomenon is shown in Figure 8A. In this preparation, recordings were obtained from 8 sites along a single trabeculum approximately 11 mm long that separated 2 areas of infarcted myocardium. At 1 recording site near the

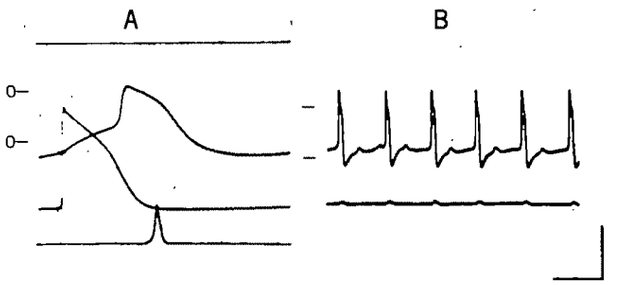



**FIGURE 5.** Exit block from an ectopic focus in diseased human ventricle. **Panel A,** action potential and upstroke velocity recordings from a cell in an abnormal area of myocardium (**upper recordings**) and a cell in relatively normal surrounding myocardium (**lower recordings**) during pacing of the normal myocardium at a cycle length of 1,200 ms. **Panel B,** recordings of the same 2 cells in the absence of pacing. Vertical calibration, 50 mV and 200 V/s. Horizontal calibration, 100 ms in left panel and 4 seconds in right panel. Data obtained from Patient 4. See text for discussion.

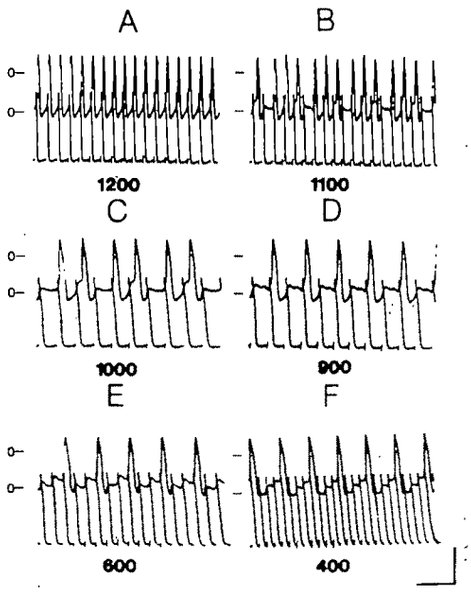



**FIGURE 6.** Frequency-dependent entrance block into an ectopic focus. Same preparation and recording sites as in Figure 5. In **panels A to F** the normal myocardium surrounding the focus was stimulated at progressively shorter cycle lengths, indicated beneath each panel in milliseconds. Vertical calibration, 50 mV. Horizontal calibration, 4 seconds in **A and B** and 2 seconds in **C to F.** See text for discussion.

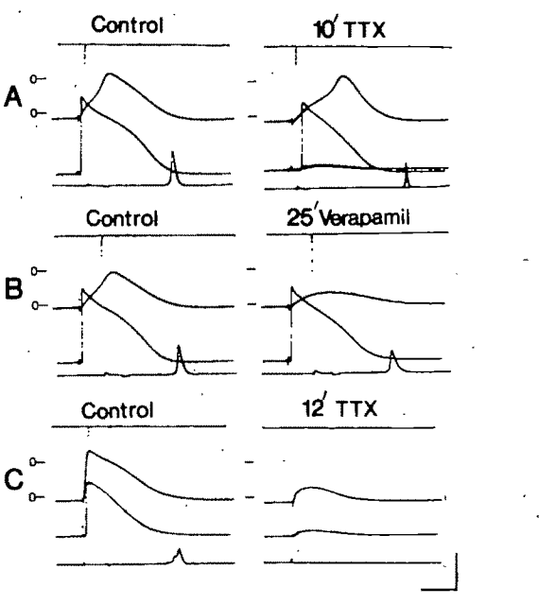



**FIGURE 7.** Effects of tetrodotoxin (TTX) and verapamil on action potentials in diseased human ventricle. **Panel A,** action potential and upstroke velocity recordings from an abnormal cell (**upper recordings**) and a relatively normal cell (**lower recordings**) before and after exposure to TTX for 10 minutes. **Panel B,** after washout of TTX the same 2 cells were exposed to verapamil for 25 minutes. **Panel C,** effects of TTX on a different piece of myocardium taken from the same patient. Vertical calibration, 200 V/s for the upstroke velocity traces and 50 mV for the action potential recordings. Horizontal calibration, 4 ms for the upstroke velocity traces and 100 ms for the action potential recordings. Data obtained from Patient 6. See text for discussion.

middle of the trabeculum (X1), afterdepolarizations of progressively increasing amplitude developed after each of 5 action potentials elicited by intracellular current injection. The fifth stimulated action potential was followed by a series of triggered action potentials that terminated with a gradual increase in cycle length and a subthreshold afterdepolarization.

Stimulated or triggered action potentials at site X1 did not propagate to other recording sites approximately 4 mm proximal or distal to X1 (sites X2 and X3), nor did triggered activity at X2 or X3 propagate to X1 or to recording sites immediately adjacent to the infarcted myocardium. An example of the lack of interaction between sites X1 and X2 is shown in Figure 8B. Spontaneous activity at X1 triggered by 2 stimulated action potentials produced no response at X2 and the subsequent triggering of action potentials at X2 did not alter existing activity at X1.

**Pacemaker modulation and annihilation:** Modulation of pacemaker activity by subthreshold depolarizing and hyperpolarizing pulses was studied in 3 preparations. Pulses delivered early in the spontaneous cycle delayed the next expected discharge, whereas those delivered later in the cycle accelerated the subsequent discharge. In the preparation shown in Figure 9A, injection of a subthreshold current pulse through the lower microelectrode relatively early in the spontaneous cycle (approximately 680 ms after initiation of the rapid portion of the preceding action potential upstroke; indicated by the left dot) produced a subthreshold depolarization in the upper record and delayed the next spontaneous discharge by 400 ms. A current pulse of the same intensity and duration delivered later in the spontaneous cycle (950 ms after the preceding upstroke; the right dot) accelerated the next discharge by 210 ms, relative to the previous 2 action potentials. This pattern of pacemaker modulation resembled previously described phase resetting patterns in other models of biologic oscillators.[11,17] Theoretic predictions from these models indicate that spontaneous activity can be annihilated by a pulse delivered at a critical phase of the pacemaker cycle, known as the singular point.[17] In accordance with these predictions, we found that pulses delivered at the singular point (in this example 930 ms after the preceding action potential upstroke) abolished pacemaker activity and this effect persisted for at least the next 2 minutes (Fig. 9B).

Single subthreshold pulses also could alter the character of subsequent spontaneous action potentials. The example shown in Figure 9C illustrates that an appropriately timed current pulse converted bimodal action potentials to action potentials with a single active component followed by a subthreshold early afterdepolarization. The presence of delayed afterdepolarizations (indicated by the arrows) after the change in action potential configuration suggests that summation of these potentials and the early afterdepolarization accompanying each spontaneous action potential may have been responsible for the second upstroke component of the bimodal action potentials.

**Effects of tetrodotoxin and verapamil:** The spontaneously active preparation shown in Figures 5 and 6 was exposed to tetrodotoxin ($5 \times 10^{-6}$ *M*) for 15

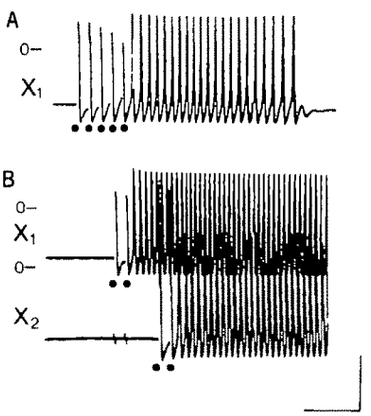



**FIGURE 8.** Triggered sustained rhythmic activity in diseased human ventricle. **Panel A,** sustained rhythmic activity triggered by a series of driven action potentials (indicated by the dots) at recording site X1. **Panel B,** initiation of triggered activity at sites X1 and X2 along the same trabeculum by intracellular current injection (indicated by the dots beneath the respective action potential recordings). For current pulses, cycle length is 2,000 ms, pulse duration 10 ms, and pulse intensity 200 nA. Vertical calibration, 50 mV; horizontal calibration, 10 seconds. Data obtained from Patient 5. See text for discussion.

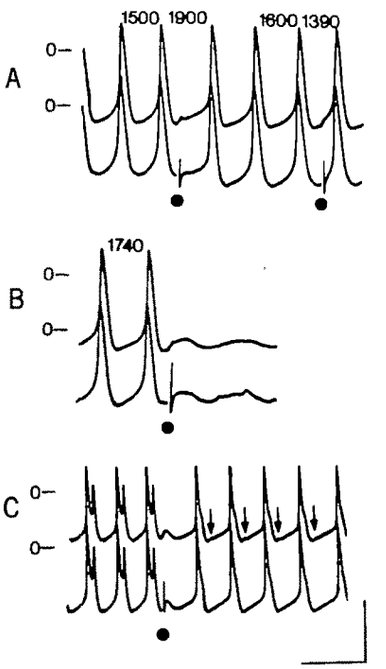



**FIGURE 9.** Modulation of pacemaker activity in diseased human ventricle by subthreshold current pulses. **Panel A,** 2 recording sites along the same trabeculum in a spontaneously active preparation. Current pulses of 30 ms in duration were injected through the lower microelectrode (**dots**). The interval between spontaneous action potentials is given in milliseconds above each interval. **Panel B,** same cells and current pulse variables as in **panel A. Panel C,** 2 recordings from a different area of the same preparation during spontaneous activity. The **dot** indicates the injection of a 30 ms current pulse and the **arrows** indicate delayed afterdepolarizations. Vertical calibration, 50 mV; horizontal calibration, 2 seconds in **A and B** and 4 seconds in **C.** Data obtained from Patient 5. See text for discussion.

minutes, followed by 30 minutes of washout, and was then exposed to verapamil ($2 \times 10^{-6}$ *M*) for 45 minutes (Fig. 10). Tetrodotoxin completely suppressed action potentials at the recording site after 10 minutes. Verapamil suppressed action potentials after 15 minutes, but low level oscillations remained. These gradually decayed over the next 45 minutes and the preparation became completely quiescent.

## Discussion

The results of this study indicate that cells with normal and abnormal action potentials existed in pieces of resected human myocardium that appeared to participate in the initiation of ventricular tachycardia at surgery. Tetrodotoxin, but not verapamil, suppressed action potentials in some abnormal cells whereas verapamil, but not tetrodotoxin, suppressed action potentials in other abnormal cells. Both groups of cells were found in areas of depressed conduction and may have contributed to the entrance and exit block, unidirectional and bidirectional block, Wenckebach-type periodicity, and summation observed in vitro. In addition, both tetrodotoxin and verapamil suppressed spontaneous activity in some preparations, suggesting that depressed fast responses and slow responses played a role in abnormal impulse formation. Subthreshold potentials induced by current injection or action potentials proximal to a zone of block altered the spontaneous discharge rate of automatic cells, annihilated pacemaker activity, and influenced the configuration of spontaneous action potentials. Afterdepolarizations following stimulated action potentials occasionally reached threshold and triggered bursts of sustained rhythmic activity.

The cellular electrophysiologic abnormalities cited herein were assumed to be related to the underlying heart disease of these patients. However, all patients had received cardioactive drugs at some point in their therapy and some patients had received antiarrhythmic agents just before or at the time of surgery (Table I). These drugs may have contributed to the in vitro electrophysiologic findings. Therefore, our results pertain to the potentially arrhythmogenic electrical properties of these preparations, regardless of the precipitating factor, rather than to the electrical properties of diseased ventricle per se.

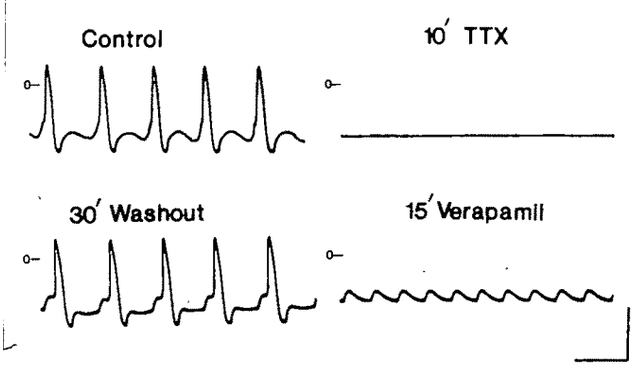



**FIGURE 10.** Effects of tetrodotoxin and verapamil on spontaneous activity in diseased human ventricle. **Upper panels,** automaticity before (Control) and after superfusion with TTX ($5 \times 10^{-6}$ *M*) for 10 minutes. **Lower panels,** automaticity after 30 minutes of washout of TTX and after superfusion with verapamil ($2 \times 10^{-6}$ *M*) for 15 minutes. Vertical calibration, 50 mV; horizontal calibration, 2 seconds. Data obtained from Patient 4. See text for discussion.

**Abnormal action potentials and conduction:** The relatively low resting membrane potential of most cells in diseased myocardium may underlie many of the abnormal action potential characteristics of these cells and the slow and frequently dysynchronous conduction in infarcted myocardium. Sustained depolarization partly inactivates fast inward sodium channels, decreasing excitability, action potential upstroke velocity, and conduction velocity.[23,25] These phenomena may contribute to the development of graded responses and summation.[26] However, we (Fig. 1) and others[1,27] recorded action potentials that had variable amplitudes in cells with nearly normal resting potentials, indicating that a normal resting potential was not necessarily associated with normal active membrane properties.

Cells with variable action potential responses to different stimulus intensities and frequencies often exhibited Wenckebach-type block. Wenckebach cycles have been postulated to involve decremental conduction culminating in block or step delays in conduction at a junction of partly refractory tissue.[18,19] The records in Figures 1 and 6 tend to support the latter concept, because the foot potential input after each stimulus was constant in amplitude, but successive action potentials were delayed in onset until block occurred. The activation delay presumably was due to increasing refractoriness produced by the progressively shorter interval between complete repolarization and the succeeding stimulus.

**Depressed fast responses and slow responses:** The suppression of action potentials and automaticity by both verapamil and tetrodotoxin suggests that depressed fast responses and slow responses coexist in diseased human ventricle and participate in abnormal impulse generation and propagation. However, we could not record from all cells in a preparation or be certain that we had impaled the dominant pacemaker cell in an ectopic area. Therefore, it is possible that tetrodotoxin or verapamil only appeared to suppress action potentials or automaticity, when they actually had produced entrance or exit block from the stimulating electrode or ectopic focus. This possibility is suggested by Figure 10B, in which verapamil initially suppressed action potentials in the recording zone, but low level oscillations remained. These potentials may have been intrinsic membrane oscillations of the recorded cell or may have been subthreshold responses to ongoing spontaneous activity in another area of the preparation. However, the eventual cessation of the low level potentials suggests that verapamil did suppress automaticity in this case.

**Automaticity:** The phase-response relation, annihilation, and alteration of action potential configuration produced in spontaneously depolarizing preparations by subthreshold and regenerative action potentials resembled that produced in in vitro models of depressed conduction.[10–13] Our observation that these phenomena can occur in diseased human ventricular myocardium

supports previous contentions that this type of oscillatory phenomenon has clinical relevance.[10,28] For example, the spontaneous discharge rate of an ectopic ventricular focus may be modulated by changes in the sinus rate and produce complex, but predictable, ventricular rhythms.[28] Sinus complexes or external stimuli that invade a spontaneously discharging region of myocardium at the appropriate time (the singular point[17]) could terminate ventricular ectopy through annihilation. The mechanism by which annihilation occurs in cardiac tissue has not been defined, but the singular point and annihilation appear to be features of several types of biologic oscillators.[11,17] Appropriately timed impulses also might change the electrocardiographic manifestation of polymorphic ventricular tachycardia[29] from 1 configuration to another, as suggested by Figure 9C. Furthermore, termination of ventricular tachycardia with a single premature stimulus could reflect annihilation of an automatic focus, rather than interruption of a reentrant pathway.

Triggered sustained rhythmic activity also may be initiated and terminated by a single stimulus.[14–16] The records in Figure 8 illustrate that this type of activity can occur in virtual isolation from surrounding myocardium, raising the possibility that in the intact heart triggered pacemakers may "control" small areas of myocardium without producing manifest ventricular arrhythmias. These findings may relate to the observation that triggered activity was seen in damaged rat myocardium in vitro at a time when no arrhythmias were apparent on the surface electrocardiogram.[22]

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## References

1. **Spear JF, Horowitz LN, Hodess AB, MacVaugh III H, Moore EN.** Cellular electrophysiology of human myocardial infarction. I. Abnormalities of cellular activation. Circulation 1979;59:247–256.
2. **Spear JF, Horowitz LN, Moore EN.** The slow response in human ventricle. In: Zipes DP, Bailey JC, Elharrar V, eds. The Slow Inward Current and Cardiac Arrhythmias. The Hague: Martinus Nijhoff, 1980:309–326.
3. **Dangman KH, Danilo P Jr, Hordof AJ, Mary-Rabine L, Reder RF, Rosen MR.** Electrophysiologic characteristics of human ventricular and Purkinje fibers. Circulation 1982;65:362–368.
4. **Singer DH, Baumgarten CM, Ten Eick RE.** Cellular electrophysiology of ventricular and other dysrhythmias: studies on diseased and ischemic heart. Prog Cardiovasc Dis 1981;24:97–156.
5. **Ten Eick RE, Baumgarten CM, Singer DH.** Ventricular dysrhythmia: membrane basis or of currents, channels, gates and cables. Prog Cardiovasc Dis 1981;24:157–188.
6. **Lazzara R, Hope RR, El-Sherif N, Scherlag BJ.** Effects of lidocaine on hypoxic and ischemic cardiac cells. Am J Cardiol 1978;41:872–879.
7. **El-Sherif N, Lazzara R.** Reentrant ventricular arrhythmias in the late myocardial infarction period. 7. Effect of verapamil and D600 and the role of the 'slow channel.' Circulation 1979;60:605–612.
8. **Lazzara R, Scherlag BJ.** Role of the slow current in the generation of arrhythmias in ischemic myocardium. In Ref. 2:399–416.
9. **Gilmour RF Jr, Zipes DP.** Electrophysiological response of vascularized hamster cardiac transplants to ischemia. Circ Res 1982;50:599–609.
10. **Jalife J, Moe GK.** A biologic model of parasystole. Am J Cardiol 1979; 43:761–772.
11. **Jalife J, Antzelevitch C.** Phase resetting and annihilation of pacemaker activity in cardiac tissue. Science 1979;206:695–697.
12. **Antzelevitch C, Jalife J, Moe GK.** Characteristics of reflection as a mechanism of reentrant arrhythmias and its relationship to parasystole. Circulation 1980;61:182–191.
13. **Antzelevitch C, Moe GK.** Electrotonically mediated delayed conduction and reentry in relation to "slow responses" in mammalian ventricular conducting tissue. Circ Res 1981;49:1129–1139.
14. **Cranefield PF.** Action potentials, afterpotentials and arrhythmias. Circ Res 1977;41:415–423.
15. **Ferrier GR.** Digitalis arrhythmias: role of oscillatory afterpotentials. Prog Cardiovasc Dis 1977;19:459–490.
16. **Wit AL, Cranefield PF, Gadsby DC.** Triggered activity. In Ref 2:437–454.
17. **Winfree AT.** Integrated view of resetting a circadian clock. J Theor Biol 1970;28:327–374.
18. **Rosenblueth A.** Mechanism of the Wenckebach-Luciani cycles. Am J Physiol 1958;194:491–494.
19. **Zipes DP, Mendez C, Moe GK.** Some examples of Wenckebach periodicity in cardiac tissues, with an appraisal of mechanisms. In: Rosenbaum M, ed. Cardiac Arrhythmias. Boston: Martinus Nijhoff, 1981, in press.
20. **Horowitz LN, Harken AH, Kastor JA, Josephson ME.** Ventricular resection guided by epicardial and endocardial mapping for treatment of recurrent ventricular tachycardia. N Engl J Med 1980;302:589–596.
21. **Rosen MR, Ilvento JP, Gelband H, Merker C.** Effects of verapamil on electrophysiologic properties of canine cardiac Purkinje fibers. J Pharmacol Exp Ther 1974;189:414–422.
22. **Gilmour RF Jr, Zipes DP.** Electrophysiological properties of rodent myocardium damaged by adrenaline. Cardiovasc Res 1980;14:582–589.
23. **Weidmann S.** The effect of the cardiac membrane potential on the rapid availability of the sodium carrier system. J Physiol (Lond) 1955;127: 213–224.
24. **Van Dam RT, Moore EN, Hoffman BF.** Initiation and conduction of impulses in partially depolarized cardiac fibers. Am J Physiol 1963;204:1133–1144.
25. **Dominguez G, Fozzard HA.** Influence of extracellular $K^+$ concentration on cable properties and excitability of sheep cardiac Purkinje fibers. Circ Res 1970;26:565–574.
26. **Cranefield PF, Hoffman BF.** Conduction of the cardiac impulse. II. Summation and inhibition. Circ Res 1971;28:220–233.
27. **Ten Eick RE, Singer DH, Solberg LE, DeBoer A.** Alterations in the electrophysiological characteristics of diseased human ventricle (abstr). Circulation 1972;45:Suppl II:II–9.
28. **Moe GK, Jalife J, Mueller WJ, Moe B.** A mathematical model of parasystole and its application to clinical arrhythmias. Circulation 1977;56:968–979.
29. **Josephson ME, Horowitz LN, Farshidi A, Spielman SR, Michelson EL, Greenspan AM.** Recurrent sustained ventricular tachycardia. IV. Pleomorphism. Circulation 1979;59:459–468.

# Biphasic Nature of Propranolol's Microelectrophysiologic Effects

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**The microelectrophysiologic effects of d,l-propranolol were observed to be biphasic when a wide range of concentrations was used in canine atrial tissue; therefore, the 2 isomers were used separately to test the hypothesis that the opposite effects of propranolol could be separated by isomeric isolation. Whole atria were detached from dog hearts and 3 by 0.5 cm strips were cut from the atria. Transmembrane action potentials were monitored from the atrial strips mounted in an isolation chamber containing Tyrode's solution. Concentrations of d-propranolol, l-propranolol, and the d,l-racemate ranging from 0.03 to 1.0 μg/ml were added to the bath and the effects observed for 60 minutes. In lower concentrations d,l-propranolol decreased the effective refractory period and activation time while increasing maximal rise velocity, action potential amplitude, and resting membrane potential. Higher concentrations produced the opposite effects. The l-isomer produced effects very similar to those of the lower concentrations of the racemate, whereas the d-form mimicked those effects of the higher concentrations of the racemic mixture. We conclude that d,l-propranolol is capable of exerting 2 opposite electropharmacologic actions, which may be demonstrated by varying the concentration of d,l-propranolol or by separating the isomers.**

The first beta-adrenergic blocking agent introduced by Powell and Slater[1] in 1958 was heralded as a major scientific and clinical tool. The later synthesis of propranolol introduced a clinically useful beta-blocking drug[2] that has rapidly become one of the most versatile and widely used chemotherapeutic agents of the day.[3]

Although the antiarrhythmic mode of action of propranolol is not fully established, 2 categories of action are often suggested: (1) specific antagonism of adrenergically induced arrhythmias at a receptor level, and (2) a quinidine-like, nonspecific, membrane-depressant, antiarrhythmic action.[4]

In a previous study,[5] the microelectrophysiologic effects of propranolol on canine isolated atrial tissue were observed to be opposite at ranges of effective clinical concentrations. The question thus arose as to whether both of these actions, that is, beta blockade and membrane depression, might be demonstrable, depending on the physiologic situation and the effective concentrations. To examine this possibility, we attempted to dissect these actions of propranolol by examining the 2 isomeric forms of the drug.

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## Methods

After anesthetization with intravenous pentobarbital sodium (30 mg/kg), the chest of adult dogs was opened through a right thoracotomy; the heart was visualized and rapidly removed. The left atrium was separated from the heart and submerged in a beaker of warmed, oxygenated Tyrode's solution. Rinsed clean of blood, the atrium was opened flat, and 3 by 0.5 cm strips were sectioned by cutting along the recessed regions between trabeculae. Each tissue sample was pinned to the paraffin floor of the 3 ml well of a lucite isolation chamber. By a system of pumped inflow and suctioned outflow, oxygenated 36°C Tyrode's solution continuously superfused the tissues at a rate of 2 ml/min. A stimulating electrode was placed on the anatomically proximal end of the tissue sample and provided double the threshold drive stimulation at a rate of 80 beats/min. A bipolar surface electrode was positioned on the distal end of the tissue for monitoring tissue electrogenic viability, whereas 2 potassium-filled, glass microelectrodes were used to impale 2 cells, separated by no more than 0.5 cm, for recording the transmembrane action potentials.

After a 30-minute equilibration period, a control photograph of the oscilloscope tracing, bearing 2 action potentials,

fast tracings of their phase O upstrokes, and a surface electrogram was taken. After establishment of the effective refractory period by the electronic, time-delayed manipulation of an extrastimulus interpolated between 2 drive stimuli, the superfusion medium was changed from normal Tyrode's solution to a drug-containing Tyrode's solution, and a timing device started. At 15-minute intervals, photographic records and effective refractory period determinations were obtained during 60 minutes of drug perfusion. The same 2 cells were monitored for the entire period of study. Each tissue sample was administered a single drug treatment at 1 concentration. At times of photographic recordings or at points of interest between, the oscilloscopic tracings were also monitored and stored on a tape recorder.

After 60 minutes of drug treatment, the bathing medium was restored to normal Tyrode's solution for 30 minutes to allow for tissue recovery and a final data sampling.

Dose-response relations were established for the 6 microelectrophysiologic variables of effective refractory period, activation time, action potential amplitude, resting membrane potential, action potential duration at 90% repolarization, and maximal rise velocity of phase O depolarization, using the racemic mixture of propranolol as well as each of the isomers separately, in concentrations ranging from 0.03 to 1.0 μg/ml.

## Results

An interesting contrast is produced by comparison of the dose-response relations of the 3 forms of propranolol (d,l; d; and l) used in these atrial experiments. Figure 1 demonstrates this effect by characterizing the action of various concentrations of each form on atrial effective refractory period. Whereas the d-isomer increases refractoriness and the l-isomer mostly decreases ERP, the racemic mixture of the 2 is biphasic in its effect. In lower concentrations, the racemate acts like the l-isomer and reduces the effective refractory period, whereas in higher concentrations it acts like the d-isomer and increases refractoriness. The d,l and d forms show the classic dose-response relation, but the l form shows a fairly flat line that would suggest a plateau effect.

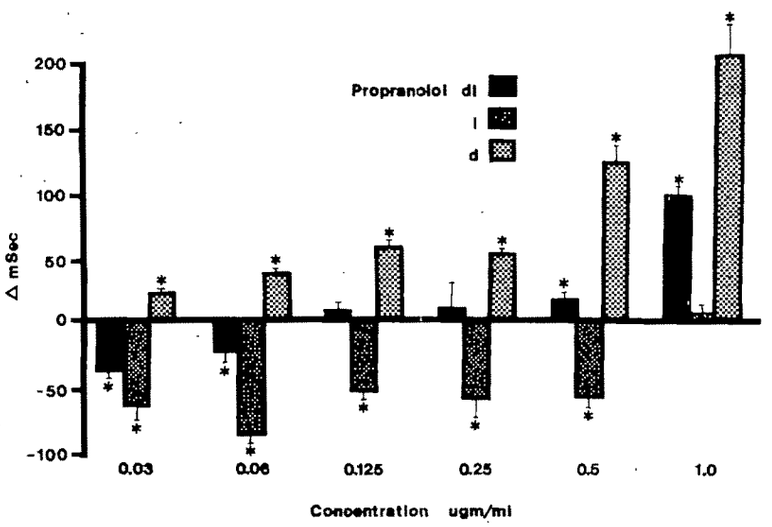



**FIGURE 1.** Comparison of the effects of d,l, d, and l-propranolol on atrial effective refractory period. **Each bar** represents the mean ± standard error. **Asterisks** indicate a significant difference from control ($p < 0.05$). See text for details.

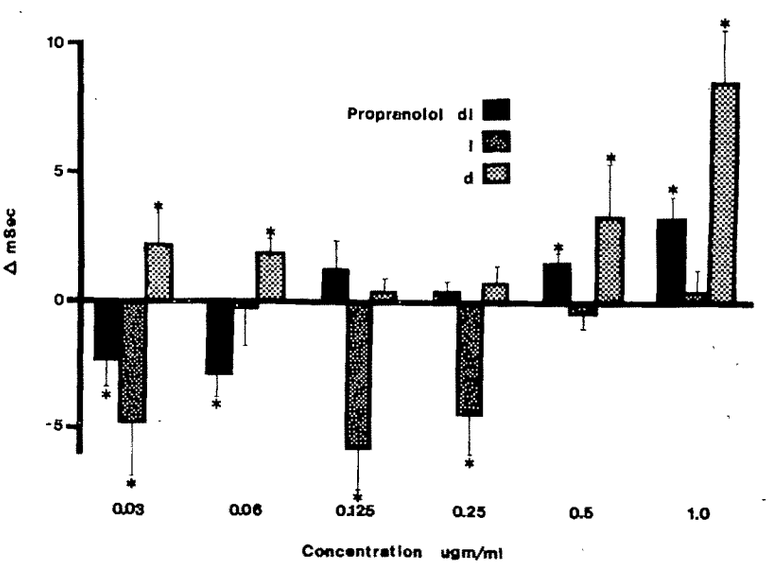



**FIGURE 2.** Effects of d,l-propranolol and the separate isomers on atrial activation time. See Figure 1 for explanation.

Figure 2 less dramatically indicates that atrial activation time is generally increased by the d-isomer, decreased by the l-isomer, and affected in both directions by the racemate, again showing the phenomenon of isomeric separation of action.

Maximal rise velocity of phase O also displays an impression of isomeric separation of action (Fig. 3). The d form tends to depress the measure, the l form may increase maximal rise velocity, and the racemic mixture fluctuates in both directions. A similar relation is seen in Figure 4 showing that lower concentrations of d,l-propranolol resemble the effects of the l-isomer by increasing the atrial action potential amplitude, whereas higher concentrations mimic the effects of the d-form by decreasing amplitude. The 0.125 to 0.25 μg/ml point on these curves repeatedly stands as the conversion position for the biphasic effects of the racemate. The relatively large standard errors that accompany the mean data from these concentrations also suggest a zone of transition.

Action potential duration and resting membrane potential were less consistently affected by these 3 forms of propranolol. A summary of the effects of propranolol's isomeric forms on the atrial potential is contained in Table I. Whereas the l- and d-isomers affect opposite actions, the racemic mixture of the 2 forms compromises the extremes by eliciting both actions, depending on the concentration administered.

**TABLE I General Effects of the Isomeric Forms of Propranolol on the Atrial Transmembrane Potential**

| | Refractory Period | Activation Time | Maximal Rise Velocity | Amplitude |
|---|---|---|---|---|
| l-propranolol | ↓ | ↓ | ↑ | ↑ |
| d,l-propranolol | ↓↑ | ↓↑ | ↑↓ | ↑↓ |
| d-propranolol | ↑ | ↑ | ↓ | ↓ |

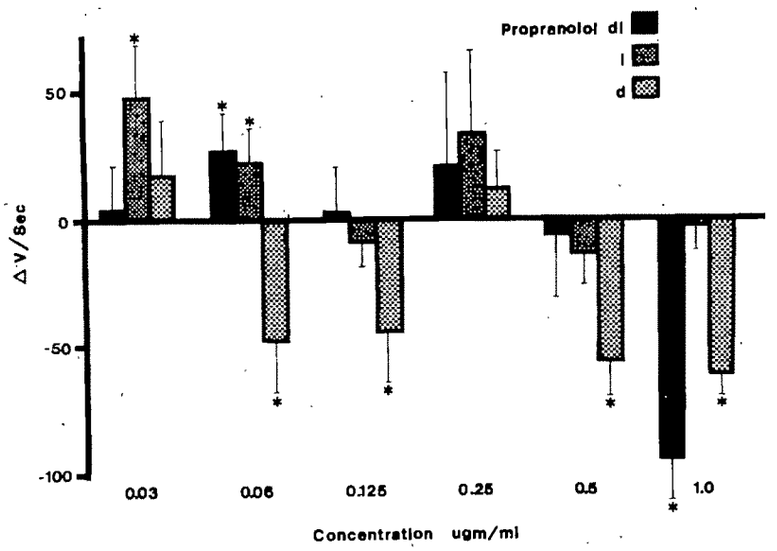



**FIGURE 3.** Effects of d,l-propranolol and the separate forms of the racemate on maximal rise velocity of phase O. See Figure 1 for details.

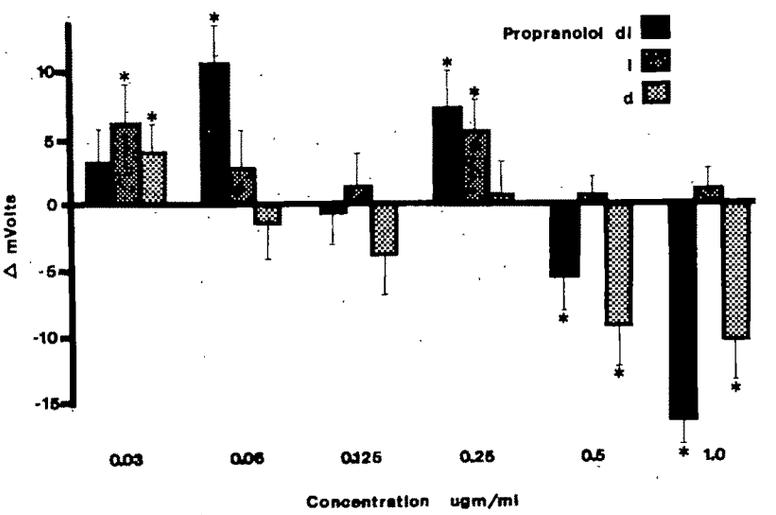



**FIGURE 4.** Response of atrial action potential amplitude to increasing concentrations of d,l, d, and l forms of propranolol. Details as in Figure 1.

## Discussion

The concentrations of propranolol used in this study (0.03 to 1.00 μg/ml) cover the range of blood levels of propranolol commonly found in clinical practice. Walle et al[6] established as a range of plasma concentrations 0.031 to 0.262 μg/ml in patients given 40 mg every 6 hours; Shand et al[7] reported peak plasma levels of 0.036 to 0.212 μg/ml from a single dose of 80 mg administered orally; Rao et al[8] studied patients chronically receiving 80 mg of propranolol every 6 hours and measured peak plasma levels of 0.125 to 0.621 and minimal levels of 0.059 to 0.55 μg/ml. Other investigators have reported similar values.[9–11]

The observations that propranolol exhibits a concentration-dependent, biphasic action on the atrial transmembrane potential, and that the separate administration of the agent's component isomers may effectively disjoin these 2 opposite sets of effects raise some interesting points. Reports conflict in their description of propranolol's microelectrophysiologic effects. Davis and Temte[12] and Vaughan Williams[13] recorded propranolol-induced alterations in the ventricular and atrial transmembrane potentials as minimally decreasing duration and only relatively prolonging refractoriness, but mainly acting to depress automatic phase 4 activity.[12,13] However, Rosen et al[14] reported that in antiarrhythmic concentrations, propranolol acted to significantly prolong duration and refractoriness, to depress rise velocity of the depolarization phase, and to decrease amplitude and resting potential, very similar to quinidine's effects on the ventricular transmembrane action potential.

In this study lower effective concentrations of d,l-propranolol shortened refractoriness and activation time, while increasing amplitude, resting potential, and maximal rate of rise of phase O. Higher concentrations accomplished the opposite, that is, refractoriness and activation time were prolonged, whereas amplitude, resting potential, and maximal rise velocity were depressed. The l-isomer of propranolol generally manifested those actions produced by the lower concentrations of the racemate, and d-propranolol, those of the higher concentrations of the racemic mixture. A logical conclusion from this interesting phenomenon is that in lower doses the action of propranolol is mainly that of beta-adrenergic blockade. This conclusion would be supported by the fact that these actions are duplicated by the l-isomer of propranolol, the form in which beta-blocking capacity is concentrated; that similar clinical concentrations only demonstrate beta blockade[15,16]; and that the flatness of the dose-response curves for the l-isomer reflects an already maximally established effect. An initial impression might be formed, considering the previously listed effects of the l-isomer, that they more resemble those of beta adrenergic agonist activity than of beta antagonism. Initial data from this laboratory suggest that the classically accepted electrophysiologic effects of the catecholamines are rate dependent, and that when administered in concentrations low enough (0.01 to 0.2 μg/ml) so that rate is unaffected and ectopy is absent, isoproterenol might increase refractoriness and slow conduction, while depressing resting potential, amplitude, and rate of rise of phase O. In higher concentrations, propranolol's beta-adrenergic blockade might be masked by the quinidine-like membrane depression known to be expressed by the d-isomer.[3]

These results, demonstrating propranolol's capacity to affect opposite electrophysiologic actions at the extreme ranges of effective concentration, might offer some explanation for propranolol's versatility as an antiarrhythmic agent. In lower concentrations, propranolol might disrupt a reentrant focus by improving conduction through a compromised region of tissue and converting retarded cellular characteristics, dependent on a slow inward current, to those that are more capable of operating by way of the fast sodium current. In higher concentrations, the agent could suppress dysrhythmias by further depressing a region of unidirectional block and of slow conduction to the point of complete block and inactivity. Thus, propranolol at different levels might be as efficacious for the treatment of a noncatecholamine-induced arrhythmia as for one produced by catecholamines.

*Conclusions:* The biphasic nature of propranolol's electrophysiologic actions may be effectively isolated by the separation of its 2 isomeric forms: the beta-blocking l-isomer eliciting the actions of the lower concentrations of the racemate, with the membrane depressant d-form demonstrating those effects of higher concentrations of the racemate. Thus, the concentration-dependent, biphasic microelectrophysiologic actions of the racemic form of propranolol might be used to explain its antiarrhythmic versatility.

## References


1. **Powell CE, Slater IH.** Blocking of inhibitory adrenergic receptors by a dichloro analog of isoproterenol. J Pharmacol Exp Ther 1958;122:480–488.
2. **Black JW, Crowther AF, Shanks RG, Smith LH, Dornhorst AC.** A new adrenergic beta receptor antagonist. Lancet 1964;1:1080–1081.
3. **Lucchesi BR, Whitsitt LS.** The pharmacology of beta adrenergic blocking agents. Prog Cardiovasc Dis 1969;11:410–430.
4. **Somani P, Lum BKB.** The antiarrhythmic actions of beta adrenergic blocking agents. J Pharmacol Exp Ther 1965;147:194–204.
5. **Iansmith DHS, Bandura JP, Nash CB.** A microelectrophysiologic analysis of the pharmacodynamic basis for quinidine-propranolol antiarrhythmic potentiation. J Pharmacol Exp Ther 1981;219:651–658.
6. **Walle T, Morrison J, Walle K, Conradi E.** Simultaneous determination of propranolol and 4-hydroxypropranolol in plasma by mass fragmentography. J Chromatogr 1975;114:351–359.
7. **Shand DG, Nuckolls EM, Oates JA.** Plasma propranolol levels in adults. Clin Pharmacol Ther 1970;11:112–120.
8. **Rao PS, Quesada LC, Mueller HS.** A simple micromethod for simultaneous determination of plasma propranolol and 4-hydroxypropranolol. Clin Chim Acta 1978;88:355–361.
9. **Ambler PK, Singh BN, Lever M.** A simple and rapid fluorometric method for the estimation of 1-(2-hydroxy-3-isopropylamino-propoxy)-naphthalene hydrochloride, propranolol, in blood. Clin Chim Acta 1974;54:373–375.
10. **Hadzija BW, Mattocks AM.** Quantitative TLC determination of propranolol in human plasma. J Pharmaceut Sci 1978;67:1307–1309.
11. **Childsey CA, Morselli P, Bianchetti G, Morganti A, Leonetti G, Zanchetti A.** Studies of the absorption and removal of propranolol in hypertensive patients during therapy. Circulation 1975;52:313–318.
12. **Davis LS, Temte TV.** Effects of propranolol on the transmembrane potentials of ventricular muscle and Purkinje fibers of the dog. Circ Res 1968;22:661–677.
13. **Vaughan Williams EM.** Mode of action of beta receptor antagonists and cardiac muscle. Am J Cardiol 1966;18:399–405.
14. **Rosen MR, Mikra DS, Danilo P.** The effects of dimethyl quaternary propranolol on the electrophysiologic properties of canine cardiac Purkinje fibers. J Pharmacol Exp Ther 1975;193:209–217.
15. **Nies AS, Shand DG.** Clinical pharmacology of beta adrenergic blocking drugs. Circulation 1975;52:6–15.
16. **Pruett IK, Walle T, Bagwell EE.** Association of *in vivo* and *in vitro* propranolol levels in canine Purkinje fibers with antiarrhythmic effects. J Pharmacol Exp Ther 1977;202:45–54.

# Cryosurgery for Cardiac Arrhythmias: Acute and Chronic Effects on Coronary Arteries

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**The use of cryosurgery near major coronary arteries for the treatment of supraventricular and ventricular tachyarrhythmias has caused concern over the possible deleterious acute and chronic effects of cryothermia on vessel patency and integrity. The present study was designed to examine both the acute and chronic effects of cryothermia on major coronary vessels in an experimental model that simulates clinical conditions. In the acute phase of the study, 10 dogs underwent direct cryothermic exposure of the left anterior descending (LAD) coronary artery while coronary artery flow and regional myocardial blood flow were calculated. Direct cryothermic exposure of the LAD resulted in total cessation of LAD blood flow 20 ± 4 seconds after institution of cryothermia. Arterial patency returned 29 ± 8 seconds after termination of cryothermic exposure. In the second phase of this study, 16 dogs had cryolesions applied directly over the LAD at myocardial temperatures of 37°C and during elective cardioplegic arrest at myocardial temperatures of 6 to 12°C. In addition, cryothermia was applied directly to the coronary sinus in these animals. The animals were allowed to live either 48 hours, 2 weeks, or 6 months after the initial procedure, and the cryolesions and underlying vessels were examined histologically. Although coronary arteriography at 6 months showed all coronary arteries to be patent, microscopic examination revealed coronary intimal hyperplasia to be present in the majority of the coronary arteries at the site of the cryolesion, particularly if the cryolesion had been applied during hypothermic, cardioplegic arrest. Cryothermia had no effect on the coronary sinus. This study provides evidence for cryothermia-induced coronary arterial damage that may produce hemodynamically significant coronary artery stenosis and suggests that caution be exercised when it is necessary to create cryolesions in the vicinity of major coronary arteries.**

Cryothermic ablation of myocardium has been advocated in a variety of surgical procedures for the management of both supraventricular and ventricular arrhythmias. Some of these procedures require the application of cryothermia in the vicinity of major coronary vessels. For example, the experimental left atrial isolation procedure[1] as well as cryothermic ablation of aberrant pathways of atrioventricular conduction[2] requires the use of cryothermia in the atrioventricular groove. In addition, cryothermic ablation of arrhythmogenic ventricular foci[3,4] may require exposure of coronary arteries to cryothermia. The use of cryosurgery near major coronary arteries has caused concern over the possible deleterious acute and chronic effects of cryothermia on vessel patency and integrity, particularly in view of previous reports of endothelial damage and intimal proliferation in both coronary[5] and noncoronary vessels[6–12] after cryothermic exposure. The purpose of this study was to examine the acute and chronic effects of cryothermia on coronary vessels in an experimental model that simulates clinical conditions and to make recommendations concerning the use of cryothermia near major coronary arteries.

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## Methods

**Experimental protocol for evaluating the acute effects of cryothermia on major coronary arteries:** Ten adult mongrel dogs weighing 24 to 26 kg were anesthetized with sodium pentobarbitol (30 mg/kg), and ventilated with room air through a cuffed endotracheal tube attached to a Harvard pump respirator. Percutaneous cannulations of the femoral

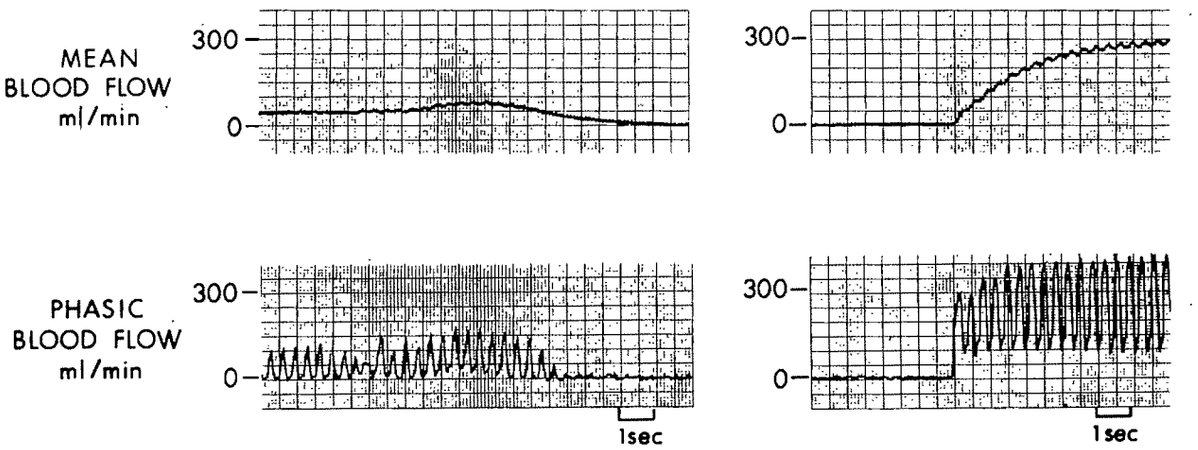



**FIGURE 1.** LAD coronary artery blood flow during direct cryothermic exposure (**left panels**) and at the time of thawing 29 ± 8 seconds after termination of cryothermic exposure (**right panels**). Coronary artery occlusion occurred an average of 20 ± 4 seconds after initiation of cryothermic exposure.

artery and vein were performed to monitor systemic arterial blood pressure and pulmonary artery pressure by way of a Swan-Ganz catheter. The heart was exposed through a left thoracotomy and a pericardial cradle was constructed. A 1 cm portion of the proximal LAD coronary artery was dissected free of surrounding connective tissue and fitted with a 2.5 mm Howell electromagnetic flow probe (Howell Instruments, Camarillo, California). The flow probes were connected to a Model HMS 1000 Howell flow meter and the signals were passed through 2 Hewlett-Packard Model 8802-A medium-gain amplifiers at filter settings of 30 Hz (phasic trace) and 1.0 Hz (mean trace). Systemic arterial blood pressure, pulmonary artery pressure, mean LAD coronary blood flow, phasic LAD coronary blood flow, and a standard lead II electrocardiogram were recorded on magnetic tape at 3¾ in/s.

Regional myocardial blood flow in the subepicardium, mid-myocardium, and subendocardium of various regions of the LAD vascular bed and of the circumflex coronary artery vascular bed was determined by the radioactive microsphere technique at the study intervals outlined below. The radioactive tracer microspheres were 8 to 10 μm in diameter and were labelled with cerium-141, iodine-125, strontium-85, or scandium-46. A total of 400,000 to 800,000 microspheres were given per injection through a left atrial catheter. A reference sample of femoral arterial blood was withdrawn at a constant rate for 2 minutes beginning 15 seconds before each microsphere injection. This allowed calculation of blood flow to a given region of myocardium in ml/g/min. The radioactive counts for each nuclide in each tissue and blood specimen were determined on a Beckman gamma 4000 scintillation counter containing a 2 inch sodium iodide crystal and employing a digital printout. Overlap for photopeaks in the same tissue specimen was corrected by the method of Rudolph and Heymann.[13]

After the heart had been instrumented, a control radioactive microsphere injection was made and control LAD blood flow, systemic arterial pressure, pulmonary artery pressure, and electrocardiographic data were obtained. A 4 mm cylindrical cryoprobe (Frigitronics, Shelton, Connecticut) cooled to −60°C with expanding nitrous oxide was applied to the LAD immediately distal to the site of the electromagnetic flow

**TABLE I Regional Myocardial Blood Flow (Mean ± Standard Error of the Mean) (ml/g/min)**

| | Control | 60 Seconds After CT* | 15 Minutes After RH | Mechanical LAD Occlusion |
|---|---|---|---|---|
| LAD EPI | 1.2 ± 0.1 | 0.3 ± 0.1 | 1.3 ± 0.1 | 0.3 ± 0* |
| LAD MID | 1.0 ± 0.1 | 0.2 ± 0.1 | 1.1 ± 0.2 | 0.1 ± 0* |
| LAD ENDO | 0.8 ± 0.1 | 0.2 ± 0.1 | 1.0 ± 0.2 | 0.1 ± 0* |
| L/L EPI | 1.2 ± 0.1 | 0.7 ± 0.2 | 1.4 ± 0.2 | 0.6 ± 0.1* |
| L/L MID | 1.0 ± 0.1 | 0.5 ± 0.1 | 1.0 ± 0.2 | 0.4 ± 0.1* |
| L/L ENDO | 0.9 ± 0.1 | 0.5 ± 0.2 | 1.0 ± 0.2 | 0.3 ± 0.1* |
| LCA EPI | 1.2 ± 0.1 | 1.4 ± 0.2 | 1.3 ± 0.2 | 1.4 ± 0.2* |
| LCA MID | 1.1 ± 0.1 | 1.4 ± 0.2 | 1.2 ± 0.2 | 1.3 ± 0.2* |
| LCA ENDO | 1.0 ± 0.1 | 1.3 ± 0.1 | 1.1 ± 0.1 | 1.3 ± 0.1 |
| PLAD EPI | 1.2 ± 0.2 | 1.5 ± 0.2 | 1.3 ± 0.1 | 1.4 ± 0.1* |
| PLAD MID | 1.2 ± 0.1 | 1.5 ± 0.1 | 1.4 ± 0.2 | 1.4 ± 0.1* |
| PLAD ENDO | 1.1 ± 0.1 | 1.3 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1 |

* $p < 0.05$.

Column 1 represents control myocardial blood flow, column 2 the myocardial blood flow after 60 seconds of direct cryothermic (CT) exposure of the LAD, column 3 the myocardial blood flow 15 minutes after reactive hyperemia, and column 4 the myocardial blood flow after mechanical occlusion of the LAD coronary artery at the site of previous cryothermic exposure.

ENDO = subendocardium; EPI = subepicardium; LAD = vascular bed of the left anterior descending coronary artery distal to the site of either cryothermic exposure or of mechanical occlusion; LCA = vascular bed of the left circumflex coronary artery; L/L = myocardium in the region of the border of the left circumflex and LAD vascular beds; MID = mid-myocardium; PLAD = LAD vascular bed proximal to the site of cryothermic exposure or mechanical occlusion; RH = reactive hyperemia.

probe for 180 seconds. The cryoprobe was applied gently enough so that similar application of a warm cryoprobe produced no change in LAD coronary flow as determined by the electromagnetic flow probe. After 60 seconds of cryothermic exposure, a second radioactive microsphere injection into the left atrium was performed. After the cryothermic exposure was completed, the LAD coronary artery was allowed to thaw, and 15 minutes after the onset of reactive hyperemia a third injection of radioactive microspheres was performed. Thirty minutes later, the LAD coronary artery was occluded with a small vascular clamp at the site of previous cryothermic occlusion for a period of 180 seconds. The fourth injection of radioactive tracer microspheres was performed 60 seconds after application of the LAD occlusive clamp. Regional myocardial blood flow data obtained during this mechanical occlusion of the LAD coronary artery were compared with regional myocardial blood flow data obtained during the period of cryothermic exposure of the LAD. Measurements of heart rate, systemic and pulmonary artery blood pressure, phasic and mean LAD coronary artery flow, regional myocardial blood flow in the areas described above, and the times from the beginning of cryothermic exposure to LAD occlusion and to return of LAD coronary flow for each intervention were obtained for analysis.

**Experimental protocol for evaluating the chronic effects of cryothermia on major coronary arteries:** Sixteen adult mongrel dogs weighing 24 to 26 kg were anesthetized with sodium pentobarbitol (30 mg/kg), and ventilated with 40% oxygen through a cuffed endotracheal tube attached to a Bennett MA-1 volume-cycled respirator. Sterile percutaneous cannulations of the femoral artery and vein were performed to monitor systemic arterial blood pressure and pulmonary artery pressure by way of a Swan-Ganz catheter. A sterile left lateral thoracotomy was performed, and the right atrium and ascending aorta were cannulated for cardiopulmonary bypass. Asanguineous priming solution and Shiley Model 100-A bubble oxygenators were used in all experiments. During cardiopulmonary bypass, the animals were perfused at 2.25 to 2.50 liters/min/$m^2$, maintaining a mean arterial perfusion pressure of 70 to 90 mm Hg. A thermistor (Instrumentation Laboratories, Boston, Massachusetts) was placed in the ventricular septum to monitor myocardial temperature. After institution of normothermic (37°C) cardiopulmonary bypass, the 4 mm cylindrical cryoprobe was applied to the proximal portion of the LAD coronary artery for 120 seconds at −60°C. The aorta was then cross-clamped and 300 ml of 4°C lactated Ringer's solution with 20 mEq potassium chloride/liter was infused into the aortic root, achieving cardioplegic arrest at a myocardial temperature of 6 to 12°C. A cryolesion was then placed over the distal LAD coronary artery and, in addition, a cryolesion was created over the coronary sinus in the posterior left atrioventricular groove. The cryolesions applied during cardioplegic arrest were performed in exactly the same manner as the one that was applied before cardioplegic arrest. The aortic cross-clamp was then released and the heart was defibrillated, and after rewarming to a ventricular septal temperature of 37°C, the animal was weaned from cardiopulmonary bypass. Before closure of the chest, stainless steel suture material was placed at the edges of each cryolesion for later identification. The animals were killed at either 48 hours, 2 weeks, or 6 months after surgery. In the animals that were allowed to live for 6 months after surgery, coronary arteriography was performed before they were killed.

At postmortem examination, the hearts were removed and the coronary arteries were examined grossly before obtaining tissue blocks of the 2 cryolesions containing sections of the LAD coronary artery. A tissue section of coronary artery not involved in a cryolesion was obtained as a control in each animal. After fixation, 8 $\mu$m sections of the coronary arteries were stained with hematoxylin and eosin, Verhoeff-van Gieson, and Masson's trichrome stains. The sections of coronary artery were examined by an independent cardiac pathologist (REI) in a single-blind fashion. The LAD coronary artery and the coronary veins were graded for degree of stenosis on a percent basis with 100% representing total occlusion. A series of other pathologic variables were graded on a scale of 0 to 4 with 0 representing absence of each variable, and 4 representing the maximal possible involvement. The variables recorded were (1) inflammation of the coronary artery adventitia, media, and overlying epicardium; (2) disruption of the coronary artery media; (3) disruption or proliferation of the coronary artery intima; (4) disruption of the internal elastic lamina; (5) calcium deposition in the arterial wall; and (6) alteration of coronary venous architecture. Coronary vessels without surrounding myocardial necrosis or fibrosis attributable to cryothermic injury were excluded from analysis. The pathologic examination of the coronary sinus was limited to a gross description, although stained microscopic sections were obtained.

## Results

**Acute effects of cryothermia on coronary arteries:** Direct cryothermic exposure of the LAD coronary artery invariably resulted in acute occlusion of the coronary artery, although none of the frozen arteries ruptured or showed noticeable dilatation after thawing. Microscopic hemorrhage within the adventitia of the coronary artery at the site of cryothermic exposure was the only immediate pathologic change detected in the coronary arteries and was prominent only after multiple cryothermic exposures at the same site. Mean LAD coronary artery flow before cryothermic exposure was 60 ± 6 ml/min, and typically decreased from that control range to 0 ml/min during the period of cryothermic application (Fig. 1). Coronary artery occlusion occurred 20 ± 4 seconds after institution of cryothermia and arterial patency returned 29 ± 8 seconds after termination of cryothermic exposure. The return of coronary artery blood flow was sudden and typically increased to levels above 300 ml/min at the peak of reactive hyperemia (Fig. 1). During the period of coronary artery occlusion secondary to the cryothermia, the myocardium distal to the cryolesion became dyskinetic and cyanotic, but the tissue regained normal color and contractile activity rapidly after restitution of coronary blood flow with thawing. There was no statistically significant difference between measurements of heart rate before and after cryothermia (152 ± 5 versus 156 ± 5 beats/min, respectively), systemic blood pressure (141/95 versus 136/89 mm Hg), or pulmonary artery diastolic pressure (11 ± 2 versus 11 ± 2 mm Hg). Regional myocardial blood flow data were analyzed for evidence of distal embolization of vascular debris after coronary artery freezing and thawing and also served to verify that cryothermic exposure directly over the LAD coronary artery had caused total occlusion as indicated by the electromagnetic flow probe tracing. These data are summarized in Table I.

Comparisons for statistical significance within each group were made using Student's $t$ test for paired data. Sixty seconds after initiation of cryothermia or mechanical coronary artery clamping, there was a statis-

tically significant decrease in myocardial blood flow to all layers of the LAD vascular bed distal to the site of the occlusion. The peripheral areas of the left circumflex coronary vascular bed also demonstrated a significant decrease in myocardial blood flow at that time. A concomitant increase in myocardial blood flow occurred in the myocardium of the LAD vascular bed proximal to the cryolesion as well as in most of the vascular bed of the left circumflex coronary artery. Myocardial blood flow returned to control levels in all vascular beds by 15 minutes after LAD freezing.

**Chronic effects of cryothermia on coronary arteries:** All coronary arteries subjected to cryothermia were grossly patent at examination 48 hours, 2 weeks, and 6 months after cryothermic exposure. In addition, no coronary artery stenoses were detectable at the cryolesion sites on biplane cineangiography 6 months after cryothermic exposure. The cryolesions created during hypothermic, cardioplegic arrest appeared larger than the cryolesions created at 37°C, an observation consistent with our previous findings.[14]

A summary of the histologic data is presented in Table II. Forty-eight hours after direct cryothermic exposure, the coronary arteries showed a mild degree (0.4 to 1.0) of inflammation in the overlying epicardium, the adventitia, and the media (Fig. 2). In addition to the presence of inflammation, the nuclei of smooth muscle cells in the arterial media were pyknotic and there was mild disruption of the arterial intima in 1 animal associated with noncircumferential fibrin deposition in the area of intimal discontinuity. In 3 animals. there was evidence of coronary venous occlusion, ranging from 25 to 100% in addition to minimal signs of fragmentation of the internal elastic lamina. The LAD coronary artery was patent at 2 weeks in all animals, although there was complete occlusion of a diagonal branch in 1 animal in which the cryolesion had been created during hypothermic, cardioplegic arrest (Fig. 3). By 2 weeks after cryothermic exposure, inflammation of the adventitia and media had cleared, but there was persistence of mild inflammation of the epicardium overlying the coronary artery at the site of cryothermic exposure. Moreover, the architecture of the coronary artery media had returned to normal by 2 weeks, while the coronary artery intima in 3 animals showed mild hyperplasia. Only minimal pathologic alterations were noted in the coronary veins at 2 weeks after cryothermic exposure.

The LAD coronary artery was patent in all animals 6 months after cryothermic exposure. However, LAD stenosis due to intimal hyperplasia was detected at the site of 4 cryolesions that had been created during hypothermic, cardioplegic arrest. The degree of stenosis in these 4 specimens ranged from 10 to 60%, and in 2 specimens the intimal hyperplasia was concentric (Fig. 4). In addition, 2 separate diagonal branches within the cryolesions showed 80% stenoses at 6 months (Fig. 5 and 6). Mild degrees of epicardial, adventitial, and medial inflammation were seen, and there was persistent mild fragmentation of the internal elastic lamina. Only 4 coronary arteries were judged completely normal at the

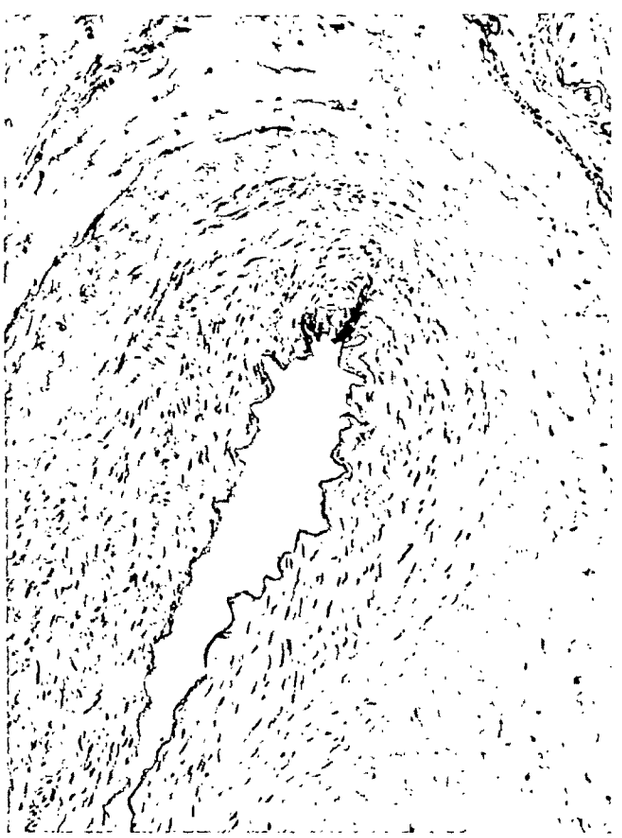


**FIGURE 2.** Hematoxylin-eosin stained section of the LAD coronary artery 48 hours after cryothermic exposure, demonstrating pyknotic nuclei of medial smooth muscle cells, mild inflammation, and vessel patency. (Magnification ×100.)

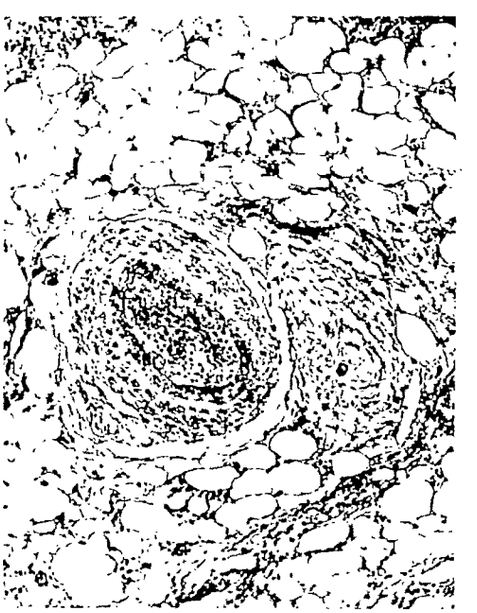


**FIGURE 3.** Complete occlusion of a diagonal branch of the LAD coronary artery 2 weeks after cryothermic exposure. (Magnification ×40, reduced 25%.)

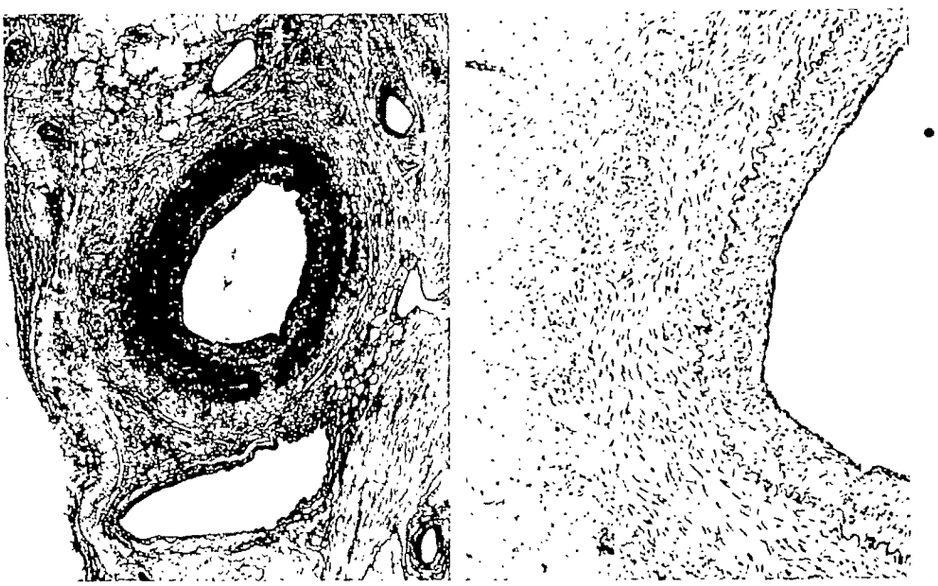


**FIGURE 4. Left panel,** Verhoeff-van Gieson stained section of LAD coronary artery 6 months after cryothermic exposure, demonstrating concentric intimal hyperplasia within well-demarcated internal elastic lamina. (Magnification ×25, reduced 27%.) **Right panel,** hemotoxylin-eosin stained section of the same coronary artery originally magnified ×100 (reduced 27%) to demonstrate the intimal proliferation, the intact internal elastic lamina, and mild inflammation of the adventitia.

site of the cryolesion 6 months after cryothermic exposure. Three of these cryolesions had been created at a myocardial temperature of 37°C and 1 had been created during hypothermic, cardioplegic arrest. No stenosis, thrombosis, or vessel wall abnormality was seen in the coronary sinus at the site of cryothermic exposure 48 hours, 2 weeks, or 6 months after the procedure.

## Discussion

The first series of experiments in this study defined the acute changes in coronary artery blood flow during and immediately after the direct exposure of a coronary artery to cryothermia. The coronary arterial wall remained intact despite multiple exposures to cryothermia and did not develop acute aneurysmal dilatation. Complete cessation and resumption of coronary artery blood flow occurred promptly after the beginning and end of cryothermia, with a typical reactive hyperemic response occurring after the resumption of coronary flow. Regional myocardial blood flow data were obtained as a possible means of detecting distal coronary embolization of debris after thawing of the frozen vessel. These data indicate that freezing of major coronary arteries causes no such acute embolization. Thus, it appears that the immediate limiting factor in the use of cryothermia near major coronary arteries is the level of acute but reversible ischemia that can be tolerated in the myocardial tissue distal to the site of the transient cryothermic occlusion.

The long-term effects of direct cryothermic application to coronary arteries and to other large arteries including the aorta, hepatic artery, femoral artery, and carotid artery have been studied previously.[5,8–12] In

**TABLE II Vascular Histology After Direct Application of Cryothermia to a Major Coronary Artery**

| | 24 to 48 Hour Survivors | | 2 Week Survivors | | 6 Month Survivors | |
|---|---|---|---|---|---|---|
| | 37°C | CP | 37°C | CP | 37°C | CP |
| Art stenosis (%) | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 42 ± 15 |
| Ven stenosis (%) | 5 ± 5 | 30 ± 20 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 |
| Ven dis | 0.6 ± 0.4 | 0.2 ± 0.2 | 0.2 ± 0.1 | 0.3 ± 0.3 | 0 ± 0 | 0.3 ± 0.3 |
| Inf epi | 1.0 ± 0.4 | 0.8 ± 0.4 | 0.8 ± 0.2 | 1.5 ± 0.3 | 0 ± 0 | 0.3 ± 0.2 |
| Inf adv | 0.4 ± 0.2 | 0.4 ± 0.2 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0.2 ± 0.2 |
| Inf med | 0.8 ± 0.4 | 0.8 ± 0.6 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0.2 ± 0.2 |
| Media | 1.4 ± 0.4 | 1.4 ± 0.7 | 0 ± 0 | 0 ± 0 | 0.3 ± 0.3 | 1.0 ± 0.5 |
| Intima | 0.4 ± 0.4 | 0.2 ± 0.2 | 0.8 ± 0.4 | 0.8 ± 0.3 | 0 ± 0 | 2.8 ± 0.7 |
| IEL | 0.6 ± 0.2 | 0.8 ± 0.4 | 0 ± 0 | 0.3 ± 0.3 | 0.3 ± 0.3 | 1.0 ± 0.4 |
| Ca dep | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 |

Each group of survivors had cryothermic exposure of major coronary arteries at both 37°C and during cardioplegic arrest at 6 to 12°C. Arterial and venous stenosis was graded on a percent basis from 0 to 100%, with the latter representing total occlusion. Qualitative parameters of vascular injury were graded on a scale of 0 to 4, with 0 representing absence of the parameter.

Art stenosis = degree of arterial stenosis; Ca dep = calcium deposition in the arterial wall; CP = cryolesions created in the arrested nonperfused heart at 6 to 12°C; IEL = disruption of the internal elastic lamina; Inf adv = inflammation of the adventitia; Inf epi = inflammation of the epicardium; Inf med = inflammation of the media; Intima = disruption or proliferation of coronary artery intima; Media = cell death or disruption of normal media; Ven dis = disruption of the venous architecture; Ven stenosis = degree of venous stenosis; 37°C = cryolesions created in the perfused beating heart at 37°C.

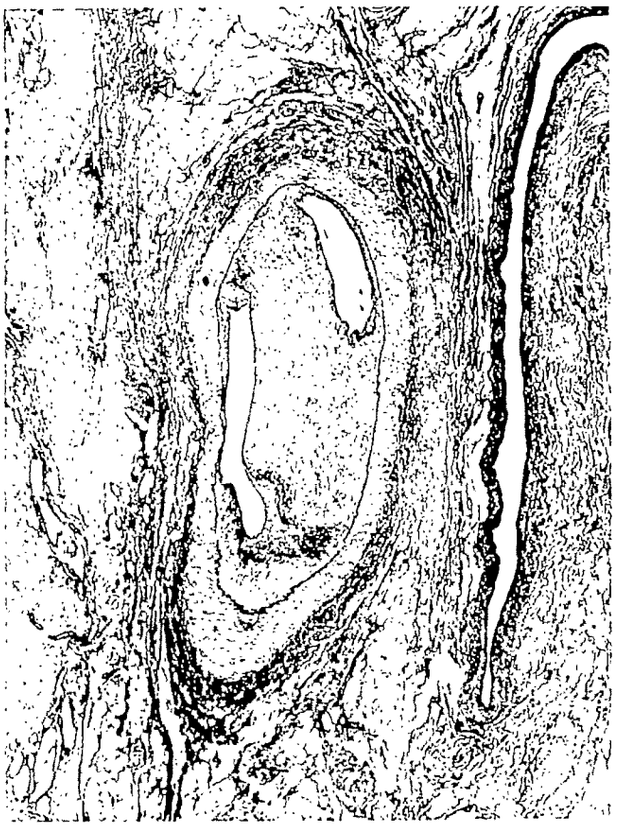


**FIGURE 5.** Diagonal branch of the LAD coronary artery (Verhoeff-van Gieson stain) 6 months after cryothermic exposure; the darkly stained internal elastic lamina marks the boundary of the markedly hyperplastic intima. (Magnification X40.)



**FIGURE 6.** Diagonal branch of the LAD coronary artery (Verhoeff-van Gieson stain) 6 months after cryothermic exposure; note the marked intimal hyperplasia similar in severity to that seen in Figure 5. (Magnification X40.)

addition, several studies have described the response of capillary endothelium to milder cryothermic exposure such as frostbite.[6,7] Those studies indicate that cryothermic exposure destroys cellular elements in the arterial wall but spares noncellular structural elements of the vessel wall. Capillary networks are destroyed by cryothermic injury, but larger arteries, such as those the size of major coronary arteries, continue to function as conduits for blood after thawing. Smooth muscle cells in the media of these arteries rapidly regenerate during the healing phase, while the intima often develops marked hyperplasia. The intimal hyperplasia has been shown to regress within 1 year after the cryothermic exposure[9]; however, if the hyperplasia was sufficiently severe, it could lead to impairment of coronary blood flow resulting in distal myocardial ischemia or infarction. The degree of intimal hyperplasia seen in cryolesions created under cardioplegic arrest in the present study progressed up to 6 months after the procedure, at which time intimal hyperplasia had produced mild to moderate stenosis of the coronary arteries. Coronary intimal hyperplasia appeared to be less severe when cryolesions were applied to the coronary arteries during normothermic perfusion, and these changes had regressed within 6 months after cryosurgery. The larger cryolesion size, and presumably more intense cryothermic exposure during cardioplegic arrest, is the most likely cause for this increased intimal hyperplasia. Of greater concern was the incidental discovery of occlusion or severe stenosis of diagonal branches of the LAD 2 weeks and 6 months postoperatively. This finding supports the recent study of Giampapa et al[10] describing the time-course of occlusion of small arteries and arterioles after cryothermia. These investigators found that the smallest vessels studied (0.33 mm in diameter) were permanently occluded immediately after cryothermia, while arteries 1.0 to 1.5 mm in diameter remained patent for up to 120 hours after cryothermic exposure.

The data obtained in the present study provide evidence for cryothermia-induced coronary arterial damage that may produce hemodynamically significant coronary stenosis. Therefore, caution should be exercised when one finds it necessary to create cryolesions in the vicinity of major coronary arteries. Furthermore, branches of these arteries (that is, coronary arteries <1.5 mm in diameter) should not be included in the cryolesion at all since they may become totally occluded postoperatively. If it is necessary to apply a cryolesion in the atrioventricular groove, for example when performing a left atrial isolation procedure or when ablating an accessory atrioventricular connection, an effort should be made to dissect a segment of the coronary artery free from the atrioventricular groove fat pad and to retract it away from the proposed site of cryothermia

application. If retraction of the coronary artery proves to be too hazardous and creation of a cryolesion is essential to the procedure, the cryolesion should be applied in the perfused heart rather than during elective cardioplegic arrest. Additionally, it is possible that the large amount of fat that surrounds coronary arteries within the atrioventricular groove provides an extra measure of protection since fat is a poor conductor of heat energy. The present study indicates that such dissection and retraction of the coronary sinus is not essential since direct application of cryothermia to the coronary sinus does not cause chronic occlusion or stenosis.

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## References

1. **Williams JM, Ungerleider RM, Lofland GK, Cox JL.** Left atrial isolation: new techniques for the treatment of supraventricular arrhythmias. J Thorac Cardiovasc Surg 1980;80:373–380.
2. **Gallagher JJ, Sealy WC, Anderson RW, Raselli J, Millar R, Campbell RWF, Harrison L, Pritchett ELC, Wallace AG.** Cryosurgical ablation of accessory atrioventricular connections: a method for correction of the pre-excitation syndrome. Circulation 177;55:471–479.
3. **Gallagher JJ, Anderson RW, Kasell J, Rice JR, Pritchett ELC, Gaulti JH, Harrison L, Wallace AG.** Cryoablation of drug-resistant ventricular tachycardia in a patient with a variant of scleroderma. Circulation 1978;57: 190–197.
4. **Camm J, Ward DE, Cory-Pearce R, Rees GM, Spurrell RAJ.** The successful cryosurgical treatment of paroxysmal ventricular tachycardia. Chest 1979;75:621–624.
5. **Mikat E, Hackel DB, Harrison L, Gallagher JJ, Wallace AG.** Reaction of the myocardium and coronary arteries to cryosurgery. Lab Invest 1977; 37:632–641.
6. **Bowers WD, Hubbard RW, Daum RC, Ashbaugh P, Nelson E.** Ultrastructural studies of muscle cells and vascular endothelium immediately after freeze-thaw injury. Cryobiology 1973;10:9–21.
7. **Rabb JM, Renaud ML, Brandi PA, Witt CW.** Effect of freezing and thawing on the microcirculation and capillary endothelium of the hamster cheek pouch. Cryobiology 1974;11:508–518.
8. **Cooper IS, Samra K, Wisniewska K.** Effects of freezing on major arteries. Stroke 1971;2:471–482.
9. **Gage AA, Fayekas G, Riley EE.** Freezing injury to large blood vessels in dogs. Surgery 1967;61:748–754.
10. **Giampapa VC, Oh C, Aufses AH.** The vascular effect of cold injury. Cryobiology 1981;18:49–54.
11. **Taylor CB, Baldwin D, Hass GM.** Localized arteriosclerotic lesions induced in the aorta of the juvenile rabbit by freezing. Arch Pathol Lab Med 1950; 49:623–640.
12. **Kindt GW, Youmans JR.** Feasibility of transarterial cooling of blood. J Cryosurg 1968;1:284–287.
13. **Heymann MA, Payne BD, Hoffman JIE, Rudolph AM.** Blood flow measurements with radionuclide-labeled particles. Prog Cardiovasc Dis 1977;20:55–79.
14. **Holman WL, Ikeshita M, Smith PK, Ungerleider RM, Williams JM, Cox JL.** Cardiac cryosurgery. I. Methods for controlling lesion size. Surgery, in press.

# Intravenous Amiodarone in the Acute Treatment of Recurrent Symptomatic Ventricular Tachycardia

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**Fifteen patients aged 59.3 ± 11.5 years (mean ± standard deviation [SD]) had recurrent symptomatic ventricular tachycardia (VT) refractory to at least 2 conventional antiarrhythmic drugs. All patients had organic heart disease; 4 had an acute myocardial infarction. The mean ejection fraction was 0.30 ± 0.09. Twelve patients had overt congestive heart failure. Five had bundle branch block. Before treatment with intravenous amiodarone, the patients had had 6 to 40 episodes of symptomatic VT over 1 to 8 days of hospitalization. All patients received an initial bolus of 5 mg of amiodarone/kg over 15 minutes. Seven patients also received a continuous infusion of 600 to 1,000 mg of amiodarone over 12 to 24 hours. Additional doses depended on the patients' clinical responses. In 11 of 15 patients, antiarrhythmic drugs that had failed to suppress VT were continued during administration of amiodarone.**

**In 12 of 15 patients acute control of VT was obtained with intravenous administration of amiodarone either alone or in combination with previously ineffective drugs. Three patients continued to have frequent episodes of VT while being treated with intravenous amiodarone. Mobitz type I atrioventricular block developed in 1 patient. No patient had high degree atrioventricular block, symptomatic hypotension, or a clinically apparent worsening of congestive heart failure.**

**The use of intravenous amiodarone represents a significant advance in the acute treatment of frequent life-threatening VT refractory to other drugs. With appropriate monitoring, it can be used safely in patients with congestive heart failure, bundle branch block, or acute myocardial infarction.**

Oral amiodarone has been found to be effective in the chronic suppression of recurrent VT.[1–7] However, because its onset of action may be delayed for several days after initiation of treatment, oral amiodarone is not suitable for acute treatment of VT.[8] Reports of use of intravenous amiodarone in the acute treatment of VT have been restricted to reports in the French literature and have involved few patients.[9–12] Our experience with the use of intravenous amiodarone in the treatment of 15 patients with recurrent symptomatic VT refractory to other antiarrhythmic drugs is reported herein.

## Methods

Fifteen patients (Table I) had recurrent symptomatic VT refractory to at least 2 conventional antiarrhythmic drugs administered in doses sufficient to attain therapeutic or supratherapeutic serum levels. These 15 patients were treated with intravenous amiodarone after informed consent was obtained. The mean age of the 11 men and 4 women was 59 ± 11 (SD) years (range 41 to 72). All patients had underlying heart disease. Three patients had left and 2 had right bundle branch block during sinus rhythm. The ejection fraction was measured by radionuclide or contrast angiography in 14 patients; the mean ejection fraction was 0.30 ± 0.09 (range 0.12 to 0.42). Twelve patients had overt congestive heart failure with an $S_3$ gallop and cardiomegaly on chest roentgenogram. Hemodynamic monitoring was performed with a flow-directed thermodilution catheter positioned in the pulmonary artery in 4 patients who had severe heart failure; these patients had a cardiac index of <1.8 liters/min/$m^2$ and a pulmonary capillary wedge pressure >25 mm Hg.

Before treatment with intravenous amiodarone, the patients were hospitalized for 1 to 8 days and had 6 to 40 episodes of symptomatic VT (Table I) documented by electrocardiographic recordings. The rate of VT was 130 to 250 beats/min. In 1 patient (Case 1), the VT was always nonsustained but was associated with symptoms of transient lightheadedness lasting 15 to 60 seconds. One patient (Case 11) had incessant VT with lightheadedness over a 24-hour period before receiving intravenous amiodarone. In the remaining 13 patients, direct-current counter shock was required 2 to 25 times to terminate episodes of VT associated with loss of consciousness or severe hypotension.

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**TABLE I Clinical Characteristics and Previous Antiarrhythmic Drug Therapy in Patients Treated With Intravenous Amiodarone**

| Case | Age (yr) & Sex | Heart Disease | Ejection Fraction | Onset of VT (days)* | Episodes of VT (n) | Rate of VT (beats/min) | DDC (n) | Unsuccessful Drug Therapy | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Intravenous | Oral |
| 1 | 47 M | IHD | 0.25 | 1 | 4 | 180 | 0 | L, PA | Q |
| 2 | 63 M | IHD | 0.27 | 4 | 25 | 160–250 | 9 | L, PA | Q, E, Pf |
| 3 | 68 F | IHD | 0.33 | 8 | 40 | 180 | 25 | L, PA, B | Q, PA |
| 4 | 71 M | CCM† | 0.22 | 3 | 10 | 240 | 2 | L, PA, B | PA, D |
| 5 | 72 M | IHD | 0.37 | 1 | 6 | 187 | 2 | L, PA, B | ... |
| 6 | 68 F | IHD | 0.35 | 4 | 15 | 150–180 | 15 | L, PA, B | ... |
| 7 | 67 F | AMI† | ... | 1 | 12 | 200 | 2 | L, PA, B | ... |
| 8 | 48 M | AMI | 0.32 | 2 | 8 | 187 | 6 | L, PA, B | ... |
| 9 | 63 M | AMI† | 0.15 | 5 | 20 | 180 | 10 | L, PA, B, Pr | ... |
| 10 | 65 M | AMI | 0.40 | 1 | 20 | 200–250 | 20 | L, PA, B | Q |
| 11 | 42 M | CCM | 0.35 | 1 | Continuous | 150 | 0 | L, PA | ... |
| 12 | 57 M | CCM | 0.42 | 7 | 16 | 160–200 | 2 | L, PA, Pr | ... |
| 13 | 72 F | IHD | 0.32 | 2 | 8 | 250 | 7 | L, PA, B | ... |
| 14 | 45 M | IHD† | 0.12 | 3 | 8 | 187–215 | 6 | L, PA, B | Q |
| 15 | 41 M | CCM | 0.34 | 2 | 15 | 130–170 | 2 | L, PA, B | PA |

* Onset of most recent episodes of VT just before treatment with intravenous amiodarone. † Severe heart failure, with cardiac index <1.8 liters/min/$m^2$ and pulmonary capillary wedge pressure >25 mm Hg.
AMI = acute myocardial infarction; B = bretylium; CCM = congestive cardiomyopathy; D = disopyramide; DDC = direct-current countershock; E = encainide; IHD = ischemic heart disease (chronic); L = lidocaine; PA = procainamide; Pf = propafenone; Pr = propranolol; Q = quinidine.

The antiarrhythmic therapies that failed to suppress VT before administration of intravenous amiodarone are summarized in Table I. The following doses were administered: intravenous lidocaine, a loading dose of 75 to 225 mg followed by a continuous infusion of 2 to 5 mg/min; intravenous procainamide, a loading dose of 600 to 1,000 mg followed by a continuous infusion of 3 to 4 mg/min; intravenous bretylium, a loading dose of 300 to 1,500 mg followed by a continuous infusion of 2 to 4 mg/min; intravenous propranolol, 10 mg; oral procainamide, 6 to 8 g/day; oral quinidine, 1.2 to 1.6 g/day; oral disopyramide, 400 mg/day; oral propafenone, 900 mg/day; and oral encainide, 240 mg/day. Attempts at overdrive suppression with atrial or ventricular pacing in 5 patients were also unsuccessful in controlling VT.

In the absence of preexisting guidelines, a flexible protocol was developed using varying doses of amiodarone to assess its safety and efficacy. All patients received an initial bolus of amiodarone, 5 mg/kg over 15 minutes. Seven patients then received a continuous infusion of 600 to 1,000 mg of amiodarone over 12 to 24 hours. Additional doses depended on the patients' clinical response.

In 11 of 15 patients, antiarrhythmic agents that had already failed to suppress VT were continued during intravenous administration of amiodarone. These medications were continued because in most cases they slowed the rate of the VT. Three patients (Cases 11, 14, and 15) were treated with 800 to 1,200 mg/day of oral amiodarone for 1 to 5 days before receiving the intravenous form. Among the remaining 12 patients, treatment with 800 mg/day of oral amiodarone was initiated within 1 to 2 days after the acute control of VT with the intravenous form. All patients underwent continuous electrocardiographic monitoring during and for at least 3 to 5 days after the administration of intravenous amiodarone.

After discharge from the hospital, patients were seen at intervals of 1 to 3 months by 1 author or the patient's referring physician. Twenty-four hour continuous ambulatory electrocardiographic recordings were obtained every 1 to 3 months.

**TABLE II Response to Treatment With Intravenous Amiodarone and Long-Term Outcome**

| Case | Bolus Dose of Am (mg/15 min) | Infusion Dose of Am (mg/24 h) | Concurrent Therapy | Recurrence of VT Acutely | Chronic Therapy (g/day) | Months of Follow-Up | VT In Follow-Up Period | Died |
|---|---|---|---|---|---|---|---|---|
| 1 | 300 | ... | ... | 0 | Am 0.6 | 10 | 0 | ... |
| 2 | 450 | 600 | ... | 0 | Am 0.4 | 7 | 0 | ... |
| 3 | 350 | 650 | ... | 0 | Am 0.8 | 0.25 | + | + |
| 4 | 300 | 1,000 | ... | 0 | Am 0.6 | 4 | 0 | ... |
| 5 | 400 | ... | PA | 0 | Am 0.4 | 9 | 0 | ... |
| 6 | 350 | 600 | PA, Br | 0 | Am 0.6 | 5 | 0 | ... |
| 7 | 300 | ... | L, Br | 0 | ... | ... | ... | +* |
| 8 | 500 | ... | L, PA, Br | + | ... | ... | ... | ... |
| | 300 | ... | L, PA, Br | 0 | Am 0.6 | 16 | 0 | ... |
| 9 | 400 | ... | PA | + | ... | ... | ... | ... |
| | 200 × 4 | ... | PA | 0 | Am 0.8, PA 4.5 | 11 | 0 | ... |
| 10 | 350 | 700 | L, PA | 0 | Am 0.8 × 3 months | 7 | 0 | ... |
| 11 | 350 | ... | Oral Am | 0 | Am 0.6 | 15 | 0 | ... |
| 12 | 300 | ... | L | 0 | Am 0.6 | 8 | 0 | ... |
| 13 | 300 × 2 | ... | L, Br | + | ... | ... | ... | + |
| 14 | 400, 100 × 6 | 1,000 × 4 | PA, L, Br, Oral Am | + | ... | ... | ... | + |
| 15 | 300, 100 × 3 | 7,00 × 4 | PA, Oral Am | + | Am 1.2, PA 8 | 4 | + | ... |

* Died from cardiogenic shock.
Am = amiodarone; Br = bretylium; L = lidocaine; PA = procainamide.

## Results

After administration of either a single bolus of amiodarone or a bolus followed by a continuous infusion of amiodarone over 12 to 24 hours, the 4 patients who were treated with amiodarone alone had no further episodes of VT (Table II).

In 6 of 11 patients who were treated with intravenous amiodarone in combination with previously ineffective drugs, there was no further VT after administration of a single bolus or a bolus followed by a continuous infusion of amiodarone over 12 to 24 hours. Two patients required additional boluses of amiodarone for control of VT. Patient 8 had 4 episodes of symptomatic VT after administration of 500 mg of intravenous amiodarone over 15 minutes. The next day, an additional bolus of 300 mg of amiodarone was given, and the patient had no further episodes of VT. Patient 9 had no further episodes of sustained VT after receiving a 400 mg bolus of amiodarone over 15 minutes; however, he continued to have 10- to 15-second bursts of nonsustained VT and was treated with an additional 400 mg of intravenous amiodarone 8 hours later. Because of continued short episodes of nonsustained VT, he was treated with 3 additional boluses of 150 mg of amiodarone every 4 hours and subsequently had no further recurrence of VT. Thus, in a total of 12 (80%) of 15 patients who had multiple episodes of symptomatic VT refractory to other antiarrhythmic drugs, acute control of VT was achieved after intravenous administration of amiodarone.

The remaining 3 patients continued to have frequent episodes of symptomatic VT despite being treated with large doses of intravenous amiodarone for several days. Patient 15 received a total of 3.4 g of intravenous amiodarone over 5 days and was treated concurrently with 1,200 mg/day of oral amiodarone and 6 to 8 g/day of oral procainamide; during the 5 days of intravenous amiodarone therapy, he had 38 episodes of symptomatic VT. VT was suppressed only after the sixth day of treatment with high dose oral amiodarone and procainamide. Patients 13 and 14 continued to have frequent episodes of VT despite treatment with intravenous amiodarone in combination with other antiarrhythmic drugs. These patients died from refractory VT. Thus, intravenous amiodarone was ineffective in providing acute control of VT in 20% of patients (3 of 15) who had frequent VT refractory to other antiarrhythmic drugs.

**Cardiovascular effects:** Three patients had asymptomatic sinus slowing from a baseline rate of 70 to 90 beats/min to 48 to 55 beats/min. No symptomatic sinus pauses occurred during or after intravenous administration of amiodarone.

One patient (Case 13) had asymptomatic Mobitz I atrioventricular block 4 hours after intravenous administration of 350 mg of amiodarone. However, no patient had high degree atrioventricular block during or after intravenous administration of amiodarone.

No patient had clinically apparent worsening of congestive heart failure. However, all 4 patients who had severe heart failure were already being treated with a continuous infusion of a sympathomimetic agent (dopamine or dobutamine) before being treated with intravenous amiodarone. In addition, no patient had symptomatic hypotension attributable to intravenous amiodarone.

**Long-term follow-up:** Patient 7 died from refractory cardiogenic shock despite the acute control of VT with intravenous amiodarone. Of the 12 patients who were discharged from the hospital, 10 were treated with amiodarone (400 to 800 mg/day) as the sole antiarrhythmic drug and 2 were treated with amiodarone (800 to 1,200 mg/day) in combination with procainamide (6 to 8 g/day). The mean duration of follow-up was 8.0 ± 4.5 months (range 1 week to 16 months). Patient 3 died suddenly 1 week after discharge from the hospital. No other patient has had a recurrence of symptomatic VT or cardiac arrest. Continuous ambulatory monitoring has revealed occasional 5- to 10-second episodes of asymptomatic VT (rate 125 beats/min) in Patient 15 and occasional 10- to 15-second episodes of asymptomatic accelerated idioventricular rhythm (rate 80 beats/min) in Patient 4.

## Discussion

This study demonstrates that intravenous amiodarone is both safe and effective in the acute control of recurrent symptomatic VT. Despite the fact that many other antiarrhythmic drugs were unsuccessful in suppressing VT, intravenous amiodarone was effective in preventing recurrent VT, either by itself or in combination with previously ineffective drugs, in 80% of the patients in this series. This finding represents a significant advance in the treatment of critically ill patients with recurrent VT.

Previous reports on the use of intravenous amiodarone in the treatment of VT have assessed the efficacy of amiodarone in providing short-term conversion of an episode of sustained VT to sinus rhythm. Benaim and Uzan,[12] Fauchier et al,[9] and Michat et al[10] reported conversion of VT to sinus rhythm with intravenous amiodarone in 6 of 12, 7 of 10, and 3 of 3 patients, respectively. In our series, episodes of VT usually required immediate conversion to sinus rhythm with direct-current countershock because of cardiovascular collapse. The 1 patient in our series (Patient 11) who had continuous stable VT for 24 hours did have conversion to sinus rhythm shortly after administration of intravenous amiodarone. Thus, the efficacy of intravenous amiodarone is demonstrated both by its ability to convert ongoing VT to sinus rhythm and by its prevention of further recurrences of VT in patients who had been having frequent bouts of life-threatening VT.

Among the patients treated with 1 or more boluses of amiodarone, short-term control of VT was obtained in 7 of 8. Among the patients who received a bolus followed by continuous infusion of 600 to 1,000 mg over 12 to 24 hours, VT was suppressed in 5 of 7. However, because of the uncontrolled nature of this study, no conclusion can be drawn regarding the relative efficacy of the bolus technique versus the bolus/constant infusion technique in suppressing VT. No deleterious effects have been observed in patients receiving a larger dose

of amiodarone in the form of a bolus followed by a constant infusion, either by itself or in combination with intravenous lidocaine, procainamide, or bretylium.

All patients in this series had depressed left ventricular function, with an ejection fraction ≤0.4 in 13 of 14 patients in whom it was measured and overt congestive heart failure in 12. Intravenous amiodarone did not result in symptomatic hypotension or a clinically apparent worsening of congestive heart failure in any patient, including the 4 who had acute myocardial infarction. Previous reports have also demonstrated that intravenous amiodarone can be administered safely to patients with acute myocardial infarction or left ventricular failure.[9,13] However, hypotension and cardiovascular collapse have been reported as complications of intravenous amiodarone.[12,14] In our series, patients with severe heart failure were already being treated with dopamine or dobutamine when they received intravenous amiodarone; this may have masked a worsening in hemodynamic status that might otherwise have occurred due to amiodarone therapy. We recommend hemodynamic monitoring whenever possible in patients with severe heart failure who are treated with intravenous amiodarone. Hypotension or an elevation in pulmonary capillary wedge pressure may necessitate treatment with intravenous sympathomimetic or preload-reducing agents, or both.

Although intravenous amiodarone resulted in asymptomatic Mobitz I atrioventricular block in 1 patient, in no patient did it precipitate high degree atrioventricular block, including the 5 patients who had underlying bundle branch block. In the series of Benaim and Uzan,[12] intravenous amiodarone did not precipitate atrioventricular block in 33 patients who had a preexisting bundle branch block. However, 2 cases of infranodal block precipitated by intravenous amiodarone in patients with a preexisting bundle branch block have been reported.[15] Thus, patients should undergo continuous electrocardiographic monitoring when being treated with intravenous amiodarone, especially in the presence of an underlying bundle branch block.

In 3 patients in our series asymptomatic sinus bradycardia developed after administration of intravenous amiodarone; however, none had a symptomatic sinus pause. This is consistent with the series studied by Touboul et al[16] in which sinus nodal function was assessed in 24 patients before and after a bolus of 5 mg/kg of amiodarone. They found a mild decrease in sinus rate in 12 of 24 patients and a mean increase of 110 ms in the sinus nodal recovery time in 17 of 24 patients. No sinus pauses occurred after intravenous administration of amiodarone. However, in our series as well as in the report by Touboul et al, no patient had symptomatic sinus nodal disease. Thus, the safety of intravenous amiodarone in patients with symptomatic sinus nodal dysfunction remains to be determined.

Our study had 2 limitations. In the majority of patients, treatment was continued with 1 or more other antiarrhythmic drug administered concurrently with intravenous amiodarone. Thus, although these other agents had failed to control VT by themselves, an additive effect of intravenous amiodarone cannot be ruled out. Second, all patients in whom VT was controlled acutely with intravenous amiodarone began treatment with daily oral amiodarone shortly thereafter. Therefore, no conclusion can be drawn regarding the duration of effect of intravenous amiodarone in suppressing VT.

## References


1. **Rosenbaum MB, Chiale PA, Halpern MS, Nau GJ, Przybylski J, Levi RJ, Lazzari JO, Elizari MV.** Clinical efficacy of amiodarone as an antiarrhythmic agent. Am J Cardiol 1976;38:934–944.
2. **Wheeler PJ, Puritz R, Ingram DV, Chamberlain DA.** Amiodarone in the treatment of refractory supraventricular and ventricular arrhythmias. Postgrad Med 1979;55:1–9.
3. **Leak D, Eydt JN.** Control of refractory cardiac arrhythmias with amiodarone. Arch Intern Med 1979;139:425–428.
4. **Podrid PJ, Lown B.** Amiodarone therapy in symptomatic, sustained refractory atrial and ventricular tachyarrhythmias. Am Heart J 1981;101: 374–379.
5. **Kaski JC, Girotti LA, Messuti H, Rutitzky B, Rosenbaum MB.** Long-term management of sustained, recurrent, symptomatic ventricular tachycardia with amiodarone. Circulation 1981;64:273–279.
6. **Heger JJ, Prystowsky EN, Jackman WM, Naccarelli GV, Warfel KA, Rinkenberger RL, Zipes DP.** Amiodarone. Clinical efficacy and electrophysiology during long-term therapy for recurrent ventricular tachycardia or ventricular fibrillation. N Engl J Med 1981;305:539–545.
7. **Hamer AW, Finerman WB Jr, Peter T, Mandell WJ.** Disparity between the clinical and electrophysiologic effects of amiodarone in the treatment of recurrent ventricular tachyarrhythmias. Am Heart J 1981;102:992–1000.
8. **Marcus FI, Fontaine GH, Frank R, Grosgogeat Y.** Clinical pharmacology and therapeutic applications of the antiarrhythmic agent, amiodarone. Am Heart J 1981;101:480–493.
9. **Fauchier JP, Brochier M, Raynaud R.** Etude clinique des effets antiarhythmiques ventriculaires de l'amiodarone (orale et injectable). Ann Cardiol Angeiol 1973;22:427–435.
10. **Michat L, Cabrol C, Cabrol A, Mattei MF, Gobin F, Bourel LM, Gandjbakhch I, Gvitraudon G.** Effets anti-arythmiques de l'amiodarone injectable en reanimation de chirurgie cardiovasculaire (letter). Nouv Presse Med 1976;5:1996.
11. **Benaim R, Denizeau JP, Melon J, Domengie B, Kolsky H, Chapelle M, Chiche P.** Les effets antiarythmiques de l'amiodarone injectable. A propos de 100 cas. Arch Mal Coeur 1976;69:513–522.
12. **Benaim R, Uzan C.** Les effets antiarythmiques de l'amiodarone injectable (a propos de 153 cas). Rev Med 1978;19:1959.
13. **Temam R.** Etude de l'amiodarone injectable algue. A propos de 50 cas. Thesis 266, Strasbourg, France, 1977.
14. **Barlllon A.** Colloque Sur l'Amiodarone. Paris: Documentation Medicale Labaz, 1977: 70.
15. **Bosc E, Souchon H, Cabasson J.** Troubles de la conduction intraventriculaire après amiodarone (letter). Nouv Presse Med 1977;6:196.
16. **Touboul P, Atallah G, Gressard A, Kirkorian G.** Effects of amiodarone on sinus node in man. Br Heart J 1979;42:573–578.

# BOOKS RECEIVED

**Advances in Cardiology, Vol 29: Psychological Problems Before and After Myocardial Infarction,** edited by H. Denolin. Basel: Karger, 1982, 155 pages, $58.75.

**Ambulatory Electrocardiographic Recording,** by Nanette Kass Wenger, Michael B. Mock and Ivar Ringqvist. Chicago: Year Book Medical, 1981, 456 pages.

**American Medical Directory,** 28th edition. Chicago: American Medical Association, 1982, 4 volumes.

**Cardiac Arrhythmias: Self-Assessment, Vol 2,** by Edward K. Chung. Baltimore: Williams & Wilkins, 1982, 450 pages, $35.00.

**Cardiac Nursing,** by Sandra L. Underhill, Susan L. Woods, Erika S. Sivarajan and C. Jean Halpenny. Philadelphia: J. B. Lippincott, 1982, 716 pages, $35.00.

**Cardiac Roentgenology: Shadows of the Heart,** by Marvin L. Daves. Chicago: Year Book Medical, 1981, 594 pages.

**Cardiomyopathy,** edited by Morie Sekiguchi and E. G. J. Olsen. Baltimore: University Park Press, 1978, 465 pages, $64.50.

**Catheterization Techniques for Invasive Cardiovascular Monitoring,** by Casey D. Blitt. Springfield, IL: Charles C. Thomas, 1981, 110 pages, $28.75.

**Clinical Ethics,** by Albert R. Jonsen, Mark Siegler and William J. Winslade. New York: MacMillan, 1982, 187 pages.

**Clinical Topics in Internal Medicine,** edited by Gennaro M. Tisi and Helen M. Ranney. Baltimore: Williams & Wilkins, 1982, 173 pages, $30.00.

**Community Control of Cardiovascular Diseases,** Published on behalf of the National Public Health Laboratory of Finland. Copenhagen: World Health Organization Regional Office for Europe, 1981, 351 pages.

**Congenital Heart Disease,** edited by William J. Rashkind. New York: Academic Press, 1982, 390 pages, $55.00.

**Coronary Artery Disease,** edited by William P. Santamore and Alfred A. Bove. Baltimore: Urban & Schwarzenberg, 1982, 296 pages, $39.50.

**Edema of the Lung,** by John S. Prichard. Springfield, IL: Charles C. Thomas, 1982, 445 pages.

**Environmental Physiology,** by Steven M. Horvath and Mohamed K. Yousef. New York: Elsevier, 1981, 468 pages, $70.00.

**Excitation and Neural Control of the Heart,** edited by Matthew N. Levy and Mario Vassalle. Baltimore: Waverly, 1982, 304 pages, $33.50 paper.

**Heart Attack: The Family Response at Home and in the Hospital,** by Edward Speedling. New York: Methuen, 1982, 173 pages, $19.95, $8.95 paper.

**Induced Skeletal Muscle Ischemia in Man: Symposium on Induced Muscle Ischemia in Man, Linkoping 1980,** edited by D. H. Lewis. Basel: Karger, 1982, 180 pages, $69.00.

**Noninvasive Methods on Cardiovascular Hemodynamics,** edited by Anton H. M. Jageneau. Amsterdam: Elsevier Biomedical Press B.V., 1981, 698 pages, $93.50.

**Nursing Administration of Critical Care,** by Arlene Hayne and Zeila Bailey. Maryland: Aspen, 1982, 293 pages.

**Paediatric Cardiology, Vol 3,** edited by A. E. Becker, G. Losekoot, C. Marcelletti and R. H. Anderson. New York: Churchill Livingstone, 1981, 485 pages, $65.00.

**Paediatric Cardiology, Vol 4,** edited by M. J. Godman. New York: Churchill Livingstone, 1981, 788 pages, $79.00.

**Pediatric Electrocardiography,** edited by Jerome Liebman, Robert Plonsey and Paul C. Gillette. Baltimore: Williams & Wilkins, 1982, 354 pages, $55.00.

**Prostaglandins, Platelets, Lipids: New Developments in Atherosclerosis,** edited by Hadley L. Conn, Eugene DeFelice and Peter Kuo. New York: Elsevier, 1981, 152 pages, $32.00.

**Pulmonary Physiology,** by Michael G. Levitzky. New York: McGraw-Hill, 1982, 271 pages, $9.95 paper.

**Regaining Health and Fitness,** by Robert C. Cantu. Brattleboro, VT: The Stephen Greene Press, 1980, 258 pages, $8.95 paper.

**Sudden Coronary Death,** edited by Henry M. Greenberg and Edward M. Dwyer, Jr. New York: The New York Academy of Sciences, 1982, 484 pages, $100.00 paper.

**Taurine in Nutrition and Neurology, Vol 139,** edited by Ryan J. Huxtable and Herminia Pasantes-Morales. New York: Plenum, 1982, 551 pages, $59.50.

**The Ventricular Septum of the Heart,** edited by A. C. G. Wenink, A. Oppenheimer-Dekker and A. J. Moulaert. The Netherlands: Martinus Nijhoff, 1981, 240 pages, $49.50.

**Treatment Strategies in Hypertension,** edited by Michael A. Weber. Miami: Anda Ven Enterprises, 1981, 256 pages, $37.50.

**Vascular Smooth Muscles: Metabolic, Ionic and Contractile Mechanisms,** edited by M. F. Crass and C. D. Barnes. New York: Academic Press, 1982, 204 pages, $32.00.

**Who's Who in Health Care,** 2nd edition. Maryland: Aspen, 1981, 612 pages.

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1. Tuttle, R. R., and Mills, J.: Dobutamine: Development of a New Catecholamine to Selectively Increase Cardiac Contractility. Circ. Res., *36*:185, 1975.

2. Goldberg, L. I., Hsieh, Y.-Y., and Resnekov, L.: Newer Catecholamines for Treatment of Heart Failure and Shock: An Update on Dopamine and a First Look at Dobutamine. Prog. Cardiovasc. Dis., *19*:327, 1977.

3. Robie, N. W., Nutter, D. O., Moody, C., and McNay, J. L.: In Vivo Analysis of Adrenergic Receptor Activity of Dobutamine. Circ. Res., *34*:663, 1974.

4. Goldberg, L. I.: Cardiovascular and Renal Actions of Dopamine: Potential Clinical Applications. Pharmacol. Rev., *24*:1, 1972.

5. Innes, I. R., and Nickerson, M.: Norepinephrine, Epinephrine, and the Sympathomimetic Amines. In The Pharmacological Basis of Therapeutics. Ed. 5 (edited by L. S. Goodman and A. Gilman), p. 477. New York: Macmillan Publishing Co., Inc., 1975.


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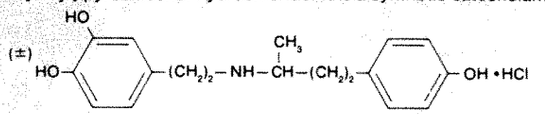
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Molecular Formula: $C_{18}H_{23}NO_3 \cdot HCl$ Molecular Weight: 337.84

The clinical formulation is supplied in a sterile lyophilized form for intravenous use only. Each vial contains 250 mg of dobutamine and 250 mg of mannitol. Hydrochloric acid is used to adjust the *p*H. The *p*H of the reconstituted solution is between 2.5 and 5.5.

**Clinical Pharmacology:** Dobutrex is a direct-acting inotropic agent whose primary activity results from stimulation of the beta receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short-term—up to several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas the output of others returned toward base-line values.

The onset of action of Dobutrex is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is two minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

**Indications and Usage:** Dobutrex is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutrex.

**Contraindication:** Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

**Warnings:** 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

**Precautions: 1. During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

*Usage Following Acute Myocardial Infarction*—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

*Usage in Pregnancy*—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

*Pediatric Use*—The safety and effectiveness of Dobutrex for use in children have not been studied.

*Drug Interactions*—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

**Adverse Reactions:** *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

*Miscellaneous Uncommon Effects*—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

*Longer-Term Safety*—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

**Overdosage:** In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

**Administration and Dosage:** *Reconstitution and Stability*—Dobutrex is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add another 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstitution time periods stated above.

*Recommended Dosage*—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

| Drug Delivery Rate (mcg/kg/min) | Infusion Delivery Rate 250 mcg/ml* (ml/kg/min) | 500 mcg/ml† (ml/kg/min) | 1000 mcg/ml‡ (ml/kg/min) |
|---|---|---|---|
| 2.5 | 0.01 | 0.005 | 0.0025 |
| 5 | 0.02 | 0.01 | 0.005 |
| 7.5 | 0.03 | 0.015 | 0.0075 |
| 10 | 0.04 | 0.02 | 0.01 |
| 12.5 | 0.05 | 0.025 | 0.0125 |
| 15 | 0.06 | 0.03 | 0.015 |

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

**How Supplied:** Vials Dobutrex® (dobutamine hydrochloride, Lilly), for Injection (lyophilized), equivalent to 250 mg dobutamine, 20-ml size, rubber-stoppered, in packages of 1. (121979)

*Additional information available to the profession on request.*

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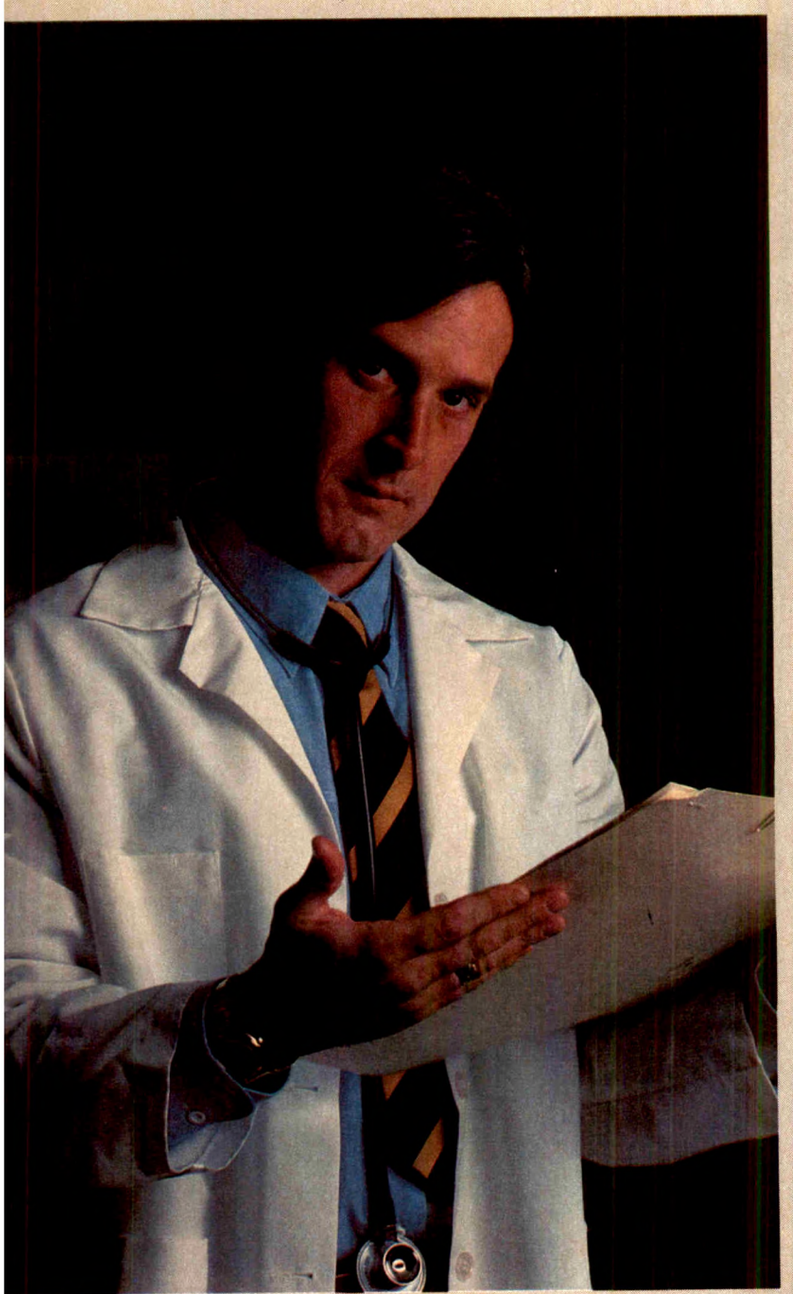
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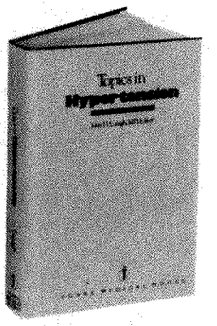
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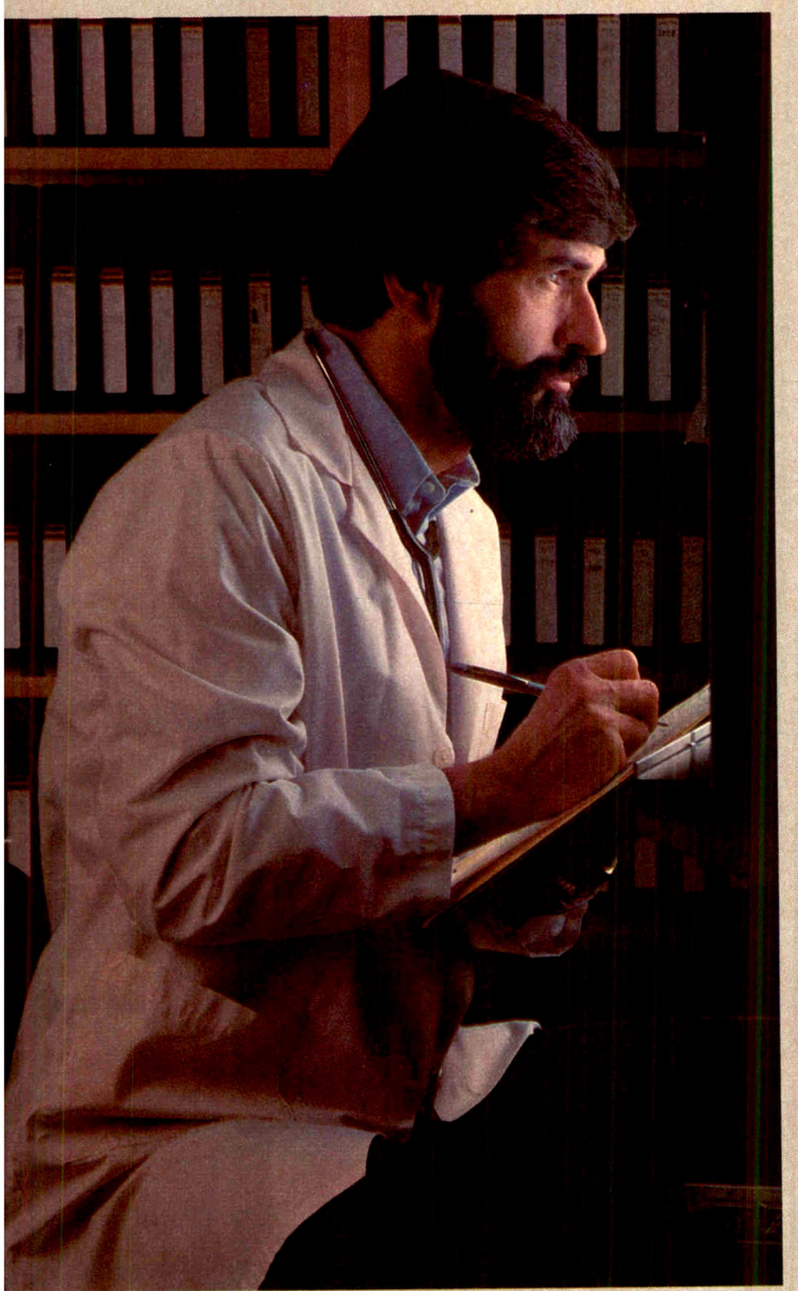
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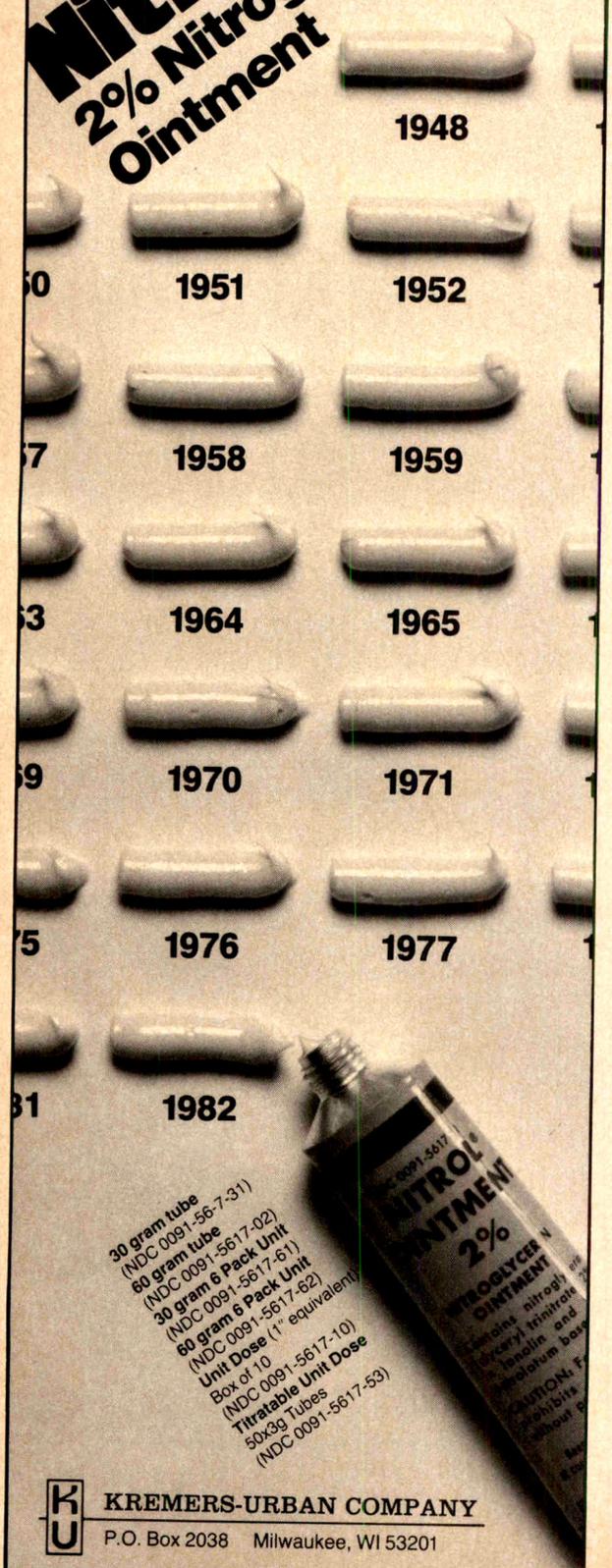
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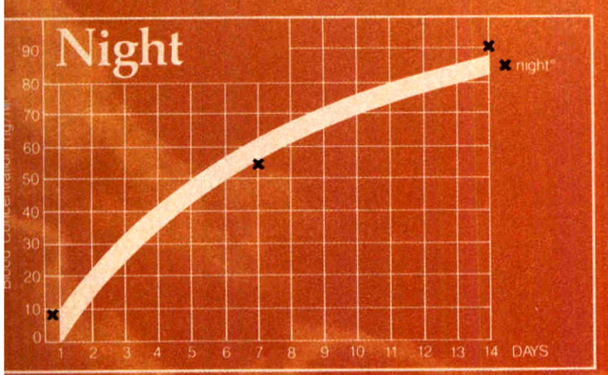
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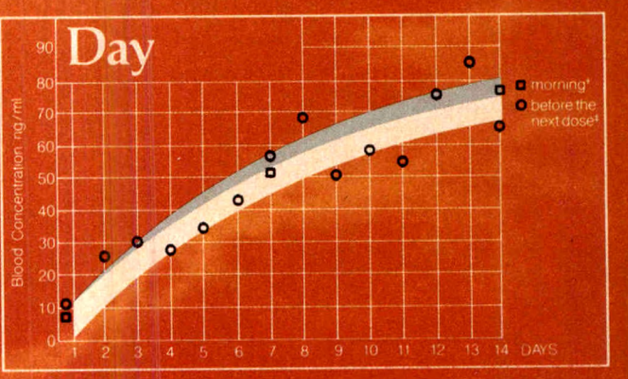
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**References:**


1. Schwarz HJ: Br J Clin Pharmacol *8*:23s, 1979: Mean of 7 patients through 5 days of therapy projected to 14 days. Data on file indicate that steady-state values for plasma concentrations are reached by day 2 or 3.
2. Sleep lab studies on patients who received RESTORIL capsules for up to 27 consecutive nights indicate that steady-state plasma concentrations are achieved by the second or third night. Data on file, Sandoz Pharmaceuticals.
3. Pishkin V, et al: J Clin Psychiatry *41*:358, 1980.
4. Roth T, et al: Br J Clin Pharmacol *8*:47, 1979.
5. Data on file, Medical Department, Sandoz Pharmaceuticals.
6. Kaplan SA, et al: J Pharm Sci *62*:1932, 1973: Mean of 4 patients through 14 days of therapy.


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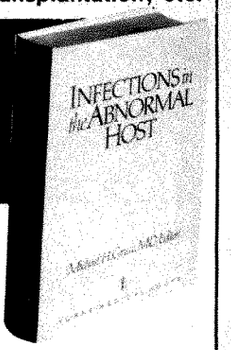

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# Alterations in Left Ventricular Filling With Beta-Adrenergic Blockade

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**Cardiac effects of beta-adrenergic blocking drugs represent a balance between depression of myocardial function and relief of pressure load. To determine the relative importance of each, cardiac and hemodynamic indexes were measured by radioisotope technique (technetium-99m–human serum albumin) in 21 patients treated with either metoprolol (n = 8) or nadolol (n = 13) for 1 month. No significant difference was found between the 2 groups, and the results were pooled. Cardiac output was significantly ($p < 0.01$) and equally reduced in responders and nonresponders (−0.96 versus −1.33 liters/min, difference not significant [NS]), and ejection fraction was not altered significantly in either. The main changes with treatment were observed in the left ventricular volume curves; responders maintained the same ejection velocity despite beta blockade and had a more rapid early ventricular filling rate ($p < 0.05$). In contrast, nonresponders had a reduced velocity of ejection ($p < 0.01$) and a slower rate of ventricular filling ($p < 0.01$), suggesting either altered relaxation rate or decreased left ventricular compliance. Thus, beta-adrenergic blockade can significantly alter ventricular diastolic function, but these effects are overshadowed by blood pressure reduction in responders.**

Most studies of the cardiac effects of beta-adrenergic blocking agents have dealt with their effects on the systolic phase of the cardiac cycle; these were assessed by measurements of cardiac output,[1–3] the first derivative of left ventricular pressure (dP/dt),[4] or ejection fraction.[5,6] However, the diastolic part of the cardiac cycle was recently shown to be an important determinant of cardiac function.[7] Adrenergic factors have been found to influence this phase markedly by their effect on ventricular relaxation.[8] We therefore analyzed the effect of beta-adrenergic blockade on diastolic filling of the heart in hypertensive patients. All were given only a beta-blocking agent, and patients with good blood pressure response were compared with those whose blood pressure was not changed in order to evaluate the relative importance of both variables: reduction of afterload, and cardiac effects of beta-adrenergic blockade.

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## Methods

The study included 21 patients with essential hypertension (4 women and 17 men) who freely consented to this investigation, which was explained to them in detail. All gave informed consent both to the drug used and to the tests required. All patients were either untreated or had discontinued previous medications (including vasodilators, methyldopa, beta-blocking agents, and diuretics, alone or in combination) for at least 3 weeks. In all, the diagnosis was established by careful examination or by tests for possible causes of secondary hypertension and evaluation of target organ involvement, as described in detail previously.[9] Their ages ranged from 19 to 55 years. Only 1 had history of coronary artery disease; he had previously undergone coronary bypass surgery but had no symptoms postoperatively, no signs of myocardial infarction, and no evidence of left ventricular dyskinesia. Three patients had electrocardiographic signs of left ventricular hypertrophy.

**Protocol:** Patients were studied before and after 1 month of beta-blockade therapy. All tests were done in the morning after an overnight fast and 30 minutes' supine rest. Each test included measurement of blood pressure (sphygmomanometer cuff) heart rate (lead II electrocardiogram), total blood volume[9] (RISA), cardiac output[10,11] (radionuclide technique), and ejection fraction[12] (gated blood pool technique). After these tests, therapy was started with either the noncardioselective beta-blocking agent nadolol (n = 13) or the relatively cardioselective agent metoprolol (n = 8) in standard doses. All tests were repeated after 4 weeks of treatment.

**Hemodynamic study:** Cardiac output and mean transit time were obtained in duplicate from the first-pass radionuclide study using technetium-99m–human serum albumin (4 and 8 mCi, respectively). Details of the method and its validation were previously reported.[10,11,13] Derived data were calculated from these measurements and from simultaneous blood pressure and heart rate values using standard formulas. Thus, mean arterial pressure, total peripheral resistance, cardiac index, stroke volume, and cardiopulmonary volume were obtained.

Left ventricular volume curves and ejection fraction were obtained by imaging (gated blood pool technique) during the equilibrium phase after the first-pass study, making use of the same circulating radioisotope. The left ventricular volume curve was then analyzed (PDP-15 system) to measure ejection fraction, maximal rates of left ventricular ejection (negative dV/dt), and filling (positive dV/dt) as explained previously in detail.[14]

*Analysis of left ventricular volume curves:* Left ventricular ejection fraction was calculated as follows: left ventricular end-diastolic counts − left ventricular end-systolic counts/left ventricular end-diastolic counts.

For rates of ejection and filling (Fig. 1), Fourier analysis was applied to fit a curve to the data points (16 in our system) by the method of least squares; the time derivative of the curve was computed with use of the Fourier transform technique as a global estimate of the tangent to the curve at each data point. Since this curve represents the radioactivity counts as a mathematical function of time, the derivatives were expressed in counts per second. The negative derivatives corresponded to the decrease in counts or ejection phase, and the positive derivatives corresponded to the increase in counts or filling phase. In this analysis we looked at the largest negative and maximal positive derivatives. These derivatives were sealed by the maximal absolute counts equivalent to the end-diastolic counts to compensate for variation in injected dose and efficiency of the acquisition system. In this way it was possible to compare data from different patients. The units of these new variables were therefore expressed in units of fractional change per second or hertz. Since these variables are proportional to the change in volume per unit time, they have been termed dV/dt.

The filling phase was further analyzed (Fig. 2) to measure the fast filling fraction (FF) and the slow filling fraction (SF) by a modification of the index described by Reduto et al[15]: FF = (ffc − ESc)/ffc = fast filling fraction and SF = (EDs − ffc)/EDc = slow filling fraction, where ffc is the junction between the fast filling and the slow filling phases, ESc = end-systolic counts, and EDc = end-diastolic counts.

**Statistical analysis:** Calculations of averages, paired and unpaired *t* tests, correlation coefficients, and statistical significance of results were performed by standard methods.[16] Values reported are mean ± standard deviation of the mean. Differences were considered statistically significant when $p < 0.05$.

## Results

**Pretreatment hemodynamic characteristics:** The hemodynamic pattern showed a wide spectrum of variations. Cardiac output ranged from 3.5 to 7.8 liters/min (normal for the laboratory 3.8 to 7.6 liters/min), heart rate ranged from 49 to 100 beats/min, and blood pressure varied from 89 to 145 mm Hg. Ejection fraction was normal in all (46 to 73%, normal for the laboratory 46 to 73%) except 3 patients, in whom it was 43 to 44%.

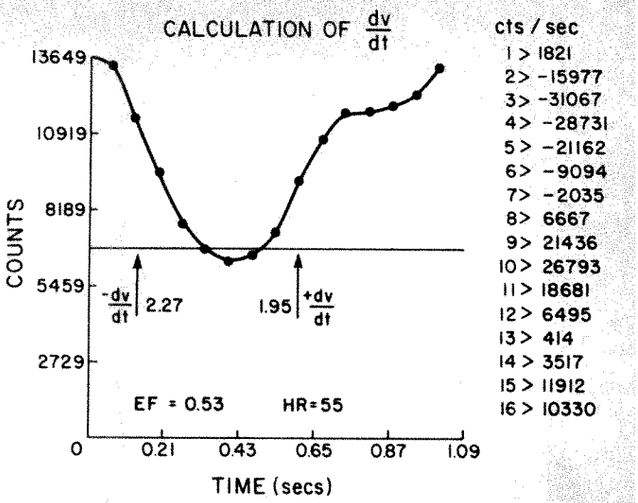



**FIGURE 1.** Left ventricular volume curve (technetium-99m–human serum albumin, gated blood pool technique) in a normal volunteer illustrating the calculation of positive and negative dV/dt. The counts per second (cts/sec) indicate the derivatives at each of the 16 data points on the curves (Fourier analysis) before normalization for end-diastolic counts. EF = ejection fraction; HR = heart rate.

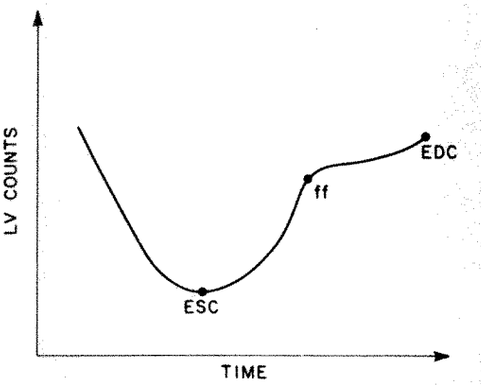



**FIGURE 2.** Left ventricular (LV) volume curve: schematic illustration of FF and SF fractions. See text for details. EDC = end-diastolic counts; ESC = end-systolic counts; ff = counts at end of fast filling phase.

**TABLE I Hemodynamic Changes During Beta-Blockade Therapy in Responders**

| | Metoprolol (n = 5) | | Nadolol (n = 7) | |
|---|---|---|---|---|
| | Control | 1 Month | Control | 1 Month |
| HR (beats/min) | 75 ± 4 | 58 ± 7* | 74 ± 12 | 57 ± 8* |
| MAP (mm Hg) | 121 ± 21 | 102 ± 18* | 115 ± 14 | 97 ± 6* |
| CO (liters/min) | 5.6 ± 1.7 | 4.8 ± 1.0* | 5.3 ± 1.0 | 4.2 ± 0.7* |
| SV (ml) | 74 ± 22 | 82 ± 14 | 72 ± 10 | 74 ± 8 |
| TPR (units·m$^2$) | 43 ± 20 | 45 ± 14 | 44 ± 13 | 46 ± 6 |
| MTT (s) | 8.4 ± 1.1 | 9.8 ± 1.9† | 8.6 ± 1.8 | 9.7 ± 1.1† |
| EF (%) | 52 ± 6 | 52 ± 7 | 48 ± 8 | 53 ± 6 |
| −dV/dt (Hz) | 2.6 ± 0.5 | 2.3 ± 0.5 | 2.5 ± 0.5 | 2.4 ± 0.4 |
| +dV/dt (Hz) | 2.4 ± 0.5 | 2.7 ± 0.2 | 2.3 ± 0.7 | 2.1 ± 0.5 |

* $p < 0.01$; † $p < 0.05$.

Values are means ± standard deviation. Differences in response to beta blockade with the 2 drugs were not statistically significant. CO = cardiac output; EF = ejection fraction; HR = heart rate; MAP = mean arterial pressure; MTT = mean transit time; SV = stroke volume; TPR = total peripheral resistance.

**TABLE II Hemodynamic Changes During Beta-Blockade Therapy in Nonresponders**

| | Metoprolol (n = 3) | | Nadolol (n = 6) | |
|---|---|---|---|---|
| | Control | 1 Month | Control | 1 Month |
| HR (beats/min) | 70 ± 27 | 58 ± 14* | 84 ± 9 | 59 ± 6* |
| MAP (mm Hg) | 117 ± 24 | 120 ± 30 | 122 ± 14 | 119 ± 18 |
| CO (liters/min) | 4.9 ± 1.3 | 3.7 ± 1.1* | 5.9 ± 1.4 | 4.5 ± 0.8* |
| SV (ml) | 73 ± 15 | 63 ± 8 | 70 ± 13 | 76 ± 14 |
| TPR (units·m$^2$) | 42 ± 15 | 58 ± 23* | 45 ± 11 | 54 ± 13* |
| MTT (s) | 9.0 ± 2.6 | 10.7 ± 2.5† | 7.7 ± 1.4 | 9.8 ± 2.1† |
| EF (%) | 58 ± 15 | 47 ± 7 | 49 ± 9 | 48 ± 10 |
| −dV/dt (Hz) | 2.5 ± 0.1 | 2.3 ± 0.2* | 2.8 ± 0.3 | 2.2 ± 0.4* |
| +dV/dt (Hz) | 2.6 ± 0.7 | 1.6 ± 0.4* | 2.7 ± 0.7 | 2.0 ± 0.6* |

* $p < 0.01$; † $p < 0.05$.

Values are means ± standard deviation. No statistically significant differences were found in the response to beta blockade with the 2 drugs. Abbreviations as in Table I.

**TABLE III Effect of Beta Blockade on Systemic Dynamics in Responders (n = 12)**

| | Before Rx | After Rx | p Value |
|---|---|---|---|
| HR (beats/min) | 75 ± 9 | 58 ± 7 | <0.01 |
| MAP (mm Hg) | 118 ± 17 | 99 ± 12 | <0.01 |
| CO (liters/min) | 5.4 ± 1.3 | 4.5 ± 0.9 | <0.01 |
| TPR (units·m$^2$) | 44 ± 15 | 46 ± 10 | NS |
| MTT (s) | 8.5 ± 1.5 | 9.7 ± 1.4 | <0.05 |
| EF (%) | 50 ± 10 | 52 ± 10 | NS |

Values are means ± standard deviation. NS = not significant; Rx = treatment; other abbreviations as in Table I.

**TABLE IV Effect of Beta Blockade on Systemic and Cardiac Dynamics in Nonresponders (n = 9)**

| | Before Rx | After Rx | p Value |
|---|---|---|---|
| HR (beats/min) | 79 ± 16 | 58 ± 9 | <0.01 |
| MAP (mm Hg) | 120 ± ± 16 | 119 ± 20 | NS |
| CO (liters/min) | 5.6 ± 1.3 | 4.2 ± 0.9 | <0.01 |
| TPR (units·m$^2$) | 44 ± 12 | 56 ± 15 | <0.01 |
| MTT (s) | 8.1 ± 1.8 | 10.1 ± 2.1 | <0.05 |
| EF (%) | 51 ± 12 | 50 ± 9 | NS |

Values are means ± standard deviation. Abbreviations as before.

**TABLE V Effect of Beta Blockade on Ventricular Volume Curve (Rate of Ejection = −dV/dt and Rate of Filling = +dV/dt)**

| | Before Rx | After Rx | p Value |
|---|---|---|---|
| Responders (n = 12) | | | |
| −dV/dt (Hz) | 2.53 ± 0.46 | 2.35 ± 0.42 | NS |
| +dV/dt (Hz) | 2.35 ± 0.63 | 2.39 ± 0.52 | NS |
| FF | 0.37 ± 0.10 | 0.45 ± 0.07 | <0.05 |
| SF | 0.18 ± 0.05 | 0.11 ± 0.06 | <0.01 |
| Nonresponders (n = 9) | | | |
| −dV/dt (Hz) | 2.87 ± 0.41 | 2.21 ± 0.33 | <0.01 |
| +dV/dt (Hz) | 2.66 ± 0.65 | 1.91 ± 0.57 | <0.01 |
| FF | 0.45 ± 0.11 | 0.34 ± 0.11 | <0.05 |
| SF | 0.17 ± 0.05 | 0.20 ± 0.08 | NS |

Values are means ± standard deviation. FF = fast filling fraction; SF = slow filling fraction; other abbreviations as before.

After 1 month of therapy, 12 patients (responders) had a decrease in blood pressure to <140/90 mm Hg (7 with nadolol and 5 with metoprolol); the others (9 patients) showed little or no response and were considered nonresponders. The hemodynamic characteristics of response were as previously described in 2 larger series.[6,12] With either drug, heart rate and cardiac output decreased and mean transit time was prolonged in both responders and nonresponders. Total peripheral resistance increased in the nonresponders but remained unchanged despite the decrease in output in responders. Moreover, in both responders and nonresponders, the initial heart rate correlated significantly with the slowing of heart rate during treatment ($r = -0.65$ and $-0.85$, respectively, $p < 0.01$ for both), and the initial cardiac output correlated with reduction of cardiac output during treatment ($r = -0.76$ and $-0.68$, respectively, $p < 0.05$ for both).

Comparison of responses to nadolol and metoprolol showed no statistically significant differences in hemodynamic changes induced by treatment, either in responders (Table I) or in nonresponders (Table II). The results with both beta-blocking agents were therefore pooled (Tables III and IV). The 2 groups had similar reduction in heart rate (75 ± 9 to 58 ± 7 beats/min in responders and 79 ± 16 to 58 ± 9 beats/min in nonresponders, $p < 0.01$ for both). The effect of beta blockade on left ventricular ejection and filling rates was evaluated from the changes recorded in negative and positive dV/dt and in the fast and slow filling fractions (positive dV/dt, FF and SF, Table V). Responders showed no significant change in the rate of ejection, while nonresponders had significant slowing of negative dV/dt. Left ventricular filling was also altered differently in responders and nonresponders. In responders, the velocity of filling in early diastole (fast filling fraction, FF) was increased. There was, therefore, a longer period of diastasis because of both the slower heart rate and the increased FF; this possibly accounted for the slower rate of filling found in the latter part of diastole (slow filling phase, SF). In nonresponders, on the other hand, peak left ventricular filling rate (positive dV/dt) and FF slowed during treatment while changes in SF were not significant.

## Discussion

A significant difference was found in the effect of beta blockade on left ventricular filling rate in patients whose blood pressure was reduced by treatment and those who showed no appreciable blood pressure response. Effective beta blockade was manifested in both groups by slowing of heart rate, reduction in cardiac output, and prolongation of mean transit time (Tables III and IV); the changes in both groups were statistically significant from control values but not statistically different from each other. As in our previous experience, total peripheral resistance did not change significantly in those whose blood pressure decreased while it increased in those with no blood pressure reduction[6,17]; this applied to both metoprolol and nadolol (Tables I and II).

The cardiac effects of beta blockade were more subtle than systemic hemodynamic effects, and their charac-

teristics were markedly influenced by the behavior of the arterial pressure. Thus, peak left ventricular ejection rate (negative dV/dt) was reduced by beta blockade when blood pressure was unchanged (nonresponders). On the other hand, negative dV/dt was not significantly changed despite the beta-adrenergic blockade when pressure was reduced, possibly because this reduction counterbalanced the negative inotropic effect of the blockade. Similar changes were seen in ventricular filling; peak left ventricular filling rate (positive dV/dt) speeded up in responders but slowed in nonresponders. This was associated with a reduction in SF in responders, probably because of the prolonged diastasis, whereas changes in SF were not significant in nonresponders. Thus, the effects of beta blockade on left ventricular filling were more apparent when not counterbalanced by a reduction in pressure load. Filling fraction in late diastole (SF) was altered in opposite direction to the rapid filling phase; it was slowed when rapid filling rate and fraction increased and was slightly increased when rapid filling was slowed.

Since no factor other than blood pressure differed significantly in responders and nonresponders, one may conclude that the slowing of ejection rate and FF in nonresponders represents the effects of beta blockade on cardiac dynamics. Beta blockade was reported to influence the hypertrophic response of the heart[18,19] and blood vessels[19] to hypertension. It might be tempting to speculate whether the improvement in rapid filling could be related to myocardial compositional changes. However, the time period involved, as well as the duration of hypertension in our patients, made this hypothesis unlikely. More relevant is the reported observation of adrenergic influences on left ventricular relaxation. It has been postulated that sympathetic stimulation increases the rate of relaxation[8]; to the extent that the rate of relaxation can influence the rate of filling,[20] it is possible that beta blockers might lead to slower filling of the left ventricle because of slower relaxation.

The hemodynamic consequences of a slower left ventricular filling might be important. Guazzi et al[21] reported that patients who had no blood pressure response to beta blockade had an increase in pulmonary wedge pressure, whereas those with a decrease in blood pressure and total peripheral resistance showed a decrease in pulmonary wedge pressure. These observations appear to agree with our findings of slowed left ventricular filling rate in nonresponders.

Finally, one may wonder whether the slower filling rate might not itself influence the adaptation of total peripheral resistance to the reduction in cardiac output during beta-blockade therapy. There are no data to support this hypothesis, but it does agree with some of the theories advanced[22] to explain the antihypertensive effects of beta-adrenergic blocking agents. Future studies to determine simultaneously left ventricular pressure and volume changes might add to our understanding of the effects of beta-blocking agents on cardiac function.

## References


1. **Lund-Johansen P, Ohm OJ.** Haemodynamic long-term effects of beta-receptor blocking agents in hypertension: a comparison between alprenolol, atenolol, metoprolol and timolol. Clin Sci Mol Med 1976;51:Suppl III: 481s–483s.
2. **Wollam GL, Cody RJ Jr, Tarazi RC, Bravo EL.** Acute hemodynamic effects and cardioselectivity of acebutolol, practolol and propranolol. Clin Pharmacol Ther 1979;25:813–820.
3. **Sannerstedt R, Wasir H.** Acute haemodynamic effects of metoprolol in hypertensive patients. Br J Clin Pharmacol 1977;4:23–26.
4. **Sangvick K, Stokkeland M, Lindseth-Ditlefsen EM, Nyberg G.** Circulation reaction at rest and during isometric and dynamic exercise in hypertensive patients: influence of different adrenergic beta-adrenoceptor antagonists. Pharmatherapeutica 1976;1:71–83.
5. **Le Winter MM, Curtis GP, Engler RL, Shabetai R, Verba J.** Effects of equiblocking doses of nadolol and propranolol on left ventricular performance. Clin Pharmacol Ther 1979;26:162–166.
6. **Fouad FM, Tarazi RC, Bravo EL.** Relation of cardiovascular response to the hypotensive effect of metoprolol. Am Heart J 1982;104:803–811.
7. **Grossman W, McLaurin LP.** Diastolic properties of the left ventricle. Ann Intern Med 1976;84:316–326.
8. **Morad M, Rolett EL.** Relaxing effects of catecholamines on mammalian heart. J Physiol 1972;224:537–558.
9. **Tarazi RC, Ibrahim MM, Dustan HP, Ferrario CM.** Cardiac factors in hypertension. Circ Res 1974;25,26:Suppl I:I-213–I-221.
10. **Fouad FM, Tarazi RC, MacIntyre WJ, Durant D.** Venous delay, a major source of error in isotopic cardiac output determination Am Heart J 1979;97:477–484.
11. **Fouad FM, Houser T, MacIntyre WJ, Cook SA, Tarazi RC.** Automated computer program for radionuclide cardiac output determination. J Nucl Med 1979;20:1301–1307.
12. **Pitts B, Strauss HW.** Evaluation of ventricular function by radioisotope technique. N Engl J Med 1977;296:1097–1099.
13. **Fouad FM, MacIntyre WJ, Tarazi RC.** Non-invasive measurement of cardiopulmonary blood volume. Evaluation of the centroid method. J Nucl Med 1981;22:205–211.
14. **Fouad FM, Tarazi RC, Gallagher JH, MacIntyre WJ, Cook SA.** Abnormal left ventricular relaxation in hypertensive patients. Clin Sci 1980;59: 411s–414s.
15. **Reduto LA, Wickemeyer WJ, Young JB, del Ventura LA, Reid JW, Glaeser DH, Quinones MA, Miller RR.** Left ventricular diastolic performance at rest and during exercise in patients with coronary artery disease. Circulation 1981;63:1228–1237.
16. **Dixon WJ, Massey FJ Jr.** Introduction to Statistical Analysis. New York: McGraw-Hill, 1969;638.
17. **Textor SC, Fouad FM, Tarazi RC, Bravo EL.** Nadolol and cardiac hemodynamics. In: Gross F, ed. International Experience with Nadolol—A Long-Acting-Blocking Agent. International Congress and Symposium Series #37. Published jointly by The Royal Society of Medicine (London), Academic Press (London) and Grune & Stratton (New York), 1981:71–76.
18. **Weiss L.** Aspects of the relation between functional and structural cardiovascular factors in primary hypertension. Acta Physiol Scand 1974;Suppl 409:58.
19. **Yamori Y, Tarazi RC, Ooshima A.** Effect of beta-receptor-blocking agents on cardiovascular structural changes in spontaneous and noradrenaline-induced hypertension in rats. Clin Sci 1980;59:457s–460s.
20. **Grossman W, McLaurin LP, Rolett EL.** Alterations in left ventricular relaxation and diastolic compliance in congestive cardiomyopathy. Cardiovasc Res 1979;13:514–522.
21. **Guazzi M, Polese A, Fiorentini C, Olivari MT, Magrini F.** Cardiac function in the treatment of arterial hypertension with propranolol. Clin Sci Mol Med 1976;51:555s–561s.
22. **Prichard BNC.** Propranolol as an antihypertensive agent. Am Heart J 1970;79:128–133.

# Intravascular Volume, Extracellular Fluid Volume, and Total Body Water in Obese and Nonobese Hypertensive Patients

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**Intraarterial blood pressure, plasma volume, extracellular and interstitial (IFV) fluid volumes, and total and intracellular (IBW) body water were evaluated in 50 men: 16 obese hypertensive patients, 16 nonobese hypertensive patients, and 18 normal subjects of similar age. In obese hypertensive subjects, the IBW/IFV ratio was significantly increased ($p < 0.01$) in comparison with both control subjects and nonobese hypertensive patients. After body weight reduction, blood pressure ($p < 0.01$), heart rate ($p < 0.05$), and the IBW/IFV ratio ($p < 0.01$) significantly decreased. The decrease in the ratio was due to an absolute increase in interstitial fluid volume, related to a shift of fluid volume from the intracellular to the interstitial space. Thus, obese hypertensive patients have an increased water cell content, causing an altered partition between the intracellular and the interstitial spaces.**

In obese hypertensive patients, a reduction of body weight appears to lower arterial blood pressure.[1] However, the underlying mechanisms are still poorly understood. Some observations suggest that the decrease in sodium intake that is concomitant with weight loss is the major factor contributing to a decrease in blood pressure.[2] On the other hand, Reisin et al[3] have shown that subjects who were losing weight had lower blood pressure than did control subjects, despite nearly equivalent, uncontrolled high sodium intake in both groups. However, in all these studies, the effects of sodium intake and body weight reduction on blood pressure were considered as being independent of each other. This interpretation is surprising since the changes in sodium intake and body weight may have independent direct effects on fluid volumes, thus modifying the blood pressure regulation.

For this reason, in the present study intravascular, extracellular, and intracellular fluid volumes were compared in nonobese and obese hypertensive patients. In the latter group fluid volumes were investigated before and after weight reduction, using a low calorie diet with moderate sodium intake.

## Methods

**Patients:** The study was performed in 50 men: 18 normal subjects and 32 patients with sustained essential hypertension. The age range was 20 to 60 years in both groups. The 50 men were untreated or had their therapy discontinued at least 4 weeks before the study. During this period, they maintained their weight within a 2 to 3 kg range. All were hospitalized for 6 days on a 90 mEq/day sodium diet. On the basis of weight, sodium, and urinary output, a steady sodium balance was assumed.

Subjects were considered normal when, on the basis of usual clinical and biologic investigations, they had a constant diastolic pressure of <90 mm Hg. Patients were considered to have had essential hypertension when diastolic pressure repeatedly measured by indirect method was ≥100 mm Hg during the untreated ambulatory period. Blood pressure determinations were done using both a normal-sized (14 by 60 cm) and a large pressure cuff (according to degree of obesity[1]), thus excluding borderline hypertension in obese patients.

Investigations included measurements of blood and urinary electrolytes, creatinine clearance, fasting blood sugar, and serum cholesterol and triglycerides, liver function tests, urinary catecholamine determinations and timed intravenous pyelography. The 32 hypertensive patients were all diagnosed as having moderate essential hypertension. Patients who had diabetes mellitus requiring insulin, cardiac disease, alcoholism, drug addiction, or psychiatric problems were excluded from the study. The mean creatinine clearance rate was 97 ± 9 ml/min/1.73 $m^2$ (±1 standard error of the mean).

According to the level of body weight, hypertensive patients were divided into 2 subgroups: nonobese (16) and obese (16). Obese patients weighed >20% above ideal weight, defined on the basis of age, sex, height, and body build, according to Metropolitan Life Insurance tables.[4] Nonobese patients weighed <10% above ideal weight. Clinical characteristics are indicated in Table I.

The protocol was approved by the Institut National de la Santé et de la Recherche Médicale (INSERM). Informed consent was obtained from the patients after a detailed description of the procedure.

The hemodynamic and fluid volume studies were performed on the third and fourth days of hospitalization, respectively. After overnight fasting, patients were brought to the laboratory without premedication at 8 A.M. Body weight was determined without shoes and in underwear only. Hemodynamic and fluid volume investigations were performed in the supine position after 10 minutes of rest.

**Hemodynamic variables:** An 18 gauge needle was placed in the brachial artery after local anesthesia. A catheter was

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**TABLE I Clinical Characteristics**

| | Control Subjects | Nonobese Hypertensive Patients | Obese Hypertensive Patients |
|---|---|---|---|
| Number | 18 | 16 | 16 |
| Age (yr) | 43.2 ± 1 | 44.4 ± 2 | 44.2 ± 3 |
| Weight (kg) | 72.3 ± 2.6 | 74.1 ± 1.7 | 99.5 ± 3† |
| Height (cm) | 169 ± 2 | 174 ± 1 | 173 ± 2 |
| Body surface area ($m^2$) | 1.83 ± 0.03 | 1.88 ± 0.02* | 2.14 ± 0.04‡ |

Values are means ±1 standard error of the mean. * $p < 0.05$, † $p < 0.001$, and ‡ $p < 0.01$, compared with control subjects.

introduced into the antecubital vein to the juncture with the subclavian vein for injection and samplings. Cardiac output was measured according to the dye-dilution method, as previously described.[5] Intraarterial blood pressure recorded throughout the study was used as the pressure reference for each patient. At the time of the investigation, diastolic blood pressure was ≥90 mm Hg in 10 nonobese hypertensive patients and in 8 obese hypertensive patients.

**Fluid volume determinations:** Inulin, albumin, and antipyrine spaces were evaluated simultaneously.

**Inulin space:** Extracellular fluid volume (EFV) was approximated to the distribution volume of inulin. The inulin space was estimated by the simple injection technique according to Ladegaard and Pederson.[6] Forty-five ml of 10% inulin solution were injected intravenously over 4.5 minutes. Blood samples were taken before administration and repeated 5, 7, 10, 15, 30, 45, 60, 79, 90, 105, 120, 150, and 180 minutes after the beginning of the injection. Inulin was measured by using the method of Roe et al.[7] The plasma inulin concentration was plotted against time on a semilogarithmic scale. A curvilinear curve was obtained and divided into 2 exponential functions according to the feathering technique.

The 2-exponential model, more valid than the monoexponential model, was used for the calculation of the inulin space and clearance.[6] The inulin distribution volume equals the product of the total clearance and the mean transit time calculated from the classical equations.[6] Inulin space and clearance were corrected for the plasma water content by a factor $p = 100 - 0.73$ pp, where 0.73 is the volume of liquid displaced by 1 g of protein in 100 ml of plasma and pp is the plasma protein concentration.[6] The reproducibility of the method was 9.5 ± 3.6%. The validity of the inulin space as an index of extracellular fluid volume has been discussed in detail elsewhere.[8,9] For this, simultaneous determinations of the bromide and the inulin space were performed. A strong positive correlation between the 2 indexes was shown. In comparison with bromide space, inulin space underestimates extracellular fluid volume by approximately 70 ± 8 ml/kg. The underestimation is similar in normotensive and hypertensive subjects.

**Albumin space[8,9]:** Plasma volume was evaluated by the isotopic dilution method using radioactive iodine-131 albumin. After withdrawal of a control sample, 3 μCi was injected at zero time; 10 minutes later a single blood sample was taken for counting and volume estimations. Plasma volume was corrected for water content by the same factor used for inulin space. Total blood volume was calculated from plasma volume and hematocrit. In 25 patients, albumin space was evaluated using serial consecutive blood samples. Activity was plotted against time. The volume was calculated from the extrapolated activity at zero time. The value was lower than that obtained from the single 10-minute sample, but the difference was not significant in normotensive (2 ± 1%) and hypertensive subjects (5 ± 3%). Thus, only the determination of intravascular volume with the single 10-minute sample was used in the present study.

**Antipyrine space:** Total body water (TBW) was estimated from the distribution volume of antipyrine, according to the method of Soberman et al.[10] For this, 1 mg of antipyrine was injected intravenously within 3 minutes. Blood samples were subsequently withdrawn at 0, 1, 2, 3, 4, and 5 hours. The antipyrine plasma level was evaluated using a previously described photometric method involving a precipitation procedure.[11] The logarithm of the plasma concentration was plotted against time and yielded a linear relation. The antipyrine clearance was calculated from the slope of the curve. Total body water was calculated as the ratio between the amount of antipyrine injected and the antipyrine plasma concentration extrapolated at zero time. Correction for plasma water content was performed as for inulin space. The reproducibility of the method was 8.3 ± 3.4%. Previous studies[10–12] have shown that the antipyrine and the deuterium spaces were similar and that the antipyrine method was valid even in obese subjects and in patients with abnormal depots of fluids.

**Dietary program:** Right after the investigations, 9 of the 16 obese hypertensive patients were placed on a dietary program. The intention was to obtain a 10 to 15% reduction of body weight in 1 month, using a low calorie diet with a moderate sodium intake. The daily diet contained 1,000 calories and consisted of 35% proteins, 35% carbohydrates, and 30% fats. Sodium intake was 90 mEq/day. During the follow-up period, which lasted for 4 weeks, all patients visited the clinic weekly. At each visit, blood pressure and weight were measured. All patients were interviewed by the dietician to ensure compliance with the dietary program. The specific dietary components were individually tailored to each patient on the basis of his regular dietary habits, after an interview by the dietician. No other treatment or concomitant hypotensive drug therapy was added. The hemodynamic and fluid variables were reexamined after weight reduction with the same procedure as in the first investigation, that is, on the third and fourth days of hospitalization, the dietary program being maintained.

**Presentation of results and statistical evaluation:** Fluid volumes were expressed in milliliters and milliliters per kilogram for presentation of the results. Body surface area could also be used, but this calculated variable is strongly correlated to body weight.[5] In fact, since the values of fluid volumes in obese and nonobese hypertensive patients depend greatly on the distribution of sex and on the choice of reference frame for the body size,[12–14] only the partition indexes of fluid volumes were studied in the present investigation. For this, intracellular body water (IBW) and interstitial fluid volume (IFV) were respectively calculated as TBW-EFV and EFV-PV differences. Three partitions indexes were defined: PV/IFV, partition index of extracellular fluid volume; EFV/TBW, partition index of total body water; and IBW/IFV, partition index between intracellular body water and interstitial fluid volume.

Means, standard errors of the mean, and correlation coefficients were calculated according to standard statistical methods.[15] Regression analysis was performed using the

**TABLE II Hemodynamic Parameters in Basal Conditions**

| | Control Subjects (n = 18) | Nonobese Hypertensive Patients (n = 16) | Obese Hypertensive Patients (n = 16) |
|---|---|---|---|
| Systolic arterial pressure (mm Hg) | 131 ± 3 | 170 ± 6* | 159 ± 7* |
| Diastolic arterial pressure (mm Hg) | 69 ± 4 | 90 ± 3* | 86 ± 4† |
| Mean arterial pressure (mm Hg) | 90 ± 2 | 117 ± 3* | 110 ± 5* |
| Cardiac output | | | |
| Ml/min | 6,354 ± 342 | 7,142 ± 206 | 7,482 ± 311 |
| Ml/min/$m^2$ | 3,621 ± 156 | 3,820 ± 173 | 3,651 ± 190 |
| Heart rate (beats/min) | 72 ± 2 | 73 ± 3 | 73 ± 4 |
| Total peripheral resistance | | | |
| Dynes s $cm^{-5}$ | 1,179 ± 69 | 1,353 ± 76‡ | 1,289 ± 91 |
| Dynes s $cm^{-5}$ $m^{-2}$ | 1,886 ± 170 | 2,505 ± 160† | 2,580 ± 139† |

Values are means ±1 standard error of the mean. * $p < 0.001$, † $p < 0.01$, and ‡ $p < 0.05$, compared with control subjects.

least-squares methods. Differences in means were assessed by Student's $t$ test in comparison with control values. When comparing the 3 groups (control subjects, and nonobese and obese hypertensive patients), the validity of the statistical analysis was confirmed by an analysis of variance. A p value of <0.05 was accepted as being statistically significant.

## Results

### Basal Values

**Hemodynamic variables (Table II):** Systolic and diastolic blood pressures were significantly increased in hypertensives ($p < 0.001$, $p < 0.01$) in comparison with normal subjects. Blood pressure was similar in obese and nonobese hypertensive patients. In control subjects and in hypertensive patients, cardiac index and heart rate were not significantly different.

**Fluid volumes (Table III):** When the absolute values of fluid volumes (in milliliters) were compared in obese and in nonobese hypertensive patients, total body water, plasma volume, and intracellular body water were significantly higher ($p < 0.05$) in the obese hypertensive group, while extracellular and interstitial fluid volumes were similar.

The PV/IFV ratio was the same in control subjects and hypertensive patients. Figure 1A illustrates that in patients with hypertension the PV/IFV ratio was negatively correlated with mean arterial pressure ($r = -0.42$, $p < 0.05$).

In the obese hypertensive group, the EFV/TBW ratio was significantly lower ($p < 0.05$) and the IBW/IFV ratio significantly higher ($p < 0.01$) than in control subjects. No comparable results were observed for the nonobese hypertensive patients. Figure 2 shows the individual values of the IBW/IFV ratio in the 3 groups of subjects: 8 of the obese hypertensive patients had values above the upper limit of normal.

**TABLE III Fluid Volumes in Basal Conditions**

| | Control Subjects (n = 18) | Nonobese Hypertensive Patients (n = 16) | Obese Hypertensive Patients (n = 16) |
|---|---|---|---|
| Plasma volume (PV) | | | |
| Ml | 2,786 ± 126 | 3,114 ± 84* | 3,423 ± 107† |
| Ml/kg | 45.6 ± 1.3 | 42.3 ± 1.4 | 35.1 ± 1.2† |
| Extracellular fluid volume (IFV) | | | |
| Ml | 9,625 ± 398 | 11,000 ± 437* | 11,395 ± 371‡ |
| Ml/kg | 152 ± 3 | 148 ± 6 | 116 ± 4† |
| Interstitial fluid volume (IFV) | | | |
| Ml | 6,935 ± 328 | 8,017 ± 420 | 8,108 ± 372* |
| Ml/kg | 112 ± 6 | 109 ± 5 | 83 ± 4† |
| Total body water (TBW) | | | |
| Ml | 31,360 ± 1,620§ | 38,990 ± 1,180‡ | 45,900 ± 1,100† |
| Ml/kg | 530 ± 30 | 530 ± 10 | 465 ± 10† |
| Intracellular body water (IBW) | | | |
| Ml | 21,564 ± 1,584§ | 27,994 ± 1,010‡ | 34,120 ± 1,005† |
| Ml/kg | 365 ± 32 | 378 ± 12 | 351 ± 10 |
| PV/IFV | 0.41 ± 0.03 | 0.41 ± 0.02 | 0.43 ± 0.02 |
| EFV/TBW | 0.31 ± 0.02§ | 0.29 ± 0.01 | 0.25 ± 0.01* |
| IBW/IFV | 3.1 ± 0.3§ | 3.5 ± 0.2 | 4.42 ± 0.25 |

Note that when the absolute values of fluid volumes (ml) were compared in obese and nonobese hypertensives, TBW, PV, and IBW were significantly higher ($p < 0.05$) in obese hypertensive patients, while EFV and IFV were similar.

Values are means ±1 standard error of the mean. * $p < 0.05$, † $p < 0.001$, ‡ $p < 0.01$, compared with control subjects. § $n = 8$ for the determination of total body water in control subjects.

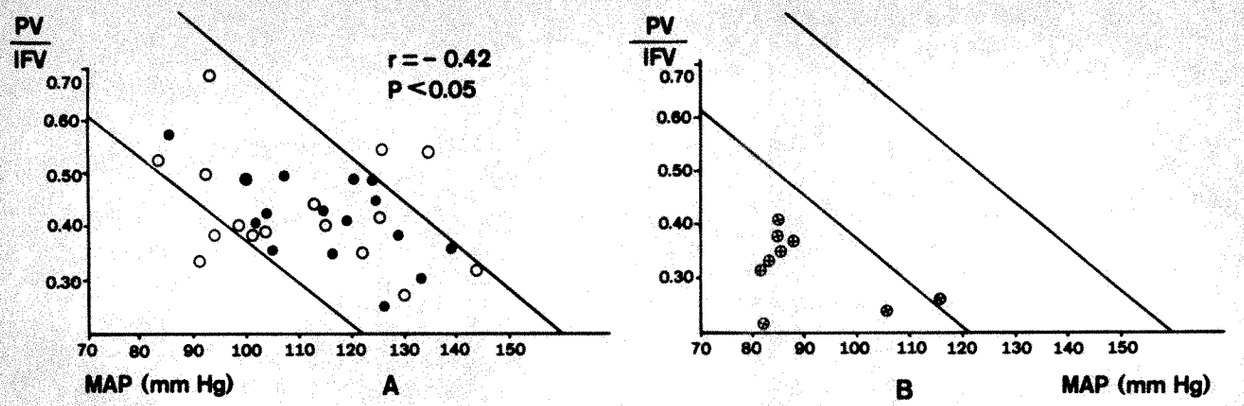



**FIGURE 1.** Relation between mean arterial pressure (MAP) and the ratio between plasma volume (PV) and interstitial fluid volume (IFV) in hypertensive patients. The relation is presented within the 95% confidence limits of the normal curve. **A,** the relation in patients studied in basal conditions. **B,** the individual values after weight loss. **Black circles** represent nonobese hypertensive patients; **white circles,** obese hypertensive patients; and **circles with crosses,** obese hypertensive patients after body weight reduction.

### Effects of Body Weight Reduction in Obese Hypertensive Patients

**Hemodynamic variables (Table IV):** After body weight reduction, blood pressure and heart rate decreased significantly ($p < 0.01$ and $p < 0.05$), whereas the cardiac index did not change significantly. Total peripheral resistance increased slightly. Plasma and urinary electrolyte levels were similar at the beginning and the end of the dietary program. No significant change in antipyrine and inulin clearance was observed.

**Fluid volumes (Table V):** When the absolute values of fluid volumes (in milliliters) were compared before and after weight reduction, plasma volume and total and intracellular body water decreased, whereas extracellular and interstitial fluid volumes increased significantly ($p < 0.05$). The latter result was observed even when extracellular and interstitial fluid volumes were expressed in milliliters per kilogram.

The PV/IFV ratio significantly decreased after weight reduction ($p < 0.05$). Figure 1B indicates that after body weight reduction, all patients were under the 95% confidence limits of the negative PV/IFV-blood pressure relation observed before weight loss (compare Fig. 1A and 1B).

The EFV/TBW ratio significantly increased ($p < 0.01$). The IBW/IFV ratio significantly decreased ($p < 0.01$) (Fig. 3) and approximated the values of controls.

## Discussion

Several difficulties arise from reported data that interpret fluid volume in obese hypertensive patients.[1,13,14] First, plasma volume was found to be increased when expressed in milliliters and milliliters per unit of height, but decreased when expressed in milliliters per kilogram. This is possibly due to the smaller blood volume per unit weight of adipose tissue compared with lean body mass.[13,14] Second, in most studies, only intravascular volume (and not interstitial and intracellular fluid volumes) was taken into consideration. This point is important since Moore et al[12] have shown that the increase in fluid volumes with body weight is different for total body water, plasma volume, and extracellular fluid volume: for the same increase in body weight, the increase in total body water and plasma volume is higher than the corresponding increase in extracellular fluid volume. This finding suggests that only the concomitant study of the 3 spaces is relevant in investigating fluid volumes in obese hypertensive patients.

In the present study, total body water, plasma volume, and extracellular fluid volume were simultaneously investigated. Further, since the problem of the reference frame to express fluid volumes is difficult to overcome,[13] only the indexes of partition of fluid volumes were analyzed. Thus, the present comments mainly concern the PV/IFV and the IBW/IFV ratios.

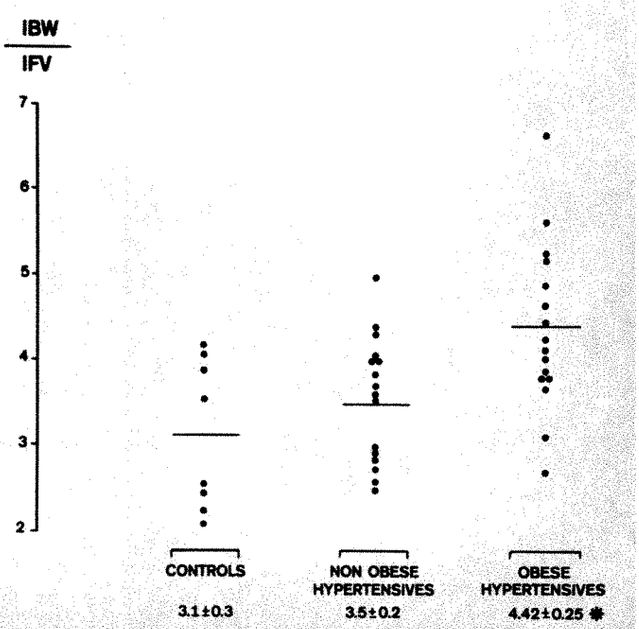



**FIGURE 2.** The ratio between intracellular body water (IBW) and interstitial fluid volume (IFV) in the 2 groups of hypertensive patients (*$p < 0.01$) in comparison with control subjects.

**TABLE IV Hemodynamic and Biologic Changes Before and After Reduction of Body Weight in 9 Obese Hypertensive Patients**

| | Before | After |
|---|---|---|
| Body weight (kg) | 98 ± 2.8 | 85.2 ± 2.8* |
| Sodium concentration in plasma water (mEq/liter) | 148 ± 0.5 | 149 ± 0.7 |
| Potassium concentration in plasma water (mEq/liter) | 4.4 ± 0.07 | 4.6 ± 0.02 |
| Urinary sodium (mEq/24 h) | 80 ± 15 | 78 ± 11 |
| Urinary potassium (mEq/24 h) | 62 ± 6 | 58 ± 7 |
| Inulin clearance (ml/min/1.73 $m^2$) | 131 ± 7 | 119 ± 5 |
| Systolic arterial pressure (mm Hg) | 155 ± 11 | 133 ± 7† |
| Diastolic arterial pressure (mm Hg) | 81 ± 6 | 70 ± 4‡ |
| Mean arterial pressure (mm Hg) | 105 ± 7 | 91 ± 5† |
| Cardiac output | | |
| Ml/min | 7,241 ± 396 | 5,843 ± 300† |
| Ml/min/$m^2$ | 3,621 ± 307 | 2,985 ± 190 |
| Heart rate (beats/min) | 71 ± 5 | 61 ± 3‡ |
| Total peripheral resistance | | |
| Dynes s $cm^{-5}$ | 1,182 ± 102 | 1,304 ± 92 |
| Dynes s $cm^{-5}$ $m^{-2}$ | 2,481 ± 189 | 2,581 ± 165 |

Values are means ±1 standard error of the mean. * $p < 0.001$; † $p < 0.01$; ‡ $p < 0.05$.

**TABLE V Fluid Volume Changes Before and After Weight Reduction in 9 Obese Hypertensive Patients**

| | Before | After |
|---|---|---|
| Plasma volume (PV) | | |
| Ml | 3,217 ± 91 | 2,929 ± 114* |
| Ml/kg | 33.1 ± 1.5 | 34.7 ± 1.7 |
| Extracellular fluid volume (EFV) | | |
| Ml | 11,106 ± 599 | 12,335 ± 425* |
| Ml/kg | 114 ± 7 | 146 ± 6† |
| Interstitial fluid volume (IFV) | | |
| Ml | 8,039 ± 642 | 9,535 ± 463* |
| Ml/kg | 82.1 ± 6.3 | 113 ± 6.1‡ |
| Total body water (TBW) | | |
| Ml | 44,690 ± 1,200 | 43,500 ± 1,100 |
| Ml/kg | 460 ± 14 | 510 ± 15* |
| Intracellular body water (IBW) | | |
| Ml | 33,779 ± 1,194 | 30,874 ± 1,233* |
| Ml/kg | 343 ± 13 | 356 ± 16 |
| PV/IFV | 0.41 ± 0.05 | 0.31 ± 0.02* |
| EFV/TBW | 0.24 ± 0.01 | 0.29 ± 0.01‡ |
| IBW/IFV | 4.46 ± 0.42 | 3.33 ± 0.24‡ |

Values are means ±1 standard error of the mean. * $p < 0.05$; † $p < 0.001$; ‡ $p < 0.01$.

**The PV/IFV ratio:** Several discrepancies exist in the literature for the evaluation of the PV/IFV ratio in patients with essential hypertension. The ratio was found to be decreased[8,16,17] or normal.[18] These differences can be explained easily on the basis of the degree of severity of the disease. We previously showed that the PV/IFV ratio in hypertensive patients was negatively related to the level of blood pressure.[8] Thus, the PV/IFV ratio is expected to be normal in mild hypertension[18] and decreased in more severe hypertension.[8,16,17] In the present study, the ratio was within the normal range in our hypertensive patients, but was negatively correlated with mean arterial pressure. Since 29 of the 47 patients had a diastolic pressure <90 mm Hg, our results exactly reflect the negative correlation between the PV/IFV ratio and blood pressure in patients with hypertension.

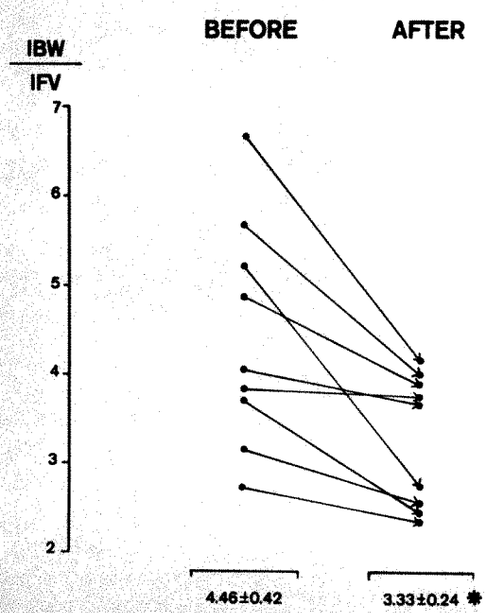



**FIGURE 3.** Obese hypertensive patients: study of the ratio between intracellular body water (IBW) and interstitial fluid volume (IFV) before and after weight reduction (*$p < 0.01$).

The altered partition of extracellular fluid volume in hypertension has been attributed to a shift of intravascular volume toward the interstitial component of the extracellular fluid volume space.[13] Since an increase in the transcapillary escape of albumin and Evans blue dye toward interstitial fluid volume[19,20] has been observed, the shift has been assumed to reflect a disturbed capillary filtration, due to an abnormality in the precapillary sphincters or in venular tone, or both.[13] However, this interpretation concerns only hypertensive patients studied in basal conditions. In particular, in the present study the decreased PV/IFV ratio after weight reduction could hardly be due to a disturbance in the capillary exchange. First, only minimal changes in plasma volume were observed. Second, after body weight reduction using a low calorie diet and moderate sodium intake, the values of the PV/IFV ratio were not inside but below the confidence limits of the curve relating PV/IFV to mean arterial pressure (Fig. 1). This result strongly suggests that the change in the PV/IFV ratio in obese hypertensive patients is related to a peculiar disturbance of interstitial fluid volume, as suggested by the study of the EFV/TBW and IBW/IFV ratios.

**EFV/TBW and IBW/IFV ratios:** The distribution of fluid volumes between the intracellular and the extracellular spaces has been poorly investigated in patients with obesity and in hypertension.[12–18] Moore et al[12] tried to evaluate the degree of hydration of adipose tissue in overweight patients. This investigator showed that if normal obesity tissue contained a large component of water, this water would be extracellular in position and rich in sodium. Therefore, if adipose tissues were very rich in water, then all obese patients should have a higher EFV/TBW ratio. On the basis of this ob-

servation, Moore et al[12] divided obese subjects into those with healthy (normal ratio) and those with nonhealthy (high ratio) obesity. However, the study was based on a small group of 9 patients, 4 men and 5 women, only 1 of whom had hypertension. On the other hand, Bauer and Brooks[18] showed that the EFV/TBW ratio was decreased in hypertensive patients; however, they failed to relate this observation to the excess weight problem existing in their patients.

The present investigation was the first to observe an altered partition of body water between the intra- and extracellular spaces in obese hypertensive patients. The most consistent finding of the study was the increase in the IBW/IFV ratio found in obese hypertensive patients. This increase might be caused either by an intracellular body water level which is too high for the level of interstitial fluid volume or by an IFV which is too low for the level of intracellular body water. However, several observations in the present study could favor the former possibility. First, in agreement with the previous observations of Moore et al,[12] extracellular and interstitial fluid volume were poorly related with body weight in comparison with total body water, plasma volume, and intracellular body water. In this respect, Table III shows that when the absolute values of fluid volumes (in milliliters) were compared in obese and nonobese hypertensive patients, total body water, plasma volume, and intracellular body water were significantly different, while extracellular and interstitial fluid volumes were similar. Second, the decrease in the IBW/IFV ratio after weight loss was due to an increase in interstitial fluid volume, which was not dependent on the reference frame to express fluid volumes (milliliters or milliliters per kilogram). Thus, the increase in interstitial fluid volume after weight loss was due to a shift of fluid volume from the intracellular to the interstitial spaces. Although the mechanism of the shift is difficult to explain, our findings strongly suggest that an absolute increase in intracellular body water exists in obese hypertensive patients when they do not undergo body weight reduction.

The increased water cell content of obese hypertensive patients is difficult to explain. The changes that were described in arterial pressure as well as with the fluid partitions could be ascribed not only to weight reduction but also to the peculiar effects of the caloric and moderate sodium restrictions, with the additional expected consequences on the hormonal and metabolic factors and on the sympathetic nervous system.[21,22] At least 3 hypotheses could be inferred from the literature. First, the role of renin could be suggested from 2 observations: (1) an increase in intracellular body water has been shown in patients with normal (but not low) renin hypertension,[18] and (2) renin decreases after weight reduction in obese patients.[23] Second, the role of sympathetic nervous activity is suggested by the hemodynamic effects of body weight reduction: the decrease in the IBW/IFV ratio after a decrease in body weight was associated with a decrease in blood pressure. Whether the decrease in pressure was due to a reduction in cardiac output or total peripheral resistance,[21] a significant decrease in heart rate was observed.[21-25] This suggests a reduction in sympathetic nervous activity, a fact which has been well documented after calorie restriction.[26,27] Finally, abnormalities in the activity of the sodium-potassium pump have also been described both in obesity[28] and in hypertension[29] and could possibly influence the partition of fluid volumes.

**Conclusion:** Whether the shift of fluid volume is a manifestation of obesity and loss of weight in general or has a particular relation to hypertension, the present findings suggest that 2 varieties of altered partition of fluid volumes might be observed: the decreased PV/IFV ratio, directly related to the level of blood pressure, and the increased IBW/IFV ratio, mainly influenced by the excess weight observed in patients with essential hypertension.

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## References


1. **Chiang BN, Perlman LV, Epstein FH.** Overweight and hypertension. Circulation 1969;21:538–588.
2. **Dahl LK, Silver L, Christie RW.** The role of salt in the fall of blood pressure accompanying reduction of obesity. N Engl J Med 1958;258:1186–1192.
3. **Reisin E, Abel R, Modan M, Silverberg DS, Eliahou HE, Modan B.** Effect of weight loss without salt restriction on the reduction of blood pressure in overweight patients. N Engl J Med 1978;298:1–6.
4. Metropolitan Life Insurance Co., New York. Frequency of overweight and underweight. Metropol Life Insur Co Stat Bull 1960;41:4–6.
5. **Safar ME, Chau NPh, London GM, Weiss YA, Milliez PL.** Cardiac output control in essential hypertension. Am J Cardiol 1976;38:332–336.
6. **Ladegaard D, Pederson MJ.** Measurements of extracellular volume and renal clearance by a single injection of inulin. Scand J Clin Lab Invest 1972;19:2–9.
7. **Roe JH, Epstein JH, Goldstein HP.** Photometric method for determination of inulin in plasma and urine. J Biol Chem 1949;178:839–845.
8. **Simon A Ch, Safar ME, Levenson JA, Aboras NE, Alexandre JM, Pauleau NE.** Extracellular fluid volume and renal indices in essential hypertension. Clin Exp Hypertens 1979;1:557–576.
9. **London GM, Safar ME, Simon AC, Alexandre JM, Levenson JA, Weiss YA.** Total effective compliance, cardiac output and fluid volumes in essential hypertension. Circulation 1978;57:995–1000.
10. **Soberman R, Brodie BB, Levy BB, Axelrod J, Hollander V, Steele M.** The use of antipyrine in the measurement of the total body water in man. J Biol Chem 1949;179:31–42.
11. **Brodie BB, Axelrod J, Soberman R, Levy BB.** The estimation of antipyrine in biological materials. J Biol Chem 1949;179:25–29.
12. **Moore FK, Olesen KH, McMurrey JD, Parker HV, Ball MR, Boyden CM.** The Body Cell Mass and Its Supporting Environment. Philadelphia: WB Saunders, 1963:58–101.
13. **Tarazi RC.** Hemodynamic role of extracellular fluid in hypertension. Circ Res 1976;38(Suppl 2):73–83.
14. **Messerli FH, Christie B, De Carvalho JGR, Aristimuno GG, Suarez DH, Dreslinski GR, Frohlich ED.** Obesity and essential hypertension. Hemodynamics, intravascular volume, sodium excretion and plasma renin activity. Arch Intern Med 1981;141:81–85.
15. **Croxton FE, Cowden DJ.** Applied General Statistics. Englewood Cliffs, NJ: Prentice-Hall, 1944:327,347,653.
16. **Tarazi RC, Dustan HP, Frohlich ED.** Relation of plasma to interstitial fluid volume in essential hypertension. Circulation 1969;40:357–364.
17. **Ibsen H, Leth A.** Plasma volume and extracellular fluid volume in essential hypertension. Acta Med Scand 1973;194:93–96.
18. **Bauer JH, Brooks CS.** Volume studies in men with mild to moderate hypertension. Am J Cardiol 1979;44:1163–1169.
19. **Ulrych M.** Plasma volume decrease and elevated Evans blue disappearance rate in essential hypertension. Clin Sci Mol Med 1973;44:197–212.
20. **Parving HH, Gyntelberg F.** Transcapillary escape rate of albumin and plasma volume in essential hypertension. Circ Res 1973;66:643–651.
21. **Reisin E, Frohlich ED.** Obesity: cardiovascular and respiratory pathophysiological alterations. Arch Intern Med 1981;141:431–433.
22. **Berchtold P, Sims EAH, Brandau K.** Obesity and Hypertension. Proceedings of a satellite symposium to the Third International Congress on Obesity. Florence, Italy, October 6–7, 1980. Int J Obes 1981;5(suppl 1):1–188.
23. **Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M.** The effect of weight reduction on blood pressure, plasma renin activity and plasma aldosterone levels in obese patients. N Engl J Med 1981;304:930–933.
24. **Backman L, Freyschuss U, Hallberg D.** Cardiovascular function in extreme obesity. Acta Med Scand 1973;193:437–445.
25. **Alexander JK, Peterson KL.** Cardiovascular effects of weight reduction. Circulation 1972;45:310–318.
26. **Jung RT, Schetty PAS, Barrand M, Callingham BA, James NPT.** Role of catecholamines in hypotensive response to dieting. Br Med J 1979;1:12–13.
27. **Landsberg L, Young JB.** Fasting, feeding and regulation of the sympathetic nervous system. N Engl J Med 1978;298:1295–1300.
28. **De Luise MB, Blackburn GL, Jeffrey SF.** Reduced activity of the red-cell sodium potassium pump in human obesity. N Engl J Med 1980;303:1017–1022.
29. **Garay RP, Dagher G, Meyer P.** An inherited sodium ion potassium cotransport defect in essential hypertension. Clin Sci 1980;59:191s–193s.

# Relation of Hemodynamic Load to Left Ventricular Hypertrophy And Performance in Hypertension

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**Left ventricular hypertrophy and dysfunction in patients with hypertension are often poorly related to the level of blood pressure. To evaluate the reasons for this, 100 untreated patients (44 ± 14 years) with essential hypertension were studied using cuff blood pressure and quantitative echocardiography to measure left ventricular mass index and end-diastolic relative wall thickness as 2 indexes of left ventricular hypertrophy. Left ventricular hypertrophy, as measured by either left ventricular mass index or end-diastolic relative wall thickness, correlated weakly with all indexes of blood pressure including systolic, diastolic, and mean blood pressure ($r = 0.16$ to $0.32$). In contrast, end-diastolic relative wall thickness, an index which assesses the severity of concentric hypertrophy, showed a closer direct relation with total peripheral resistance ($r = 0.52$, $p < 0.001$) and a significant inverse relation with cardiac index ($r = -0.47$, $p < 0.001$). Left ventricular performance as assessed by fractional systolic shortening of left ventricular internal dimensions was not significantly related to left ventricular mass index, blood pressure, or peak systolic wall stress, but declined significantly with increasing mean systolic wall stress ($r = -0.42$, $p < 0.001$) and even more with increasing end-systolic wall stress ($r = -0.71$, $p < 0.001$).**

**It is concluded that in patients with hypertension (1) left ventricular hypertrophy is correlated only modestly with measurements of resting blood pressure; and (2) the classic pattern of concentric left ventricular hypertrophy, as measured by relative wall thickness, is more closely related to the "typical" hypertensive abnormality of elevated peripheral resistance, suggesting that these anatomic and hemodynamic changes may be pathophysiologically interdependent. Furthermore, left ventricular performance declines when the pressure overload in hypertension is not offset by compensating hypertrophy, allowing wall stresses to increase.**

Progression of hypertensive heart disease from adaptive left ventricular hypertrophy with compensated ventricular function to severe hypertrophy with left ventricular failure is thought to be related to the severity and duration of hypertension. In patients with hypertension, increasing levels of blood pressure have been associated with greater anatomic,[1] echocardiographic,[2–5] or electrocardiographic[6,7] evidence of left ventricular hypertrophy. These abnormalities become more marked in the presence of prolonged duration of hypertension, or evidence of damage to other target organs.[2,8,9] Thus, moderate left ventricular hypertrophy is associated with reduced exercise capacity[10] and more severe hypertrophy with congestive heart failure in man.[1] In most patients with moderate degrees of hypertension, resting left ventricular performance has been reported to remain normal,[2,11] suggesting successful compensatory hypertrophy, whereas left ventricular function may deteriorate in the face of more severe hypertension.[2]

These observations support the applicability to hypertension of Meerson's hypothesis that heart disease evolves through stages of physiologic hyperfunction and compensatory hypertrophy before ventricular failure supervenes.[12] However, most studies have reported group averages, which obscure the great variability in cardiac findings among patients with a similar level of hypertension. Thus, it is common to encounter patients with moderately severe hypertension but no evidence of left ventricular hypertrophy. In other patients only mild hypertension precedes the development of myocardial failure. Partial explanations for these discordances have been provided by reports of diverse hemodynamic profiles in hypertension[13–15] and by the finding that left ventricular function in patients with hypertension or aortic stenosis was regulated by levels of left ventricular wall stresses, which are determined by the relation between hemodynamic load and left ventricular hypertrophy.[16–18] It has further been suggested by Folkow[19] and Lund-Johansen[20] that alterations in cardiac anatomy caused by hypertension might influence the hemodynamic pattern in patients with hypertension. We have undertaken the present study

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to answer 2 questions raised by the foregoing observations: (1) Do hemodynamic factors other than the level of blood pressure influence the degree and pattern of hypertensive left ventricular hypertrophy? and (2) What is the relation between the degree of left ventricular hypertrophy and cardiac performance in hypertensive subjects? Specifically, does the level of left ventricular wall stress, governed by the match between pressure overload and mycardial hypertrophy, regulate cardiac function in patients with essential hypertension?

## Methods

**Patients:** A total of 100 patients with essential hypertension underwent echocardiography, cardiovascular history, and physical examination. The study population consisted of 69 men and 31 women aged 18 to 69 years (mean 44 ± 14) with a body surface area of 1.50 to 2.8 $m^2$ (mean 1.90 ± 0.29). At the time of the study, no patients had received any antihypertensive or other cardioactive medication for at least 3 weeks. All patients with evidence by history, physical examination, or electrocardiography of coronary artery disease or significant valvular disease were excluded, but 3 patients had mitral valve prolapse with no evidence on physical examination or echocardiography of significant mitral regurgitation. Blood pressure was determined by cuff sphygmomanometry at the time of the echocardiogram, using phases 1 and 5 of the Korotkoff sounds.

**Echocardiographic studies:** M-mode echocardiograms were performed in the partial left decubitus position using 13-mm, 2.25-mHz transducers and either a Picker Echoview 80C or Smith-Kline Ekoline 20A echograph with a Honeywell 1856A strip chart recorder on light-sensitive paper at 50 mm/s. Simultaneous visualization throughout the cardiac cycle of interventricular septal thickness (IVS), left ventricular internal dimension (LVID), and posterior wall thickness (PWT) was sought at or just below the tips of the mitral valve leaflets. All echocardiograms were coded and read blindly and independently by 2 investigators (RBD and DDS). Differences between readers of 1 mm in measurement of IVS and PWT and of 2 mm in measurement of LVID were averaged; greater differences were resolved by review of the coded echocardiogram.

At end-diastole, 2 sets of points were identified. The first was selected according to the recommendation of the American Society of Echocardiography for measurement of IVS, LVID, and PWT.[21] End-systolic measurements were also made using American Society of Echocardiography criteria. The second set of end-diastolic points was selected at the peak of the R wave of the simultaneous electrocardiogram using the alternative Penn convention, in which the thickness of endocardial interfaces is excluded from IVS and PWT, and included in LVID.[22] Left ventricular mass (LVM) was calculated using Penn convention measurements in the following equation[22]: $LVM = 1.04\,[(LVID_p + PWT_p + IVS_p)^3 - (LVID_p)^3] - 14$ g. Relative wall thickness (RWT = 2PWT/LVID) at end-diastole and end-systole was calculated as an index of concentric left ventricular hypertrophy.[23] Left ventricular performance was assessed by measurement of systolic fractional shortening of the left ventricular internal dimension: Fractional shortening = $(LVID_d - LVID_s)/LVID_d$. Left ventricular volumes at end-diastole (LVEDV) and end-systole (LVESV) were estimated by the cube function formula[24] and used to calculate stroke volume as LVEDV − LVESV; cardiac output was calculated as stroke volume × heart rate. Total peripheral resistance (TPR) was calculated by the following formula[25]: TPR = (mean BP (mm Hg) ×80)/cardiac output (liters), where BP = blood pressure.

Since afterload is best expressed as wall stress, peak and end-systolic meridional wall stress were calculated by the noninvasive method of Wilson et al,[26] using echocardiographic dimensions and cuff blood pressure in the following formulas: Peak systolic stress = $0.86\,[(0.334 \times LVID_d \times \text{systolic BP})/PWT_d \times (1 + PWT_d/LVID_d)] - 27 \times 10^3$ dynes/$cm^2$ and End-systolic stress = $0.98\,[(0.334 \times LVID_s \times \text{systolic BP})/PWT_s \times (1 + PWT_s/LVID_s)] - 2 \times 10^3$ dynes/$cm^2$. In addition, the mean LV systolic wall stress index of Quinones et al[27] was calculated by use of the following formula: Mean wall stress index = Systolic BP × $[(LVID_d + LVID_s)/2(PWT_d + PWT_s)]$.

**Statistics:** A Hewlett-Packard programmable calculator was used to perform least-squares linear regression and Student's $t$ test.[28]

## Results

**Hemodynamics:** Systolic blood pressure was 154 ± 18 mm Hg, diastolic pressure was 90 ± 10 mm Hg, and mean blood pressure 117 ± 11 mm Hg (range 105 to 157). The stroke index was 48 ± 12 ml/$m^2$ (normal value for this laboratory derived from 79 subjects[29] 45 ± 13, difference not significant [NS]), and the cardiac index was 3.45 ± 1.01 liters/min/$m^2$ (normal 3.15 ± 1.0, NS). Total peripheral resistance was 1,539 ± 445 ($p < 0.05$ versus normal 1,243 ± 235).

**Echocardiographic findings:** Interventricular septal thickness was 1.2 ± 0.3 cm and posterior wall thickness was 1.1 ± 0.2 cm ($p < 0.01$ versus normal values); left ventricular internal dimension was 5.0 ± 0.6 cm (NS versus normal findings of 4.8 ± 0.5 cm). Diastolic relative wall thickness was 0.43 ± 0.09 ($p < 0.02$ versus normal 0.34 ± 0.04), while systolic relative wall thickness was 1.08 ± 0.27 ($p < 0.02$ versus normal 0.90 ± 0.19). Left ventricular mass index ranged from 68 to 236 g/$m^2$ (mean = 118 ± 31 g/$m^2$, $p < 0.001$ versus normal of 70 ± 25 g/$m^2$). In 56 patients, left ventricular mass index fell within the 95% confidence limits of normal in this laboratory (≤119 g/$m^2$),[29] while the remaining 44 patients had definite left ventricular hypertrophy. Mean left ventricular fractional shortening in systole was 37 ± 6%, ranging from 23 to 55%; in only 3 patients did it fall below the 95% confidence limits of normal in this laboratory.

**Relation of hemodynamic variables to left ventricular hypertrophy:** To evaluate the relation between hemodynamic measurements and anatomic changes in patients with hypertension, we used 2 separate indexes of left ventricular hypertrophy, left ventricular mass index, and relative wall thickness. Only modest relations were observed between left ventricular mass index and mean blood pressure ($r = 0.32$, $p < 0.005$), systolic blood pressure ($r = 0.32$, $p < 0.005$), or diastolic blood pressure ($r = 0.26$, $p < 0.02$) (Table I). Left ventricular mass index exhibited a similar, relatively weak correlation with stroke index ($r = 0.27$, $p < 0.01$) or the product of mean blood pressure and stroke index, which approximates stroke work index ($r = 0.31$, $p < 0.005$). A slightly closer relation was observed between end-systolic volume index and left ventricular mass index ($r = 0.44$, $p < 0.001$).

Diastolic relative wall thickness, a measure of the severity of concentric left ventricular hypertrophy, showed an even weaker correlation with the level of

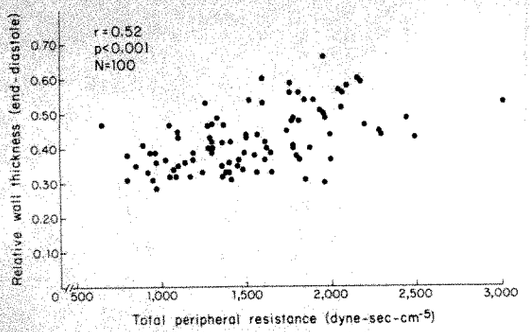



**FIGURE 1.** Left ventricular relative wall thickness at end-diastole (**vertical axis**) is directly related to total peripheral resistance (**horizontal axis**) in untreated hypertensive patients ($r = 0.52$, $p < 0.001$).

blood pressure ($r = 0.16$, $0.05 < p < 0.10$). In contrast, diastolic relative wall thickness exhibited a moderate direct correlation with total peripheral resistance ($r = 0.52$, $p < 0.001$) (Fig. 1). Furthermore, there was a significant inverse relation between increasing diastolic relative wall thickness and decreasing cardiac index ($r = 0.47$, $p < 0.001$) (Fig. 2). Figure 3 illustrates that for any level of blood pressure, patients with lower levels of cardiac index tended to have a higher relative wall thickness, and vice versa.

**Determinants of left ventricular performance:** Left ventricular performance, as measured by systolic fractional shortening of left ventricular internal dimension was unrelated to left ventricular mass index ($r = 0.04$, $p > 0.70$), mean blood pressure ($r = 0.04$, $p > 0.70$), or peak systolic wall stress ($r = 0.14$, $p > 0.10$). In contrast, there were highly significant negative correlations between mean or end-systolic left ventricular wall stress and left ventricular fractional shortening. Figure 4 demonstrates that left ventricular fractional shortening decreased moderately in patients as the mean systolic meridional wall stress index increased ($r = -0.42$, $p < 0.001$). Figure 5 depicts the even closer negative relation between left ventricular fractional shortening and end-systolic wall stress ($r = -0.71$, $p < 0.0001$).

**TABLE I Hemodynamic Determinants of Left Ventricular Hypertrophy in Hypertension**

| | Correlation Versus Left Ventricular Mass Index | | Correlation Versus End-Diastolic Relative Wall Thickness | |
|---|---|---|---|---|
| Variable | r | p | r | p |
| Mean blood pressure | 0.32 | <0.005 | 0.17 | NS |
| Systolic blood pressure | 0.32 | <0.005 | 0.16 | NS |
| Diastolic blood pressure | 0.26 | <0.02 | 0.14 | NS |
| Cardiac index | 0.26 | <0.02 | −0.47 | <0.001 |
| Stoke volume | 0.27 | <0.01 | −0.45 | <0.001 |
| Stroke work index | 0.31 | <0.005 | −0.38 | <0.001 |
| End-systolic volume index | 0.44 | <0.001 | −0.23 | <0.05 |
| Peripheral resistance | −0.20 | NS | 0.52 | <0.001 |
| Heart rate | −0.07 | NS | 0.05 | NS |

NS = not significant.

## Discussion

The findings of the present study provide answers to the 2 questions posed at the outset. First, it is apparent that concentric left ventricular hypertrophy, as manifested by increased end-diastolic relative wall thickness, is directly related to peripheral resistance. Further, an inverse relation is observed between relative wall thickness and cardiac output in patients with mild to moderate hypertension. However, a second index of left ventricular hypertrophy—left ventricular mass index—was also increased in patients with hypertension, but was poorly correlated with hemodynamic measurements. Therefore, only a small portion of the variation in total left ventricular mass which occurs among such patients can be directly attributed to differences in resting blood pressure, cardiac output, or stroke work. In regard to the second question, it is apparent that left ventricular performance in hypertension is determined to a significant degree by the adequacy of left ventricular hypertrophy to compensate for the pressure overload. Thus, left ventricular systolic performance was inversely related to measures of wall stress, especially end-systolic wall stress, indicating that performance was depressed in patients in whom the hemodynamic load on the left ventricle had not elicited proportional ventricular hypertrophy.

**Hemodynamic determinants of hypertensive ventricular hypertrophy:** The finding that concentric left ventricular hypertrophy is more closely related to peripheral resistance than to blood pressure alone in patients with hypertension suggests that a direct, pathophysiologically important relation exists between these 2 classic features of hypertension. It is well known that although a high peripheral resistance, associated with a normal to low cardiac output, characterizes groups of patients with longstanding essential hypertension, hemodynamic profiles in hypertension are in fact quite diverse.[13–15,30] Thus, high cardiac output and relatively normal peripheral resistance are often seen in the early stages of essential hypertension,[31,32] in patients with hyperdynamic essential hypertension,[33] and in many patients with renal artery hypertension.[14] Both Folkow[19] and Lund-Johansen[20,32] have suggested that

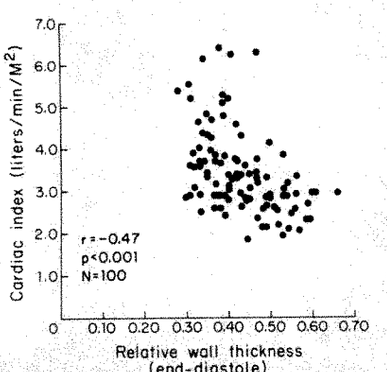



**FIGURE 2.** Cardiac index (**vertical axis**) is inversely related to left ventricular relative wall thickness at end-diastole (**horizontal axis**) ($r = -0.47$, $p < 0.001$).

changes in cardiac and peripheral vascular anatomy might play a role in the change in hemodynamic pattern to high peripheral resistance and normal to low cardiac output in patients with severe hypertension.

Most previous studies of hypertensive left ventricular hypertrophy have partially obscured this anatomic and hemodynamic variability by comparing group means for hemodynamic parameters and indexes of left ventricular hypertrophy. On average, our patients showed the expected increase in peripheral resistance, left ventricular mass and relative wall thickness with a normal cardiac index. However, the present study differs from previous reports in regarding both left ventricular mass and hemodynamic measurements as continuous variables. Our findings are in accord with the modest relation that has been shown in previous studies between blood pressure level and either heart size,[34] left ventricular mass,[4] or thickening of the left ventricular wall.[11,23,35] For the first time, we have also examined directly the relation of hypertensive cardiac hypertrophy to other hemodynamic variables, including stroke volume, end-systolic volume, and total peripheral resistance. In the present series, the relation between these other variables and left ventricular mass index were similar to or even closer than that between blood pressure and left ventricular mass.

This result is, at first glance, surprising, but can in fact be predicted from an examination of the role hemodynamic factors play in the genesis of myocardial hypertrophy. Both experimental studies[36,37] and theoretical analyses[38–42] indicate that left ventricular hypertrophy occurs in such a way as to normalize left ventricular wall stress. To accomplish this, increases in blood pressure (without a change in stroke volume) induce an increase in ventricular relative wall thickness, and hence absolute wall thickness. An increase in either stroke volume or end-systolic volume necessitates an increase in end-diastolic chamber volume and radius. Since, in the absence of a change in blood pressure, relative wall thickness stays constant, absolute left ventricular wall thickness increases in proportion to the increase in chamber radius. In any of these cases the left ventricular myocardial volume and mass are increased.

In the present series the severity of concentric left ventricular hypertrophy, as reflected by end-diastolic relative wall thickness, correlated better with total peripheral resistance than with the level of blood pressure. Furthermore, a significant inverse relation was observed between relative wall thickness at end-diastole and cardiac index. As illustrated in Figure 3, at any given level of blood pressure, patients with lower cardiac indexes tended to have higher end-diastolic wall thickness. A possible explanation for these relations is that increased left ventricular chamber stiffness due to increased relative wall thickness may impair diastolic left ventricular filling,[43,44] causing a secondary reduction in stroke volume and cardiac output. Such a reduction in cardiac output would, in turn, cause the measured level of blood pressure to be lower for any level of peripheral resistance than it would otherwise have been. Thus, an increased left ventricular relative wall thickness may participate in the reduction in cardiac output which is observed in many patients with severe hypertension. Such a reduction in cardiac output would, in turn, tend to moderate the increase in blood pressure produced by a given increase in peripheral resistance.

Despite the findings of the present study that resting blood pressure, stroke volume, and end-systolic volume are all related modestly to left ventricular mass in patients with essential hypertension, the majority of the total variability in left ventricular mass remains unex-

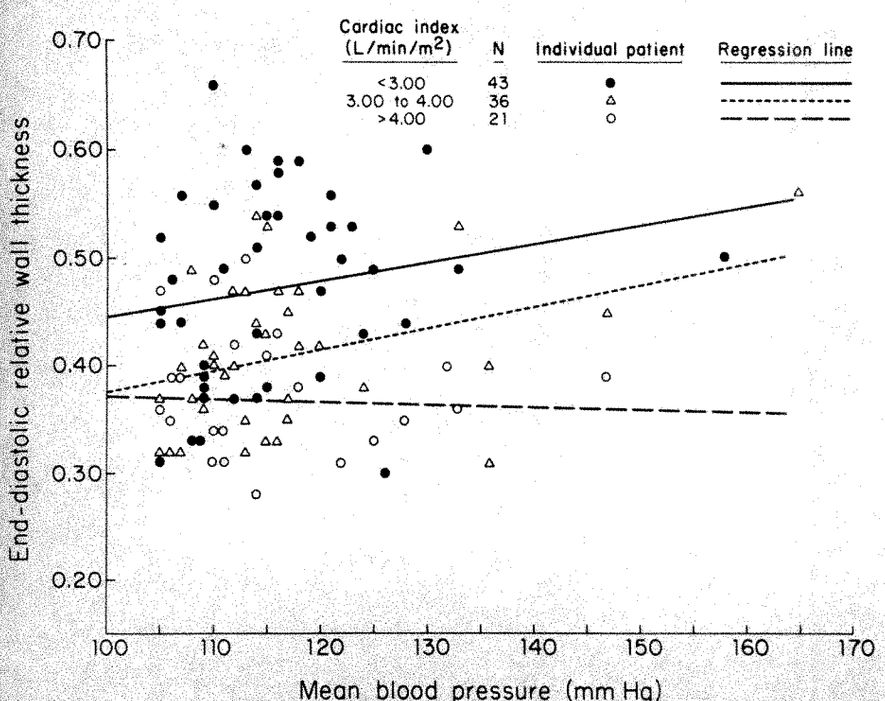



**FIGURE 3.** Relation between end-diastolic relative wall thickness (**vertical axis**) and mean blood pressure (**horizontal axis**), with patients classified according to level of cardiac index. At any level of blood pressure, relative wall thickness is greater in patients with a lower cardiac index.

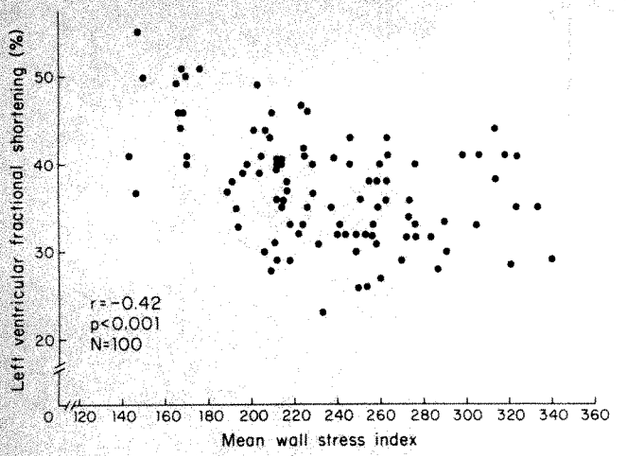



**FIGURE 4.** Left ventricular systolic performance, measured by the percent fractional shortening of left ventricular internal dimension (**vertical axis**) is inversely related to the mean left ventricular wall stress index (**horizontal axis**) ($r = -0.42$, $p < 0.001$).

plained by these parameters. Several factors may account for this. First, this study has used only resting hemodynamic measurements. It has been shown that office measurements of blood pressure may be poorly related to blood pressure throughout the day,[45–47] and that hypertensive patients have exaggerated blood pressure increased during exercise, occupational work,[48] or other forms of stress. Thus, the description of hemodynamic load in this and other studies is undoubtedly incomplete, since it is based solely on resting measurement. Second, myocardial contractility has an indirect effect on left ventricular hypertrophy. With impaired contractility, left ventricular end-systolic volume increases; as long as stroke volume remains constant, this necessitates an increase in end-diastolic volume, thus augmenting left ventricular hypertrophy, as we have demonstrated in this study. Third, age and increasing duration of hypertension[49,50] have been reported to increase left ventricular mass for a given level of blood pressure, whereas equally effective antihypertensive drugs have been reported to have disparate effects on left ventricular hypertrophy.[51–53] Finally, there is limited experimental evidence suggesting that norepinephrine or the renin-angiotensin system may play a direct role in cardiac hypertrophy beyond that mediated by their augmentation of blood pressure.[54–57]

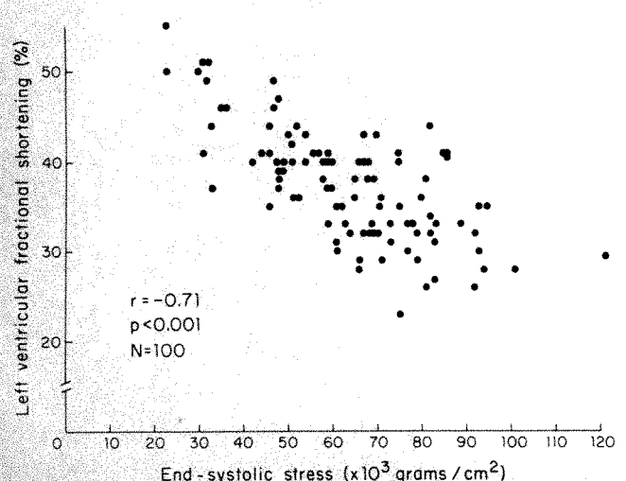



**FIGURE 5.** Left ventricular systolic performance, measured by percent fractional shortening of left ventricular internal dimension (**vertical axis**) decreases linearly with increasing end-systolic wall stress (**horizontal axis**) ($r = -0.71$, $p < 0.001$).

**Determinants of left ventricular performance in hypertension:** The present study confirms previous reports that left ventricular hypertrophy in patients with mild to moderate hypertension is largely a compensatory mechanism, since resting left ventricular fractional shortening was well maintained and was unrelated to abnormalities of left ventricular mass index. In contrast, left ventricular fractional shortening decreased moderately with increased mean systolic wall stress index (Fig. 4), and in a linear fashion with increasing end-systolic left ventricular wall stress (Fig. 5).

These findings demonstrate that patients with chronic hypertension and compensated left ventricular function show the same marked dependence of left ventricular performance on afterload, expressed as wall stress, as has been shown experimentally in response to acute interventions[58] and in patients with hypertension whose blood pressure is lowered acutely[59] or subacutely.[60] This effect would be largely masked had we relied on blood pressure alone as the measure of afterload. The closer relation of left ventricular shortening to estimated end-systolic stress than to peak systolic stress is concordant with a fundamental principle of cardiac mechanics: left ventricular contraction is terminated when wall stress (force) and chamber diameter intersect the ventricle's isometric force-length line.[61–63] Since peak systolic wall stress always occurs at a point below this sloping line, it would be expected to have only an indirect influence on left ventricular contraction, whereas, there is an obligatory relation between end-systolic wall stress and end-systolic left ventricular internal dimension in a given patient. The close negative relation observed in this study between end-systolic stress and left ventricular fractional shortening is the more impressive because it does not take into account absolute left ventricular internal dimension (the true abscissa), the effects variations in preload may have on left ventricular internal dimension (and hence on the fractional shortening required to reach a given end-systolic point), or the effects differences in intrinsic myocardial contractility or catecholamine levels might have on increasing or decreasing the end-systolic force-length line in individual patients.

**Clinical implications:** The echocardiogram provides a useful tool for assessing the anatomic and functional response of the heart in patients with hypertension.[64] Left ventricular relative wall thickness at end-diastole exhibits a significant relation with elevated total peripheral resistance, the typical hemodynamic abnormality of chronic hypertension. Furthermore, an inverse relation is observed between this index of concentric left ventricular hypertrophy and cardiac output, suggesting that increased chamber stiffness due to concentric hypertrophy may play a role in the reduction of cardiac

output in many patients with hypertension. In contrast, left ventricular mass index, another index of left ventricular hypertrophy, was not closely related to any hemodynamic measurement. Finally, left ventricular systolic performance was inversely related to mean and especially end-systolic left ventricular wall stress. These findings illustrate the extensive evaluation of cardiac anatomy and function in patients with hypertension that can be accomplished using clinically applicable echocardiographic methods.

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## References

1. **Jones RS.** The weight of the heart and its chambers in hypertensive cardiovascular disease with and without failure. Circulation 1953;7:357–369.
2. **Dunn FG, Chandraratna P, deCarvalho JGR, Basta LL, Frohlich ED.** Pathophysiologic assessment of hypertensive heart disease with echocardiography. Am J Cardiol 1979;39:789–795.
3. **Ross AM, Pisarczyk MJ, Calabresi M, Crocco CJ.** Echocardiographic and clinical correlations in systemic hypertension. J Clin Ultrasound 1978;6:95–99.
4. **Savage DD, Drayer JIM, Henry WL, Mathews EC Jr, Ware JH, Gardin JM, Cohen ER, Epstein SE, Laragh JH.** Echocardiographic assessment of cardiac anatomy and function in hypertensive subjects. Circulation 1979;59:623–632.
5. **Schlant RC, Felner JM, Blumenstein BA, Heymsfield S, Gilbert CA, Schulman N, Tuttle EP.** Echocardiographic studies of left ventricular anatomy and function before and after treatment of essential hypertension (abstr). Am J Cardiol 1977;39:296.
6. **Frohlich ED, Tarazi RC, Dustan HP.** Clinical-physiological correlations in the development of hypertensive heart disease. Circulation 1971;44:446–455.
7. **Dunn RA, Zenner RJ, Pipberger HV.** Serial electrocardiograms in hypertensive cardiovascular disease. Circulation 1977;56:416–423.
8. **Sokolow M, Werdegar D, Kain HK, Hinman AT.** Relationship between level of blood pressure measured casually and by portable recorders and severity of complications in essential hypertension. Circulation 1966;34:279–298.
9. **Breslin DG, Gifford RW Jr, Fairbairn JF II.** Essential hypertension: a twenty-year follow-up study. Circulation 1966;33:87–97.
10. **Wong HE, Kass IS, Bruce RA.** Impaired maximal exercise performance with hypertensive cardiovascular disease. Circulation 1969;39:633–638.
11. **Karliner JS, Williams D, Gorwit J, Crawford MH, O'Rourke RA.** Left ventricular performance in patients with left ventricular hypertrophy caused by systemic arterial hypertension. Br Heart J 1977;39:1239–1245.
12. **Meerson FZ.** The Myocardium in Hyperfunction, Hypertrophy and Heart Failure. Monograph 26. New York: American Heart Association, 1969.
13. **Frohlich ED, Tarazi RC, Dustan ED.** Re-examination of the hemodynamics of hypertension. Am J Med Sci 1969;257:9–23.
14. **Tarazi RC, Ibrahim MM, Dustan HP, Ferrario CM.** Cardiac factors in hypertension. Circ Res 1974;34:Suppl I:I-213–I-221.
15. **Safar ME, Chau NP, Weiss YA, London GM, Milliez PL.** Control of cardiac output in essential hypertension. Am J Cardiol 1976;38:332–336.
16. **Strauer B-E.** Ventricular function and coronary hemodynamics in hypertensive heart disease. Am J Cardiol 1979;44:999–1006.
17. **Grossman W, Jones D, McLaurin LP.** Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975;56:56–64.
18. **Gunther S, Grossman W.** Determinants of left ventricular function in pressure-overload hypertrophy in man. Circulation 1979;59:679–688.
19. **Folkow B.** Cardiovascular structural adaption: its role in the initiation and maintenance of primary hypertension. Clin Sci Mol Med 1978;55: Suppl 4:1s–2s.
20. **Lund-Johansen P.** Haemodynamics in essential hypertension. Clin Sci 1980;59:343s–354s.
21. **Sahn DJ, DeMaria A, Kisslo J, Weyman A.** The Committee on M-mode Standardization of the American Society of Echocardiography. Recommendations regarding quantification in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–1083.
22. **Devereux RB, Reichek N.** Echocardiographic determination of left ventricular mass in man. Circulation 1977;55:613–618.
23. **Reichek N, Devereux RB.** Reliable estimation of peak left ventricular systolic pressure by M-mode echocardiographic-determined end-diastolic relative wall thickness: identification of severe valvular aortic stenosis in adult patients. Am Heart J 1982;103:202–209.
24. **Pombo JF, Troy BL, Russell RO Jr.** Left ventricular volumes and ejection fraction by echocardiography. Circulation 1971;43:480–490.
25. **Yang SS, Bentivoglio MS, Maranhao V, Goldberg H.** From Cardiac Catheterization Data to Hemodynamic Parameters. 2nd ed. Philadelphia: Davis, 1978:90–91.
26. **Wilson JR, Reichek N, Hirshfeld J, Keller CA.** Noninvasive assessment of load reduction in patients with asymptomatic aortic regurgitation. Am J Med 1980;68:664–674.
27. **Quinones MA, Mokotoff D, Nouri S, Winters WL Jr, Miller RR.** Noninvasive quantification of left ventricular wall stress. Validation of method and application to assessment of chronic pressure overload. Am J Cardiol 1980;45:782–790.
28. **Armitage P.** Statistical Methods in Medical Research. New York: John Wiley, 1971:121–124.
29. **Devereux RB, Savage DD, Drayer JIM, Laragh JH.** Left ventricular hypertrophy and function in high, normal and low-renin forms of essential hypertension. Hypertension 1982; 4:524–531.
30. **Frohlich ED.** Hemodynamics of hypertension. In: Genest J, Koiv E, Kuchel O, eds. Hypertension: Physiopathology and Treatment. New York: McGraw-Hill, 1977:15–49.
31. **Weiss YA, Safar ME, London GM, Simon AC, Levenson JA, Milliez PM.** Repeat hemodynamic measurements in borderline hypertension. Am J Med 1978;64:382–387.
32. **Lund-Johansen P.** Hemodynamic alterations in hypertension-spontaneous changes and effects of drug therapy. A review. Acta Med Scand 1977; Suppl 603:1–14.
33. **Ibrahim MM, Tarazi RC, Dustan HP, Bravo EL, Gifford RW Jr.** Hyperkinetic heart in severe hypertension: a separate clinical hemodynamic entity. Am J Cardiol 1975;35:667–674.
34. **Ramirez EA, Garcia Pont PH.** Relation of arterial blood pressure to the transverse diameter of the heart in compensated hypertensive heart disease. Circulation 1965,31:542–550.
35. **Shkhvatsabaya IK, Usubaliyev NN, Yuranev AP, Panfiolov VV.** The interrelations of cardiac and vascular wall hypertrophy in arterial hypertension. Cardiovasc Rev Rep 1981;2:1145–1149.
36. **Sasayama S, Ross J Jr, Franklin D, Bloor CM, Bishop S, Dillery RB.** Adaption of the left ventricle to chronic pressure overload. Circ Res 1976;38:172–178.
37. **Spotnitz HM, Sonnenblick EH.** Structural conditions in the hypertrophied and failing heart. Am J Cardiol 1973;32:398–406.
38. **Badeer HS.** The stimulus to hypertrophy of the myocardium. Circulation 1964;30:128–136.
39. **Ford LE.** Heart size. Circ Res 1976;39:297–303.
40. **Wikman-Coffelt J, Parmley WW, Mason DT.** The cardiac hypertrophy process. Analyses of factors determioning pathological vs. physiological development. Circ Res 1979;45:697–707.
41. **Devereux RB, Reichek N.** Left ventricular hypertrophy. Cardiovasc Rev Rep 1980;1:55–68.
42. **Grossman W.** Cardiac hypertrophy: useful adaptation or pathologic process? Am J Med 1980;69:576–584.
43. **Mirsky I, Parmley WW.** Assessment of passive elastic stiffness for isolated muscle and the intact heart. Circ Res 1973;33:233–243.
44. **Glantz SA, Parmley WW.** Factors which affect the diastolic pressure-volume curve. Circ Res 1978;42:171–180.
45. **Littler WA, West MJ, Honour AJ, Sleight P.** The variability of arterial pressure. Am Heart J 1978;95:180–186.
46. **Goldberg AD, Raferty EB, Cashman PMM, Stott FD.** Study of untreated hypertensive subjects by means of continuous intra-arterial blood pressure recordings. Br Heart J 1978;40:656–664.
47. **Irving JB, Kerr F, Ewing DJ, Kirby BJ.** Value of prolonged recording of blood pressure in assessment of hypertension. Br Heart J 1974;36:859–866.
48. **Devereux RB, Pickering TG, Harshfield GA, Kleinert HD, Jason M, Borer JS, Laragh JH.** Relation of hypertensive left ventricular hypertrophy to clinic, home, work and exercise blood pressures (abstr). Circulation 1981;64:Suppl IV:IV-321.
49. **Lakatta EG.** Alterations in the cardiovascular system that occur in advanced age. Fed Proc 1979;44:994–998.
50. **Pfeffer J, Pfeffer M, Fletcher P, Braunwald E.** Alterations of cardiac performance in rats with established spontaneous hypertension. Am J Cardiol 1979;44:994–998.
51. **Sen S, Tarazi RC, Khairallah PA, Bumpus FM.** Cardiac hypertrophy in spontaneously hypertensive rats. Circ Res 1974;35:775–782.
52. **Sen S, Tarazi RC, Bumpus FM.** Cardiac hypertrophy and antihypertensive therapy. Cardiovasc Res 1977;11:427–433.
53. **Devereux RB, Savage DD, Sachs I, Laragh JH.** Effect of blood pressure control on left ventricular hypertrophy and function in hypertension (abstr). Circulation 1980;62:Suppl III:III-33.
54. **Ostman-Smith I.** Cardiac sympathetic nerves as the final common pathway in the induction of adaptive cardiac hypertrophy. Clin Sci 1981;61:265–272.
55. **Laks MM, Morady F, Swan HJC.** Myocardial hypertrophy produced by chronic infusion of subhypertensive doses of norepinephrine in the dog. Chest 1973; 64:75–78.
56. **Robertson AL, Kairallah PA.** Angiotensin II: rapid localization in nuclei of smooth and cardiac muscle. Science 1971;172;1138–1140.
57. **Frohlich ED, Tarazi RC.** Is arterial pressure the sole factor responsible for hypertensive cardiac hypertrophy? Am J Cardiol 1979;44:959–963.
58. **Mahler F, Ross J Jr, O'Rourke RA, Covell J.** Effects of changes in preload, afterload and inotropic state on ejection and isovolumic phase measures of contractility in the conscious dog. Am J Cardiol 1975;35:626–634.
59. **Takhashi M, Sasayama S, Kawai C, Kotoura H.** Contractile performance of the hypertrophied ventricles in patients with systemic hypertension. Circulation 1980,62:116–126.
60. **Khatri I, Gottdiener J, Notargiacomo A, Fries E.** Effect of therapy on left ventricular function in hypertension. Clin Sci 1980;59:435s–439s.
61. **Weber KT, Janicki JS, Hefner LL.** Left ventricular force-length relations of isovolumic and ejection contractions. Am J Physiol 1976;213:337–343.
62. **Sagawa K.** The ventricular pressure-volume diagram revisited. Circ Res 1978;43:677–687.
63. **Marsh JD, Green LH, Wynne J, Cohn PF, Grossman W.** Left ventricular end-systolic pressure-dimension and stress-length relations in normal human subjects. Am J Cardiol 1979;44:1311–1317.
64. **Devereux RB.** Noninvasive evaluation of cardiac anatomy and function in patients with hypertension. Cardiovasc Rev Reports 1982;3:313–323.




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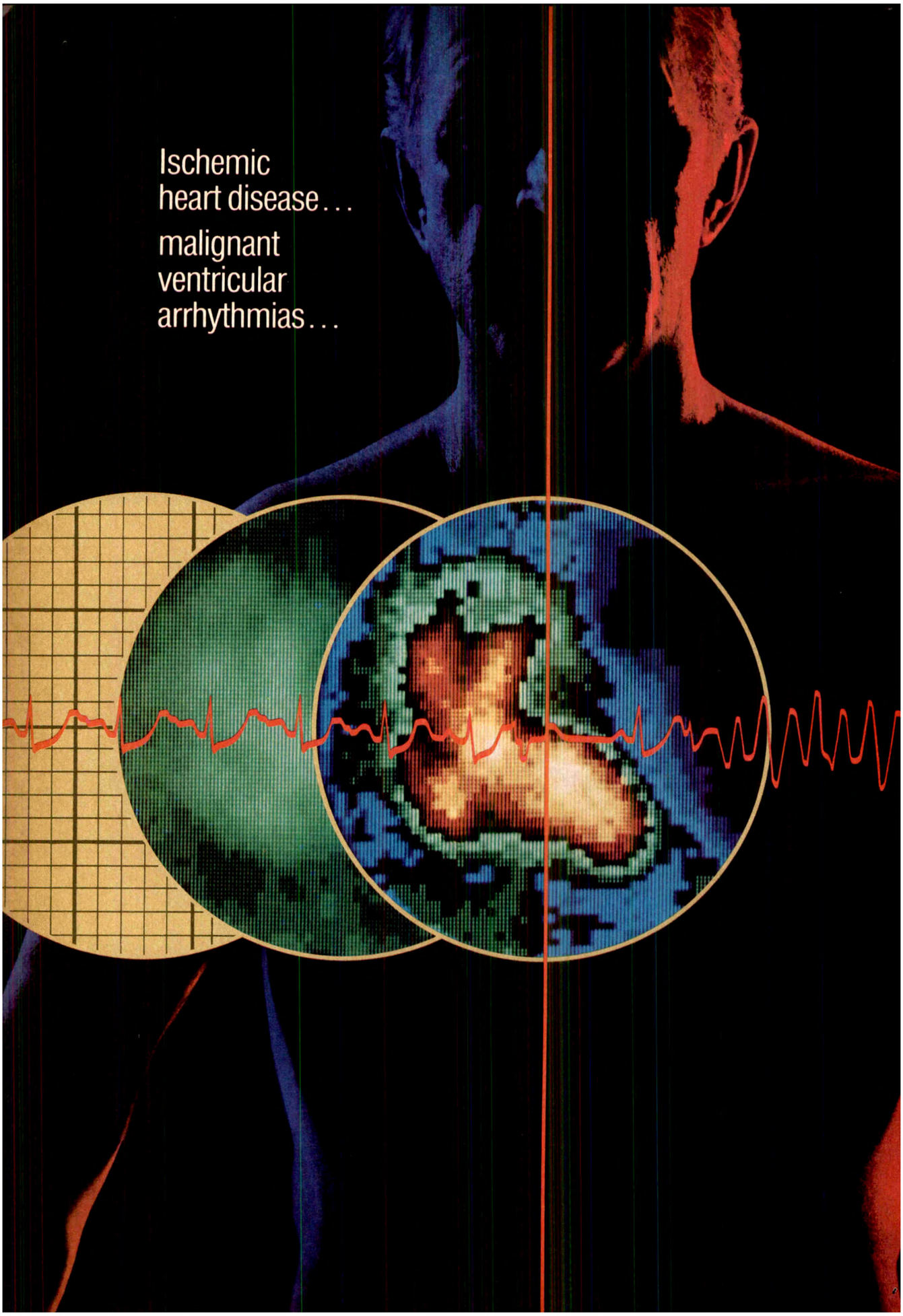
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References: **1.** Lown B, Podrid PJ, Graboys TB, et al: *Curr Probl Cardiol* 4:13-14, 1980. **2.** Schulze RA Jr, Strauss HW, Pitt B: *Am J Med* 62:192-199, 1977. **3.** Pine MB, Aronow WS: *Ration Drug Ther* 14:1-5, 1980. **4.** Kastor JA, Horowitz LN, Harken AH, et al: *N Engl J Med* 304: 1004-1020, 1981. **5.** Podrid PJ: *Patient Care* 15:100-132, 1981.

Please turn page for brief summary of prescribing information.

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**QUINAGLUTE® (quinidine gluconate) DURA-TABS®**
**INDICATIONS AND USAGE:** Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:
**1. Ventricular arrhythmias:** Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).
**2. Junctional (nodal) arrhythmias:** A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).
**CONTRAINDICATIONS:** 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
**WARNINGS:** 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.
2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.
3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.
4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.
5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.
7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.
8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
**PRECAUTIONS: General:** The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.
**Drug Interactions:**

| *Drug* | *Effect* |
|---|---|
| Quinidine with anticholinergic drugs | Additive vagolytic effect |
| Quinidine with cholinergic drugs | Antagonism of cholinergic effects |
| Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics | Alkalinization of urine resulting in decreased excretion of quinidine |
| Quinidine with coumarin anticoagulants | Reduction of clotting factor concentrations |
| Quinidine with tubocurare, succinylcholine and decamethonium | Potentiation of neuromuscular blockade |
| Quinidine with phenothiazines and reserpine | Additive cardiac depressive effects |
| Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin) | Decreased plasma half-life of quinidine |
| Quinidine with digoxin | Increased plasma concentrations of digoxin (see WARNINGS) |

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
**Pregnancy:** *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.
**Nursing Mothers:** Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.
**Pediatric Use:** There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.
**ADVERSE REACTIONS:** Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.
Less frequently encountered adverse reactions:
**Cardiovascular:** Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.
**Hematologic:** Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.
**Central Nervous System:** Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
**Dermatologic:** Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
**Hypersensitivity Reactions:** Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.
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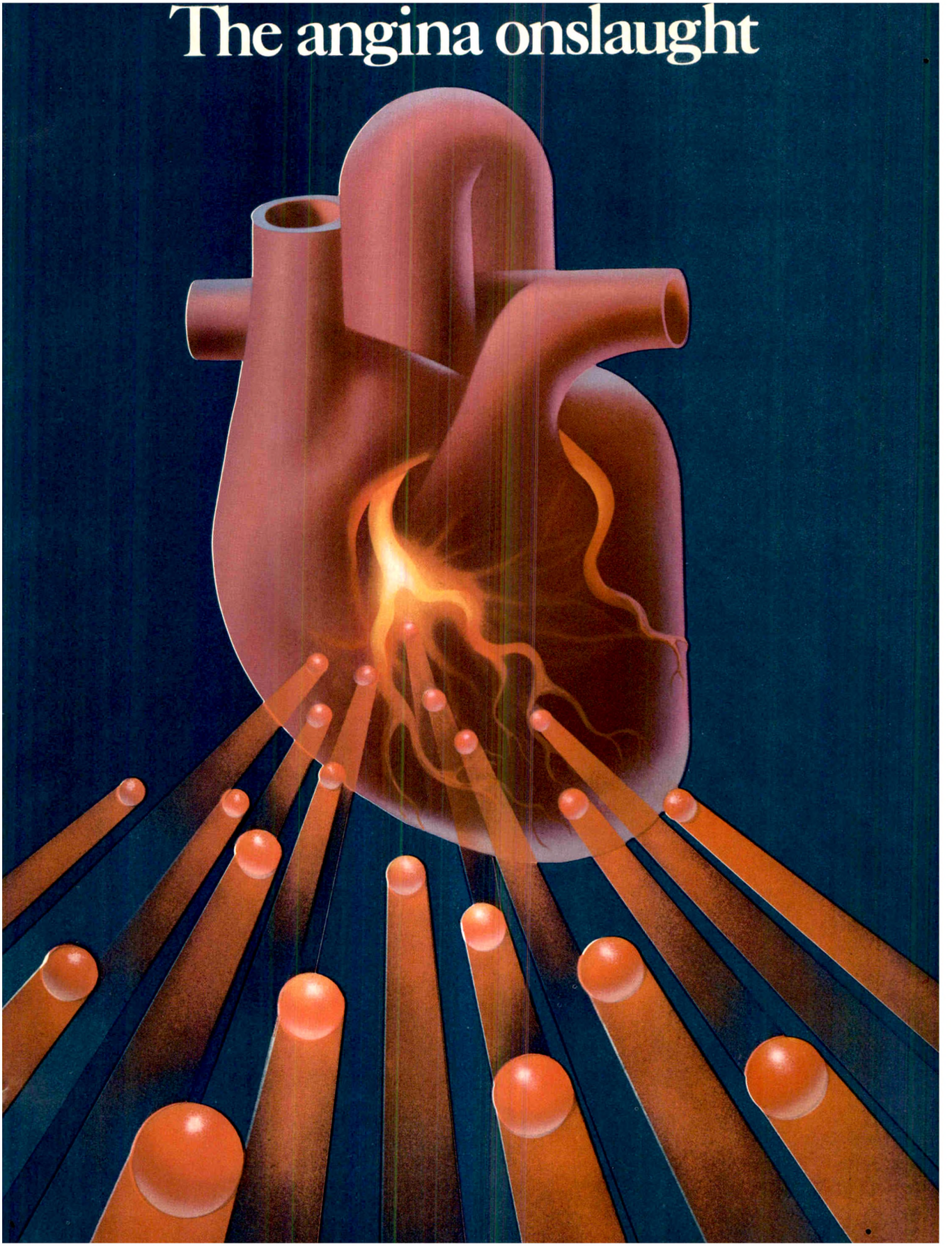
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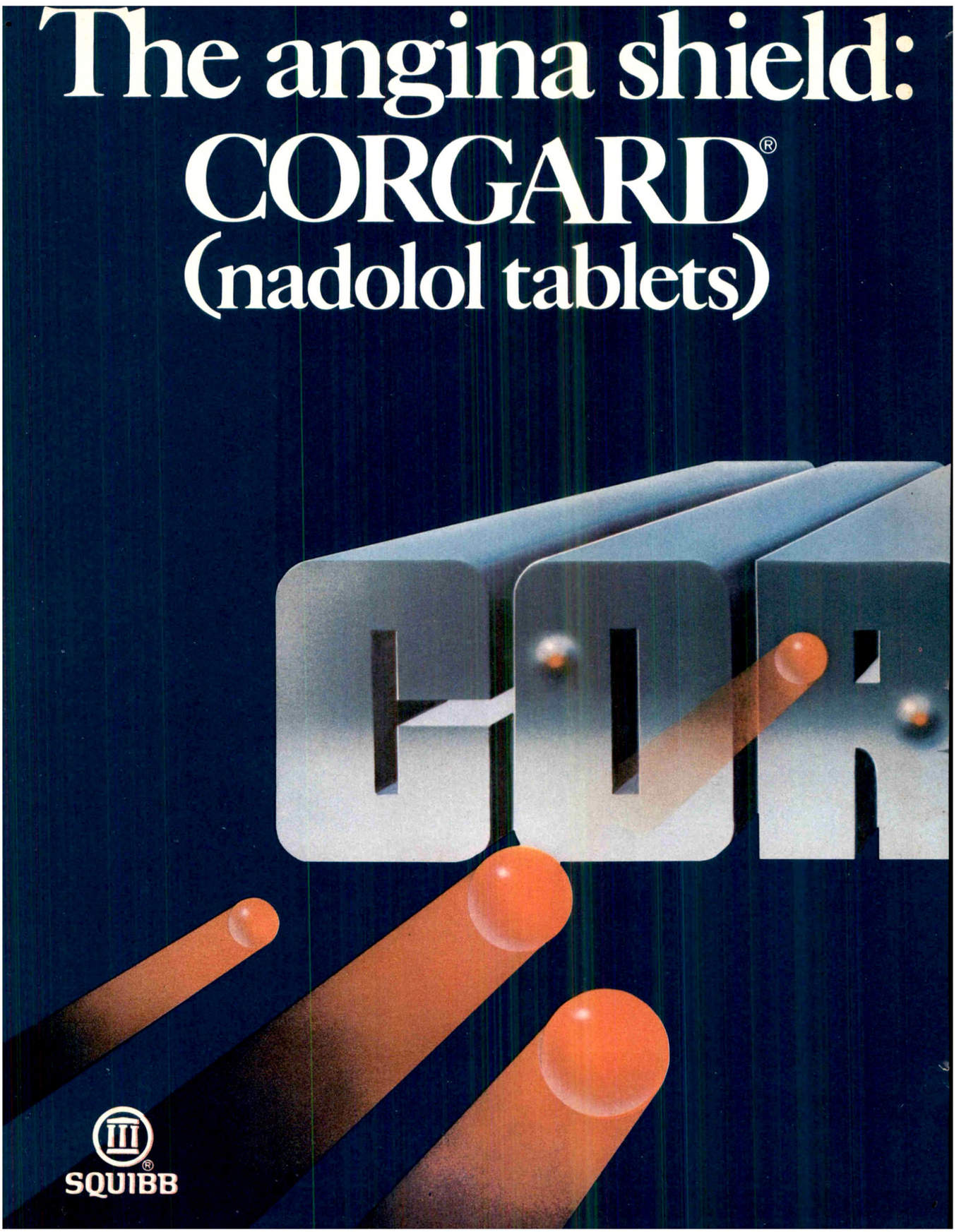
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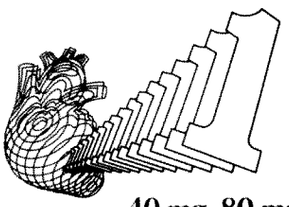
*For a full discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary on next page.

# CORGARD® (nadolol tablets)

## The only once-a-day beta-blocker for both angina pectoris and hypertension

*se see next page for brief summary.*

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**DESCRIPTION:** Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

**CONTRAINDICATIONS:** Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

**WARNINGS: Cardiac Failure** — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal** — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)** — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

**Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

**Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

**Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

**PRECAUTIONS: Impaired Hepatic or Renal Function** — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

**Information for Patients** — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

**Drug Interactions** — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

**Carcinogenesis, Mutagenesis, Impairment of Fertility** — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

**Pregnancy** — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

**Nursing Mothers** — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

**Pediatric Use** — Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

**Cardiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

**Potential Adverse Effects:** Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

**OVERDOSAGE:** Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

**Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

**Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

**Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

**Bronchospasm** — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

**DOSAGE:** For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

**HOW SUPPLIED:** In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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# Failure of Dobutamine to Increase Exercise Capacity Despite Hemodynamic Improvement in Severe Chronic Heart Failure

CAROL S. MASKIN, MD, ROBERT FORMAN, MD, EDMUND H. SONNENBLICK, MD, WILLIAM H. FRISHMAN, MD, and THIERRY H. LeJEMTEL, MD

**The acute hemodynamic and metabolic effects of dobutamine administered during exercise were studied in 8 patients with severe chronic heart failure. Exercise was performed on an upright bicycle ergometer using a graded protocol. During exercise performed without administration of dobutamine, exhaustion occurred after 4.5 ± 1.2 minutes of exercise. The cardiac index increased from 1.61 ± 0.25 to 2.67 ± 0.59 liters/min/m$^2$ ($p < 0.001$), the arteriovenous oxygen difference from 7.8 ± 1.7 to 12.5 ± 2.4 ml/100 ml ($p < 0.001$), and oxygen uptake from 7.9 ± 3.0 to 41.2 ± 15.7 mg/100 ml ($p < 0.001$). During exercise performed with the administration of dobutamine, the cardiac index was significantly greater than during the control state, 3.23 ± 0.78 versus 2.67 ± 0.59 liters/min/m$^2$ ($p < 0.001$), while the arteriovenous oxygen difference was significantly lower, 11.2 ± 2.1 vs 12.5 ± 2.4 ml/100 ml ($p < 0.01$). The arterial lactate level was not significantly changed, 45.3 ± 17.6 versus 41.2 ± 15.7 mg/100 ml. Although the dobutamine level tended to increase maximal oxygen uptake compared with the control period of exercise, 9.1 ± 1.2 versus 8.5 ± 1.4 ml/kg/min ($p < 0.05$), it did not significantly increase exercise capacity, 4.8 ± 1.5 versus 4.5 ± 1.2 min. Thus administration of dobutamine in patients with severe chronic heart failure increased the cardiac index during maximal exercise but failed to increase exercise capacity. Since arteriovenous oxygen difference is reduced, dobutamine probably increases blood flow to the nonexercising tissues and not to the actively metabolizing muscles.**

In patients with severe congestive heart failure, there is an inadequate increase in cardiac output during exercise which limits maximal oxygen uptake and exercise capacity.[1–3] When these patients are treated acutely with vasodilators, a higher cardiac output is reached at the point of exhaustion, but an increase in maximal oxygen uptake or exercise capacity does not occur.[4–7] Indeed, the increase in cardiac output produced by vasodilators is accompanied by a concomitant reduction in arteriovenous oxygen difference, which probably reflects a shunting of blood to organs other than exercising muscles.[8]

The effects of an acute inotropic intervention on exercise capacity and maximal oxygen uptake have not been thoroughly investigated. Although cardiac glycosides may increase cardiac output somewhat during exercise in the patient with heart failure,[9] the effects of this on exercise capacity and maximal oxygen uptake have not been studied. Recently the short-term administration of amrinone, a new nonglycosidic, nonadrenergic agent, has been shown to increase the capacity to perform exercise at a fixed work load.[10] However, whether inotropic therapy can acutely increase maximal oxygen uptake using a graded protocol is still unknown. Therefore, the effects of dobutamine, a synthesized catecholamine,[11] on exercise capacity and maximal oxygen uptake in patients with severe congestive heart failure were studied.

## Methods

**Patient population:** Seven men and 1 woman with severe chronic congestive heart failure were studied. The average patient age was 54.7 years (range 49 to 61). Three patients had ischemic heart disease as documented by coronary arteriography and prior myocardial infarction. Four had idiopathic cardiomyopathy, and one had persistent heart failure after successful mitral valve replacement. The mean duration of heart failure was 29 months (range 10 to 60). All were severely restricted in activity before elective hospital admission, 5

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**TABLE I Hemodynamic and Metabolic Measurements During Exercise in the Control State**

| Patient | BSA | W | HGB | HR (beats/min) | | MAP (mm Hg) | | CI (liters/min/m²) | | PCWP (mm Hg) | | SVR (units) | | $AVO_2$ (ml/100 ml) | | $VO_2$ (ml/kg/min) | | Lactate (mg/100 ml) | | Duration (min) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | CR | CEx | CR | CEx | CR | CEx | CR | CEx | CR | CEx | CR | CEx | CR | CEx | CR | CEx | |
| 1 | 2.1 | 88 | 13.5 | 111 | 140 | 85 | 80 | 1.53 | 2.62 | 30 | 39 | 23.4 | 14.5 | 9.0 | 13.6 | 3.3 | 8.5 | 9.3 | 43.9 | 5.5 |
| 2 | 1.8 | 68 | 11.0 | 110 | 150 | 86 | 94 | 1.63 | 2.69 | 33 | 41 | 29.4 | 19.4 | 8.6 | 11.5 | 3.7 | 8.2 | 7.2 | 56.4 | 3.0 |
| 3 | 1.7 | 67 | 12.5 | 82 | 110 | 64 | 75 | 1.84 | 2.64 | 22 | 35 | 20.4 | 16.7 | 6.2 | 10.0 | 2.9 | 6.7 | 5.5 | 21.5 | 3.0 |
| 4 | 1.8 | 60 | 12.5 | 72 | 102 | 66 | 70 | 1.70 | 2.51 | 32 | 44 | 21.6 | 15.5 | 7.8 | 13.4 | 4.0 | 10.1 | 6.3 | 27.3 | 5.0 |
| 5 | 2.0 | 82 | 12.8 | 94 | 125 | 100 | 125 | 1.72 | 3.37 | 8 | 39 | 29.1 | 18.5 | 6.2 | 10.8 | 2.6 | 8.9 | 4.1 | 39.1 | 6.0 |
| 6 | 2.1 | 86 | 16.0 | 109 | 170 | 125 | 135 | 1.30 | 2.23 | 34 | 50 | 45.8 | 28.8 | 10.7 | 17.1 | 3.4 | 8.9 | 13.9 | 70.1 | 5.0 |
| 7 | 1.9 | 72 | 13.0 | 92 | 132 | 87 | 115 | 1.92 | 3.56 | 9 | 20 | 23.8 | 17.0 | 5.9 | 10.3 | 3.0 | 10.2 | 9.9 | 34.7 | 5.0 |
| 8 | 1.9 | 69 | 12.6 | 100 | 125 | 100 | 125 | 1.20 | 1.71 | 24 | 44 | 43.9 | 38.5 | 8.2 | 13.5 | 2.7 | 6.3 | 7.4 | 36.4 | 3.5 |
| Mean | ... | ... | ... | 96.3 | 131.8 | 89.1 | 102.4 | 1.61 | 2.67 | 24.0 | 39.0 | 29.7 | 21.1 | 7.8 | 12.5 | 3.2 | 8.5 | 7.9 | 41.2 | 4.5 |
| ±SD | ... | ... | ... | 14.1 | 21.8 | 19.7 | 25.7 | 0.25 | 0.59 | 10.5 | 8.9 | 9.9 | 8.3 | 1.7 | 2.4 | 0.5 | 1.4 | 3.0 | 15.7 | 1.2 |
| p CEx versus CR | ... | ... | ... | <0.001 | | <0.001 | | <0.001 | | <0.001 | | <0.001 | | <0.001 | | <0.001 | | <0.001 | | ... |

$AVO_2$ = arteriovenous oxygen difference; BSA = body surface area ($m^2$); CEx = control state exercise to exhaustion; CI = cardiac index; CR = control state at rest; HGB = hemoglobin (g/100 ml); HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; $VO_2$ = oxygen uptake; W = weight (kg).

being in New York Heart Association class IV and three in class III, despite optimal therapy with digitalis and diuretics. The mean digoxin level immediately before the study was 1.4 ± 0.5 mg/ml. Left ventricular ejection fraction, determined by gated radionuclide technique, averaged 23% (range 20 to 35). Sinus rhythm was present in all but 1 patient, who had atrial fibrillation. Patients were maintained on their usual doses of digoxin and furosemide, while nitrates, when taken, were discontinued 2 days before the study. No patient had had angina or a myocardial infarction within 3 months of the study. Studies were conducted in the coronary care unit. The nature, potential benefits, and possible risks of the study were fully explained to patients, who then gave written informed consent.

**Hemodynamics:** One day before the study, catheterization of the right side of the heart was performed in all patients using a triple-lumen flow-directed balloon-tipped thermodilution catheter (Edwards Laboratories), which was introduced percutaneously via a subclavian vein and advanced to a pulmonary wedge position by aid of fluoroscopy. On the day of the study, an intraarterial indwelling catheter was inserted percutaneously into a radial artery for measurement of systemic arterial pressure and for withdrawal of blood samples. Systemic arterial, pulmonary arterial, and pulmonary capillary wedge pressures were determined using Gould Statham P23ID transducers and recorded on an Electronics for Medicine photographic recorder. Heart rate was recorded continuously from a bedside electrocardiographic monitoring device. Cardiac output was determined in triplicate by thermodilution technique using iced 5% dextrose and a bedside computer (model 9250A), and confirmed by the Fick method using determination of oxygen consumption, and pulmonary artery and radial artery oxygen contents ($r = 0.96$, $n = 48$). Resting hemodynamic variables were measured with the patient sitting upright on the bicycle ergometer. The pressure transducers were positioned at the level of the fourth intercostal space. Two sets of similar resting determinations were obtained at intervals of 10 minutes. During the control period of exercise, pulmonary arterial pressure, mean systemic arterial pressure, and heart rate were monitored and measurements of cardiac output repeated continuously. At the end of each work load, as well as at the end of exercise, pulmonary capillary wedge pressure was measured. The following day, dobutamine was administered intravenously for 1 hour and the exercise protocol repeated to exhaustion. Hemodynamic measurements were performed as before. Derived hemodynamic values were calculated as follows: Cardiac index = cardiac output/body surface area (liters/min/$m^2$); Stroke volume index = cardiac index ×1,000/heart rate (ml/$m^2$); Systemic vascular resistance = mean arterial pressure/cardiac output (units).

**Oxygen uptake:** Measurements of mixed expired oxygen, mixed expired carbon dioxide, expired volume, expired gas temperature (°C), and barometric pressure were performed at rest while patients were sitting on the bicycle and every 30 seconds throughout exercise using a metabolic measurement cart (Beckman Instruments). Oxygen uptake (ml/kg/min) was calculated using standard formulas.[12] Patients were breathing through a mouthpiece and a low resistance, nonrebreathing, 3-way valve with a nose clamp. The oxygen analyzer (OM-11 Beckman Instruments) and carbon dioxide analyzer (LB-2 Beckman Instruments) were calibrated using an analyzed mixture of approximately 4% carbon dioxide and 16% oxygen in nitrogen. This calibration was made within 1 hour of the testing.

**Oxygen content and arterial lactate level:** All samples were evaluated in triplicate for oxygen content (volumes per unit) using a Lex-$O_2$ CON-TL oxygen analyzer (Lexington

Instruments). Multiple temperature and barometric pressure corrections were made throughout each study, and calibration of the Lex-$O_2$ CON-TL was considered optimal if 3 consecutive readings for dry air were within ±0.1 volume/100 ml. During the control period of exercise, systemic arterial ($SAO_2$) and pulmonary arterial ($PAO_2$) contents were measured at rest, at the end of each work load, and at exhaustion. Measurements were similarly performed during exercise and while on dobutamine. Arteriovenous oxygen difference in ml/100 ml was calculated as $SAO_2 - PAO_2$.

Arterial lactate concentration was measured by the enzymatic spectrofluorometric technique and expressed as mg/100 ml. Lactate determinations were made at the same times as oxygen contents.

**Exercise protocol:** Exercise testing was performed with the patient upright on an electronically braked bicycle ergometer (Warren E. Collins, Braintree, Massachusetts) with feet secured to the pedals. Two exercise tests were performed within 72 hours of the control period of exercise in the postabsorptive state and at least 4 hours after administration of furosemide, to determine reproducibility and to familiarize patients with the equipment. The initial work load was 25 W for 3 minutes. This load was increased every 3 minutes by 12.5 W until exhaustion. Patients pedaled at a frequency of at least 35 rpm. While receiving dobutamine, patients performed graded exercises in a similar fashion until exhaustion.

**Dobutamine administration:** After baseline determinations of hemodynamic function and systemic and pulmonary arterial oxygen contents in the supine position, dobutamine was infused at an initial rate of 5 μg/kg/min for 15 minutes. Measurements were repeated and the dose increased by 2 μg/kg/min every 5 minutes until maximal cardiac output was reached or adverse effects were elicited. Adverse effects were defined as a 10% increase in either heart rate or systolic arterial pressure above control values, or an increase in ventricular premature beats >5 beats/min above levels at rest. The optimal rate of infusion was defined as the value producing the largest increase in cardiac output without precipitating adverse effects. Dobutamine was then infused at the optimal dose level for 60 minutes. Resting hemodynamic and metabolic determinations were performed while patients were sitting on the bicycle, and the exercise protocol was then repeated.

**Statistical analysis:** The results are expressed as means ± standard deviations. Hemodynamic and metabolic changes were assessed using 2 factors within subjects analysis of variance model. Each patient was assessed at rest and at maximal exercise both before and during administration of dobutamine for a total of 4 observations.

Hemodynamic and metabolic variables were analyzed as a function of the effect of exercise (rest versus maximal exercise), the effect of the drug (control versus dobutamine administration), and the interaction of the 2 factors. In the presence of exercise-drug interactions, F tests were performed using orthogonal contrasts to determine the simple effects of the drug at maximal exercise.

## Results

While resting upright on the bicycle, the mean cardiac index averaged 1.61 ± 0.25 liters/min/$m^2$, and pulmonary capillary wedge pressure, 24.0 ± 10.5 mm Hg. Hemodynamic and metabolic variables are detailed in Table I. In the control state, exercise was sustained for 4.5 ± 1.2 minutes (Fig. 1), at which point the average cardiac index had increased to 2.67 ± 0.59 liters/min/$m^2$ ($p < 0.001$) and pulmonary capillary wedge pressure to 39.0 ± 8.9 mm Hg ($p < 0.001$). The limited increase in cardiac index during maximal exercise was due to a less than adequate increase in both heart rate, from 96.3 ± 14.1 to 131.8 ± 21.8 beats/min ($p < 0.001$), and stroke volume index, from 17.2 ± 4.7 to 20.9 ± 5.6 ml/$m^2$ ($p < 0.001$) (Fig. 2). At the point of exhaustion oxygen uptake had reached a plateau of 8.5 ± 1.4 ml/kg/min while the arteriovenous oxygen difference increased from 7.8 ± 1.7 at rest to 12.5 ± 2.4 ml/100 ml ($p < 0.001$) (Fig. 3). Blood lactate had increased from a control level of 7.9 ± 3.0 to 41.2 ± 15.7 mg/100 ml ($p < 0.001$) at the end of exercise.

Administration of dobutamine increased the resting cardiac index substantially in all patients from 1.61 ±

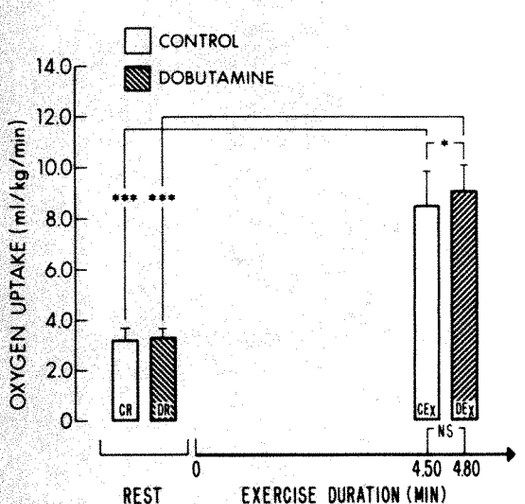



**FIGURE 1.** Oxygen uptake related to duration of exercise. At rest oxygen uptake is similar in the control period (CR) and during dobutamine administration (DR). The duration of exercise is not significantly different during the control period (CEx) and during dobutamine administration (DEx). Oxygen uptake is increased significantly during maximal exercise and tends to be slightly higher during administration of dobutamine than during the control period. NS = not significant. * $p < 0.01$; *** $p < 0.001$.

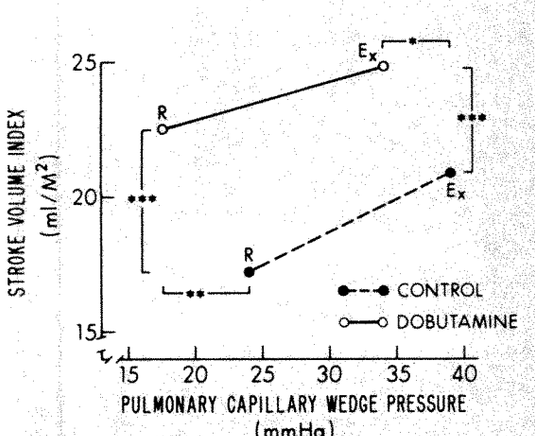



**FIGURE 2.** Relation between stroke volume index and pulmonary capillary wedge pressure during the control period of exercise and during exercise performed on dobutamine. Ex = exhaustion; R = rest. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

**TABLE II Hemodynamic and Metabolic Measurements During Exercise on Dobutamine**

| Patient | HR (beats/min) | | MAP (mm Hg) | | CI (liters/min/m²) | | PCWP (mm Hg) | | SVR (units) | | $AVO_2$ (ml/100 ml) | | $VO_2$ (ml/kg/min) | | Lactate (mg/100 ml) | | Duration (min) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | DR | DEx | DR | DEx | DR | DEx | DR | DEx | DR | DEx | DR | DEx | DR | DEx | DR | DEx | |
| 1 | 126 | 150 | 80 | 76 | 1.97 | 2.63 | 28 | 24 | 19.3 | 13.8 | 7.2 | 13.7 | 3.4 | 8.6 | 14.5 | 43.1 | 6.0 |
| 2 | 120 | 150 | 85 | 88 | 2.10 | 2.62 | 30 | 40 | 22.5 | 18.6 | 6.3 | 11.8 | 3.5 | 8.2 | 6.9 | 75.2 | 3.0 |
| 3 | 85 | 110 | 56 | 78 | 2.51 | 3.06 | 18 | 33 | 13.1 | 15.0 | 5.0 | 9.0 | 3.2 | 7.0 | 8.7 | 20.6 | 3.0 |
| 4 | 70 | 100 | 65 | 72 | 2.22 | 3.30 | 26 | 38 | 16.3 | 12.1 | 6.0 | 11.0 | 4.0 | 10.9 | 7.5 | 27.1 | 4.0 |
| 5 | 92 | 125 | 100 | 118 | 2.55 | 4.42 | 4 | 30 | 19.6 | 13.3 | 4.5 | 8.9 | 2.8 | 9.6 | 6.1 | 40.5 | 7.5 |
| 6 | 118 | 168 | 90 | 112 | 2.22 | 2.75 | 14 | 44 | 19.3 | 19.4 | 7.1 | 14.1 | 3.6 | 9.5 | 12.7 | 63.1 | 5.0 |
| 7 | 105 | 140 | 75 | 112 | 2.40 | 4.46 | 6 | 20 | 16.4 | 13.2 | 5.2 | 9.0 | 3.3 | 10.6 | 6.6 | 45.2 | 5.0 |
| 8 | 92 | 130 | 95 | 125 | 1.37 | 2.66 | 14 | 44 | 36.5 | 24.8 | 7.5 | 12.3 | 2.8 | 8.9 | 8.9 | 48.0 | 5.0 |
| Mean | 101.0 | 134.1 | 80.8 | 97.6 | 2.17 | 3.24 | 17.5 | 34.1 | 20.4 | 16.3 | 6.1 | 11.2 | 3.3 | 9.1 | 8.9 | 45.3 | 4.8 |
| ± SD | 19.5 | 22.5 | 15.0 | 21.3 | 0.38 | 0.78 | 9.8 | 9.0 | 7.1 | 4.3 | 1.1 | 2.1 | 0.4 | 1.2 | 3.0 | 17.6 | 1.5 |
| p DEx versus DR | <0.001 | | <0.001 | | <0.001 | | <0.001 | | <0.05 | | <0.001 | | <0.001 | | <0.001 | | |

$AVO_2$ = arteriovenous oxygen difference; CI = cardiac index; DEx = dobutamine exercise to exhaustion; DR = dobutamine at rest; HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; $VO_2$ = oxygen consumption.




**FIGURE 3. Upper panel,** cardiac index at rest and at exhaustion during the control period and during exercise while the patient was receiving dobutamine. ** $p < 0.01$. **Middle panel,** arteriovenous oxygen difference at rest and exhaustion. ** $p < 0.01$; *** $p < 0.001$. **Lower panel,** oxygen uptake at rest and exhaustion. * $p < 0.05$.

0.25 to 2.17 ± 0.38 liters/min/m² ($p < 0.001$). Stroke volume index increased from 17.2 ± 4.7 to 22.5 ± 6.7 ml/m² ($p < 0.001$), while pulmonary capillary wedge pressure decreased from 24 ± 10.5 to 17.5 ± 9.8 mm Hg ($p < 0.01$) (Fig. 2). The resting heart rate was increased slightly from 96.3 ± 14.1 to 101.0 ± 19.5 beats/min ($p < 0.05$) and mean arterial pressure decreased from 89.1 ± 19.7 to 80.8 ± 15.0 mm Hg ($p < 0.05$). Oxygen uptake at rest was unchanged by dobutamine, and the arteriovenous oxygen difference decreased from 7.8 ± 1.7 to 6.1 ± 1.1 ml/100 ml ($p < 0.001$) (Fig. 3).

The optimal rate of infusion of dobutamine averaged 7.8 μg/kg/min (range 5 to 12). In 4 patients (1, 2, 6, and 7), the rate of infusion was limited by an excessive increase in heart rate, while in 2 others (4 and 8) an augmentation in ventricular premature beats was the limiting factor. A maximal increase in cardiac output was obtained in the remaining 2 patients (3 and 5).

Dobutamine therapy did not increase the duration of exercise significantly compared with the control period: 4.8 ± 1.5 versus 4.5 ± 1.2 minutes. Thus although oxygen uptake reached a higher plateau during exercise performed on dobutamine, 9.1 ± 1.2 versus 8.5 ± 1.4 ml/kg/min ($p < 0.05$), the change was not clinically meaningful (Fig. 1). The increase in cardiac performance observed at rest while dobutamine was administered was maintained at maximal exercise (Fig. 2). The

stroke volume index was significantly higher and pulmonary capillary wedge pressure lower than during the control period of exercise: 24.8 ± 7.9 versus 20.9 ± 5.6 ml/m$^2$ ($p < 0.001$) and 34.1 ± 9.01 versus 39.0 ± 8.9 mm Hg ($p < 0.05$), respectively. In Table II, the hemodynamic and metabolic parameters are detailed for the 8 patients during exercise performed while receiving dobutamine. At the point of exhaustion, mean arterial pressure tended to be lower on dobutamine than during the control period of exercise 97.6 ± 21.3 versus 102.4 ± 25.7 mm Hg ($p < 0.05$), while the maximal heart rate was similar, 134.1 ± 22.5 versus 131.8 ± 21.8 beats/min (difference not significant [NS]). The arteriovenous oxygen difference was lower during exercise performed while on dobutamine than in the control state, 11.2 ± 2.1 versus 12.5 ± 2.4 mg/100 ml ($p < 0.01$). Nevertheless, blood lactate levels were similar in both states, 45.3 ± 17.6 versus 41.2 ± 15.7 mg/100 ml (NS).

## Discussion

The present study shows that the acute administration of dobutamine improves cardiac output not only at rest but also during maximal exercise in patients with severe heart failure. However, exercise capacity was not improved.

At rest, left ventricular function was substantially depressed in our patients as demonstrated by a very low cardiac index and an elevated pulmonary wedge pressure. During exercise, a markedly diminished cardiac reserve was evidenced by a maximal oxygen uptake, ≤10 ml/kg/min, which is compatible with functional class IV of the New York Heart Association.[13] In patients with severe heart failure, inadequate augmentation of cardiac output during exercise is due to both impaired heart rate response, which parallels the degree of left ventricular dysfunction,[14] and limited ability to increase stroke volume despite a further increase in ventricular filling pressure.[15,16] In addition, patients with chronic heart failure demonstrate an abnormal peripheral vascular response to exercise which further limits maximal oxygen uptake.[17] A limited vasodilator response in exercising muscles has been observed in such patients and attributed to an increase in sodium and water content of the arteriolar wall,[18,19] increased tissue pressures,[20] an abnormal level of vasoconstriction in active muscle secondary to an exaggerated sympathoadrenal response to exercise,[21] or a combination of these. Furthermore, peripheral muscles of patients with heart failure may be unable to extract oxygen maximally due to metabolic and ultrastructural changes produced by prolonged physical inactivity.[22,23]

The rationale for the use of inotropic agents in the treatment of heart failure is to mobilize residual myocardial contractile reserve and thereby improve cardiac performance both at rest and during exercise. In the failing heart, the presence of contractile reserve has been demonstrated by the phenomenon of postextrasystolic potentiation[24] as utilized in paired stimulation.[25] However, whether inotropic agents can substantially augment cardiac performance and effect improvement in functional capacity is still controversial in patients with severe heart failure.[26]

Although cardiac glycosides increase myocardial contractility in patients with heart failure,[27] variable effects on cardiac performance at rest have been observed.[9,28–36] Differing responses to digitalis therapy in myocardial disease may be related to the natural course of congestive heart failure and the severity of disease. At an early stage, when cardiomegaly is present without circulatory failure, the increased myocardial contractility produced by digitalis may offer little or no change in already normal resting cardiac output and ventricular filling pressure.[29,31,32] Indeed, cardiac output may actually decrease if the peripheral effects of glycosides augment peripheral resistance.[32] When the disease process is more advanced and clinical evidence of congestive heart failure is present, the increase in myocardial contractility produced by digitalis tends to improve cardiac performance.[9,28,33,34] During terminal stages of the disease, a similar increase in myocardial contractility may no longer be sufficient to improve cardiac performance in the presence of an excessive increase in afterload.[35,36] A beneficial effect of digitalis therapy on maximal oxygen uptake has yet to be demonstrated.

Catecholamines, and especially dobutamine, increase myocardial contractility and improve resting hemodynamics in patients with heart failure.[37–41] Dobutamine augments myocardial contractility by direct stimulation of myocardial beta-1 receptors, resulting in increased levels of intracellular cyclic AMP.[42] In patients with heart failure the amount of cyclic AMP generated after incubation of lymphocytes with isoproterenol has been shown to be lower than in normal subjects.[43] Whether myocardial beta-1 receptors are similarly altered and whether such alteration limits myocardial responsiveness to beta-1 stimulation is not yet known.

Dobutamine also stimulates beta-2 adrenoreceptors, which mediate vasodilatation in the peripheral vessels.[11] This nonspecific vasodilatation induced by dobutamine may have contributed to the increased cardiac output in our patients both at rest and during exercise. However, since our patients were unable to exercise longer, the circulation to the exercising muscles probably did not benefit from the increased cardiac output. This observation may be explained by the following reasoning. In humans vascular beta-2 adrenoreceptors are located in the precapillary sphincters,[44] and the site of beta-adrenergic stimulation is different from the site of nerve-mediated vasoconstriction.[45] During maximal exercise the local release of metabolites in active muscles completely dilates precapillary sphincters,[46] while neurally released norepinephrine does not stimulate beta-2 adrenoreceptors.[47,48] Thus stimulation of beta-2 adrenoreceptors by dobutamine cannot further increase vasodilatation and blood flow to exercising muscles. In contrast, precapillary sphincters in the mesenteric bed are not exposed to local metabolites during exercise and can therefore be dilated by administration of dobutamine. Consequently, mesenteric blood flow is increased by dobutamine at rest[49] and probably during exercise. This increase in blood flow to tissues metabolically less active than the exercising muscles would explain the decrease in systemic arteriovenous oxygen difference

noted in patients receiving dobutamine. Although not fully understood, a similar phenomenon has been observed in patients with heart failure after administration of vasodilating agents.[4,6,7,50]

In patients with heart failure both dyspnea, which is related in part to an excessive increase in left ventricular diastolic pressure, and fatigue, which is due to a limited increase in cardiac output, are thought to limit exercise. Our patients receiving dobutamine were unable to exercise longer despite a higher cardiac output and lower ventricular diastolic pressure. This suggests that the factor limiting exercise was not the elevated diastolic filling pressure but rather inadequate oxygen delivery and peripheral accumulation of metabolites, probably lactate, in the exercising muscles.[51] Although lactate concentrations in muscle were not measured in this study, blood lactate levels at the point of exhaustion were similar whether dobutamine was being infused or not. Lower blood lactate levels might have been anticipated during dobutamine infusion since the cardiac output was higher while the level of exercise was comparable to that of the control state. However, administration of dobutamine may have increased lactate production in the exercising muscles.[52]

## References


1. **Ross J Jr, Gault JH, Mason DT, Linhart JW, Braunwald E.** Left ventricular performance during muscular exercise in patients with and without cardiac dysfunction. Circulation 1966;34:597–608.
2. **Epstein SE, Beiser GD, Stampfer M, Robinson BF, Braunwald E.** Characterization of the circulatory response to maximal upright exercise in normal subjects and patients with heart disease. Circulation 1967;35: 1049–1062.
3. **Franciosa JA, Zeische S, Wilen M.** Functional capacity of patients with chronic left ventricular failure. Am J Med 1979;67:460–466.
4. **Rubin SA, Chatterjee K, Ports TA, Felberg HJ, Brundage BH, Parmley WW.** Influence of short-term oral hydralazine therapy on exercise hemodynamics in patients with severe chronic heart failure. Am J Cardiol 1979;44: 1183–1189.
5. **Moskowitz RM, Kinney EL, Zelis RF.** Hemodynamic and metabolic response to upright exercise in patients with congestive heart failure. Chest 1979; 76:640–646.
6. **Franciosa JA, Goldsmith SR, Cohn JN.** Contrasting immediate and long-term effects of isosorbide dinitrate on exercise in congestive heart failure. Am J Med 1980;69:559–566.
7. **Fitchett DH, Pathe M, Pardy R, Despas R.** Effect of vasodilator drugs on exercise performance in cardiac failure. Br Heart J 1980;44:215–220.
8. **Flaim SF, Weltzel RL, Zelis R.** Mechanism of action of nitroglycerin during exercise in a rat model of heart failure. Improvement of blood flow to the renal splanchnic and cutaneous beds. Circ Res 1981;49:458–468.
9. **Arnold SB, Byrd RC, Meister W, Melman K, Cheitlin MD, Brestow JD, Parmley WW, Chatterjee K.** Long-term digitalis therapy improves left ventricular function in heart failure. N Engl J Med 1980;303:1443–1448.
10. **Siskind SJ, Sonnenblick EH, Forman R, Scheuer J, LeJemtel TH.** Acute substantial benefit of inotropic therapy with amrinone on exercise hemodynamics and metabolism in severe congestive heart failure. Circulation 1981;64:966–972.
11. **Sonnenblick EH, Frishman WH, LeJemtel TH.** Dobutamine: a new synthetic cardioactive sympathetic amine. N Engl J Med 1979;300:17–22.
12. **Wilmore JH, Costill DL.** Adequacy of the Holdane transformation in the computation of exercise $VO_2$ in humans. J Appl Physiol 1973;35:85–89.
13. **Patterson JA, Naughton J, Pietras RJ, Gunnar RM.** Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. Am J Cardiol 1972;30:757–762.
14. **Goldstein RE, Beiser GD, Stampfer M, Epstein SE.** Impairment of autonomically mediated heart rate control in patients with cardiac dysfunction. Circ Res 1975;36:571–578.
15. **Harvey RM, Smith WM, Parker JO, Ferrer M.** The response of the abnormal heart to exercise. Circulation 1962;26:341–362.
16. **Gelberg HJ, Rubin SA, Ports TA, Brundage BH, Parmley WW, Chatterjee K.** Detection of left ventricular functional reserve by supine exercise hemodynamics in patients with severe chronic heart failure. Am J Cardiol 1979;44:1062–1067.
17. **Donald KW, Wormald PN, Taylor SH, Bishop JM.** Changes in the oxygen content of femoral venous blood and leg blood flow during leg exercise in relation to cardiac output response. Clin Sci 1957;16:567–591.
18. **Zelis R, Delea CS, Coleman HN, Mason DT.** Arterial sodium content in experimental congestive heart failure. Circulation 1970;41:213–216.
19. **Zelis R, Mason DT.** Diminished forearm arteriolar dilator capacity produced by mineralocorticord induced salt retention in man. Implications concerning congestive heart failure and vascular stiffness. Circulation 1970;41: 589–592.
20. **Zelis R, Lee G, Mason DT.** Influence of experimental edema of metabolically determined blood flow. Circ Res 1974;34:482–490.
21. **Zelis R, Flaim SF, Nellis S, Longhurst J, Moskowitz R.** Autonomic adjustments to congestive heart failure and their consequences. In: Fishman AP, ed. Heart Failure. Washington: Hemisphere Publishing, 1978:237–247.
22. **Hermanssen L, Wachtlava M.** Capillary density of skeletal muscle in well-trained and untrained men. J Appl Physiol 1971;30:860–863.
23. **Varnaurskas E, Bjorntrop P, Fahlen M, Prerovsky I, Stenberg J.** Effects of physical training on exercise blood flow and enzymatic activity in skeletal muscle. Cardiovasc Res 1970;4:418–422.
24. **Dyke SH, Urschel CW, Sonnenblick EH, Gorlin R, Cohn PF.** Detection of latent function in acutely ischemic myocardium in dogs: comparison of pharmacologic inotropic stimulation and post extra-systolic potentiation (PESP). Circ Res 1975;36:490–497.
25. **Braunwald E, Ross J Jr, Frommer PL, Williams JF, Sonnenblick EH, Gault JH.** Clinical observations on paired electrical stimulation of the heart. Effects on ventricular performance and heart rate. Am J Med 1964;37:700–711.
26. **Katz AM.** A new inotropic drug: its promise and a caution. N Engl J Med 1979;301:1193–1197.
27. **Hoeschen RJ, Cuddy TE.** Dose response relation between therapeutic levels of serum digoxin and systolic time intervals. Am J Cardiol 1975;35:469–472.
28. **Braunwald E, Bloodwell RD, Goldbert LI, Morrow AG.** Observations in man on the effects of digitalis preparations on the contractility of the nonfailing heart and on total vascular resistance. J Clin Invest 1961;40:52–59.
29. **Murphy GW, Schreiner BF, Bleakley PL, Yu PN.** Left ventricular performance following digitalization in patients with and without heart failure. Circulation 1964;30:358–369.
30. **Kleinman JH, Ingels NB, Daughters GO, Stinson EB, Alderman EL, Goldman RH.** Left ventricular dynamics during long-term digoxin treatment in patients with stable coronary artery disease. Am J Cardiol 1978;41: 937–942.
31. **Harvey RM, Ferrer MI, Cathcart RT, Alexander JK.** Some effects of digoxin on the heart and circulation in man, digoxin in enlarged hearts not in clinical congestive failure. Circulation 1951;4:366–377.
32. **Dresdale DT, Uyceoglu YZ, Michtom RJ, Schultz M, Lunger M.** Effect of lanatoside C on cardiovascular hemodynamics. Acute digitalizing doses in subjects with normal hearts and with heart disease without failure. Am J Cardiol 1959;4:88–99.
33. **Vogel R, Frischnecht J, Steele P.** Short- and long-term effects of digitalis on resting and post handgrip hemodynamics in patients with coronary artery disease. Am J Cardiol 1977;40:171–176.
34. **Ferrer IM, Conroy RJ, Harvey RM.** Some effects of digoxin upon the heart and circulation in man. Circulation 1960;21:373–385.
35. **Cohn K, Selzer A, Kersh ES, Karpman LS, Goldschlager N.** Variability of the hemodynamic responses to acute digitalization in chronic cardiac failure due to cardiomyopathy and coronary artery disease. Am J Cardiol 1975; 35:461–468.
36. **Firth BJ, Dehmer GJ, Corbett JR, Lewis SE, Parkey RW, Willerson JT.** Effect of chronic oral digoxin therapy on ventricular function at rest and peak exercise in patients with ischemic heart disease. Am J Cardiol 1980;46: 481–490.
37. **Akhtar N, Mikulic E, Cohn JN, Chandhry MH.** Hemodynamic effect of dobutamine in patients with severe heart failure. Am J Cardiol 1975;36: 202–205.
38. **Leier CV, Webel J, Bush CA.** The cardiovascular effects of the continuous infusion of dobutamine in patients with severe cardiac failure. Circulation 1977;56:468–472.
39. **Berkowitz C, McKeever L, Croke RP, Jacobs WR, Loeb HS, Gunnar RM.** Comparative responses to dobutamine and nitroprusside in patients with chronic low output cardiac failure. Circulation 1977;56:918–924.
40. **Mikulic E, Cohn JN, Franciosa JA.** Comparative hemodynamic effects of inotropic and vasodilator drugs in severe heart failure. Circulation 1977; 56:528–533.
41. **Willerson JY, Hutton I, Watson JT, Platt MR, Templeton GH.** Influence of dobutamine on regional myocardial blood flow and ventricular performance during acute and chronic myocardial ischemia in dogs. Circulation 1976; 53:828–833.
42. **Tuttle RR, Hillman CC, Toomey RE.** Differential $\beta$-adrenergic sensitivity of atrial and ventricular tissue assessed by chronotropic and inotropic and cyclic AMP responses to isoprenaline and dobutamine. Cardiovasc Res 1976;10:452–458.
43. **Thomas JA, Marks BH.** Plasma norepinephrine in congestive heart failure. Am J Cardiol 1978;41:233–243.
44. **Lindvall J, Hillman J.** Noradrenaline evoked beta-adrenergic dilatation of precapillary sphincters in skeletal muscle. Acta Physiol Scand 1978; 102:126–128.
45. **Cohen RA, Coffman JD.** $\beta$-adrenergic vasodilator mechanism in the finger. Circ Res 1981;49:1196–1201.
46. **Cobbold A, Folkow B, Kjellmer I, Mellander S.** Nervous and local chemical control of precapillary sphincters in skeletal muscle as measured by changes in filtration coefficient. Acta Physiol Scan 1963;57:180–192.
47. **Childsey CA, Harrison DC, Braunwald E.** Augmentation of the plasma norepinephrine response to exercise in patients with congestive heart failure. N Engl J Med 1962;267:650–654.
48. **Glick G, Epstein SE, Wechsler AS, Braunwald E.** Physiological differences between the effects of neuronally released and blood borne norepinephrine on beta-adrenergic receptors in the arterial bed of the dog. Circulation 1967;21:217–227.
49. **Ross G.** Effects of epinephrine and norepinephrine on the mesenteric circulation of the cat. Am J Physiol 1967;212:1037–1042.
50. **Rubin SA, Chatterjee K, Gelberg HJ, Ports TA, Brundage BH, Parmley WW.** Paradox of improved exercise but not resting hemodynamics with short-term prazosin in chronic heart failure. Am J Cardiol 1979;43:810–815.
51. **Karlsson J, Saltin B.** Lactate, ATP, and CP in working muscles during exhaustive exercise in man. J Appl Physiol 1970;29:598–602.
52. **Issekutz B Jr.** Role of beta-adrenergic receptors in mobilization of energy sources in exercising dogs. J Appl Physiol 1978;44:869–876.

# Quantitative Differences in the Hemodynamic Effects of Captopril and Nitroprusside in Severe Chronic Heart Failure

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**The hemodynamic effects of oral captopril and intravenous nitroprusside were compared in 15 patients with severe chronic congestive heart failure. At doses of both drugs titrated so as to produce similar decreases in systemic vascular resistance in each patient, nitroprusside produced substantially greater increases in cardiac index (+0.67 versus +0.31 liters/min/m$^2$, p <0.01) but smaller decreases in mean arterial pressure (−18.4 versus −11.0 mm Hg, p <0.01) than did captopril. This finding was due to a significant decrease in heart rate with captopril (−7 beats/min, p <0.01) which was not seen with nitroprusside, since changes in stroke volume index with both drugs were similar. Nitroprusside produced a decrease in pulmonary arteriolar resistance quantitatively similar to the decrease in systemic vascular resistance, but the decrease in pulmonary arteriolar resistance with captopril was not significant. Despite similar decreases in systemic resistance, captopril produced a greater decrease in left ventricular filling pressure (−10.2 versus −6.9 mm Hg, p <0.01) but a smaller decrease in mean right atrial pressure (−3.1 versus −5.3 mm Hg, p <0.01) than did nitroprusside.**

**Thus, captopril has actions independent of its systemic vasodilator effects which account for the quantitative differences observed in its hemodynamic responses compared with those of nitroprusside in patients with severe chronic heart failure. These differences support experimental evidence that angiotensin, in addition to its direct systemic arterial vasoconstrictor actions, exerts positive chronotropic effects and alters ventricular compliance but has minimal direct effects on the limb venous circulation and on the pulmonary vasculature.**

All vasodilator drugs used in the management of patients with severe chronic heart failure are thought to exert their beneficial hemodynamic and clinical effects by acting on the peripheral circulation and thereby altering the loadings conditions that modulate cardiac performance.[1] Although these drugs may also directly improve myocardial contractility, coronary blood flow, or ventricular compliance,[2–7] it is difficult to determine to what extent such effects contribute to the hemodynamic changes caused by their use in humans. This is largely because changes in ventricular performance produced by changes in loading conditions are qualitatively similar to those that might be expected to result from an improvement in contractility or compliance.

Captopril is an orally effective inhibitor of the angiotensin-converting enzyme[8] which produces substantial hemodynamic and clinical improvement in patients with severe chronic heart failure.[9–13] It differs from direct-acting vasodilator drugs in that it exerts its effects not by a direct agonist action on the peripheral vasculature, but by inhibiting the circulatory responses to the endogenous vasoconstrictor angiotensin.[1,8] Because its administration is accompanied by both increases in cardiac output and decreases in ventricular filling pressure, captopril has been thought by many investigators to produce balanced vasodilation of peripheral arteries and veins in a fashion similar to nitroprusside.[14] Limb plethysmographic studies, however, have failed to confirm that captopril has important effects on the limb peripheral circulation in patients with heart failure.[15] This suggests that captopril improves cardiac performance by acting on regional circulations other than those in the extremities[15] or through mechanisms that do not involve systemic vasodilation.[2]

We sought to investigate this hypothesis by comparing the central hemodynamic effects of captopril with those of nitroprusside in patients with severe heart failure. The differences we observed in the responses to these 2 drugs suggest that captopril exerts some of its effects by mechanisms independent of its vasodilator actions.

## Methods

**Patient population:** We evaluated 15 patients with severe chronic heart failure who had persistent dyspnea, fatigue, or both at rest or on minimal exertion despite optimal conventional therapy with digitalis and diuretic agents. They included 9 men and 6 women aged 29 to 83 years (mean 66). The cause of heart failure was ischemic cardiomyopathy in 6 patients, idiopathic or alcoholic cardiomyopathy in 8 patients,

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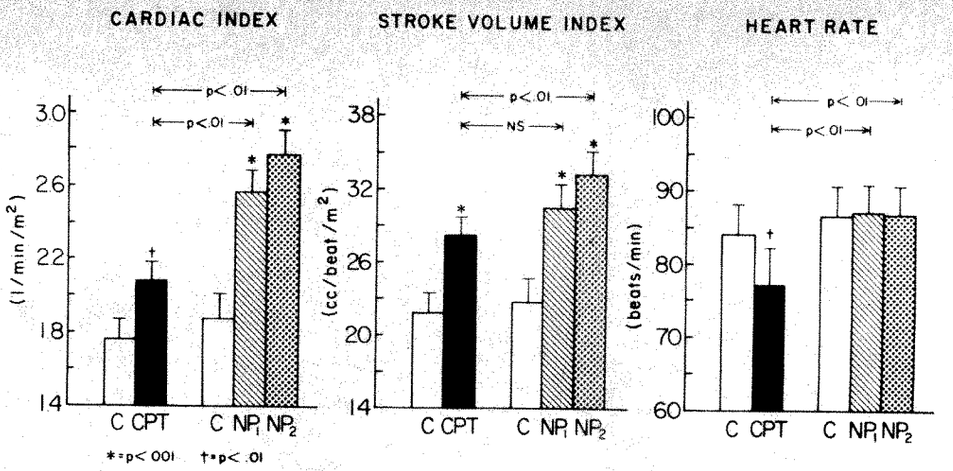



**FIGURE 1.** Changes in cardiac index, stroke volume index, and heart rate with captopril (CPT) and nitroprusside (NP), the latter titrated to 2 dose levels: $NP_1$, doses (104 μg/min) which produced captopril-like decreases in systemic vascular resistance, and $NP_2$, doses (180 μg/min) which produced captopril-like decreases in left ventricular filling pressure. All values are expressed as mean ± standard error of the mean. **Asterisks** and **daggers** represent significance of changes with each drug compared to its control values. P values above the bars represent significance of the hemodynamic changes with captopril compared with those produced by nitroprusside. C = control; NS = not significant.

and primary aortic valvular regurgitation with advanced ventricular dysfunction in 1 patient. The duration of heart failure was 11 months to 10 years. Normal sinus rhythm was present in 10 patients, atrial fibrillation in 4, and a ventricular pacemaker rhythm in 1.

**Hemodynamic measurements:** All patients were studied during a period of relative clinical stability. Bed rest was maintained, and all medications were withheld for 12 hours before evaluation. After written informed consent was obtained, right heart catheterization was performed with a triple-lumen flow-directed catheter for measurement of right atrial, pulmonary arterial, and pulmonary capillary wedge pressures. Arterial cannulas were inserted into the radial artery of all patients for measurement of systemic pressures. Measurements were made with zero reference level at the mid-axillary line with the patient in a supine position. Left ventricular filling pressure was measured as the mean pulmonary capillary wedge pressure. Thermodilution cardiac outputs were determined in triplicate by a bedside cardiac output computer with the use of iced injectate. Heart rates were derived from a continuously recorded electrocardiogram.

**Drug administration:** A protocol was designed to compare oral captopril with an intravenous infusion of nitroprusside titrated so as to achieve a similar reduction in systemic vascular resistance and left ventricular filling pressure in each patient under similar baseline hemodynamic conditions. Baseline determinations of the following variables were made repeatedly over 1 to 2 hours (with a variation <10%) before any drug intervention to ensure stability of the hemodynamic state: mean arterial pressure, heart rate, left ventricular filling pressure, mean pulmonary artery pressure, mean right atrial pressure, and cardiac output.

Each patient received both nitroprusside and captopril. Nine patients received nitroprusside first and captopril thereafter; the order was reversed in the other 6 patients. The administrations of the 2 drugs were separated by at least 24 hours.

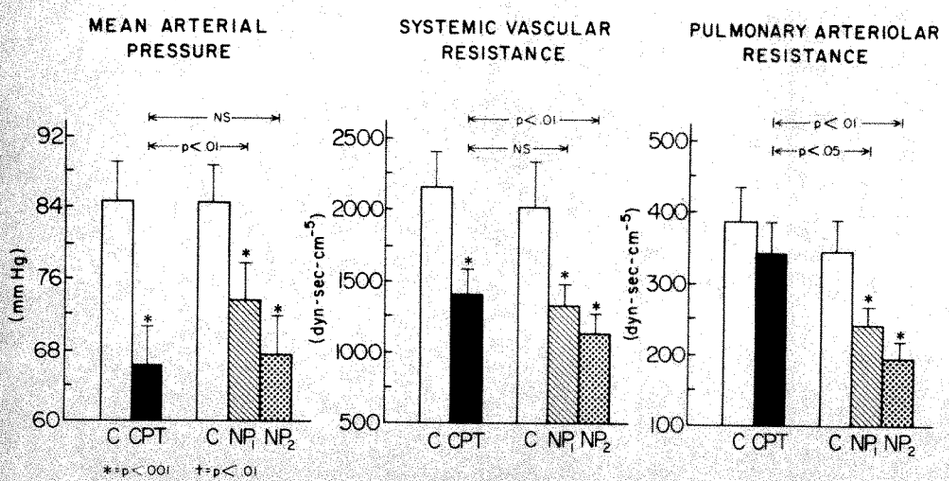



**FIGURE 2.** Changes in mean arterial pressure, systemic vascular resistance, and pulmonary arteriolar resistance with captopril (CPT) and nitroprusside (NP). Format and abbreviations as in Figure 1.

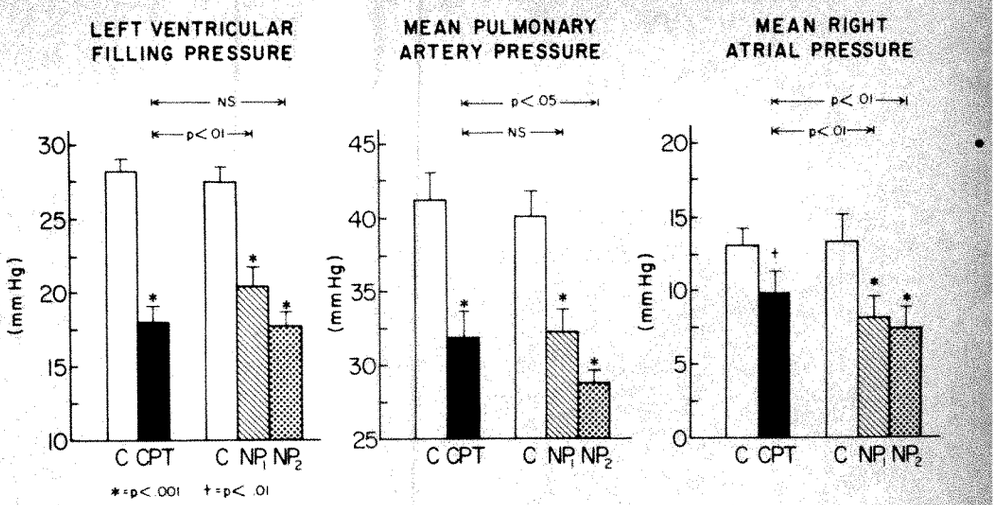



**FIGURE 3.** Changes in left ventricular filling pressure, mean pulmonary artery pressure, and mean right atrial pressure with captopril (CPT) and nitroprusside (NP). Format and abbreviations as in Figure 1.

Sodium nitroprusside was administered in a fashion similar to that previously described.[16] Briefly, 50 mg of the drug (Nipride®) was reconstituted in 250 ml of 5% dextrose in water and infused by peripheral vein at controlled rates determined by an IVAC 530 infusion pump apparatus. The infusion rate was initially 16 μg/min and was increased to 33, 67, 107, 213, and 330 μg/min with increments every 30 minutes; all hemodynamic variables were redetermined 20 minutes after each increment in the nitroprusside infusion. After the maximal dose of nitroprusside was infused, the drug was discontinued and hemodynamic variables were permitted to return to control values.

Captopril was administered as 25 mg orally. This dose was chosen because of its established effectiveness in previous evaluations of this agent.[9,11-13] After captopril administration, all hemodynamic variables were redetermined at 30-minute intervals for 3 hours.

**Data analysis:** Mean systemic and pulmonary artery pressures were determined by electronic filtration. Derived hemodynamic variables were calculated as follows: cardiac index (CI) = CO/body surface area (liter/min/$m^2$); stroke volume index (SVI) = CI/HR (ml/beat/$m^2$); systemic vascular resistance (SVR) = 80 × (MAP − MRAP)/CO (dynes s $cm^{-5}$); pulmonary arteriolar resistance (PAR) = 80 × (MPAP − LVFP)/CO (dynes s $cm^{-5}$), where CO denotes cardiac output, HR = heart rate, MAP = mean arterial pressure, MRAP = mean right atrial pressure, MPAP = mean pulmonary artery pressure, and LVFP = left ventricular filling pressure.

The hemodynamic responses at the time of maximal captopril effect (30 to 120 minutes after drug administration) were noted. The range of infused rates of nitroprusside was then examined retrospectively and 2 doses were selected for comparative analysis: (1) the dose of nitroprusside which produced a percent reduction in systemic vascular resistance in each patient of magnitude similar to that produced by captopril ($NP_1$), and (2) the dose of nitroprusside which produced a reduction in left ventricular filling pressure in each patient of magnitude similar to that produced by captopril ($NP_2$). The hemodynamic effects of each drug were compared to their respective control values by the *t* test for paired data. The magnitude of the hemodynamic responses to captopril and to both dose levels of nitroprusside were compared by analysis of variance; Duncan's multiple range test was used to differentiate among mean responses.[17] Group data are expressed as mean ± standard error of the mean.

## Results

The control hemodynamic variables before the administration of captopril and nitroprusside were similar. With both drugs, cardiac and stroke volume indexes increased in association with decreases in right and left ventricular filling pressures, in mean systemic and pulmonary arterial pressures, and in systemic vascular resistance ($p < 0.01$ or $p < 0.001$ for all variables). The hemodynamic responses to the administration of each drug are shown in Figures 1 to 3.

**Comparative responses at matched reductions in systemic resistance:** The doses of nitroprusside which produced decreases in systemic vascular resistance similar to those observed with captopril in each patient ranged from 16 to 330 μg/min (mean 104 ± 27). At this dose, nitroprusside produced substantial decreases in pulmonary arteriolar resistance as well ($p < 0.001$) and the magnitude of this effect was similar to that observed in the systemic circulation (−30 versus −34%, respectively). In contrast, captopril produced no significant decreases in pulmonary arteriolar resistance (−11%, $p > 0.10$), and the magnitude of the decrease in vascular resistance in the systemic circuit with captopril in each patient always exceeded that observed in the pulmonary circulation. The effects of nitroprusside and captopril on pulmonary arteriolar resistance differed significantly, $p < 0.01$.

Despite similar decreases in systemic vascular resistance with both drugs, nitroprusside produced significantly greater increases in cardiac index (+0.69 versus +0.31 liters/min/$m^2$, $p < 0.01$) and smaller decreases in mean arterial pressure (−11.0 versus −18.4 mm Hg, $p < 0.01$) than captopril. The smaller increase in cardiac index with captopril was associated with a decrease in heart rate (−7 beats/min, $p < 0.01$), whereas no significant changes in heart rate were observed with nitroprusside. Changes in stroke volume index with both drugs were similar (+7.9 ml/beat/$m^2$ with nitroprusside and +6.3 ml/beat/$m^2$ with captopril).

Despite similar decreases in systemic vascular resistance with both drugs, captopril produced substantially

greater decreases in left ventricular filling pressure (−10.2 mm Hg versus −6.9 mm Hg, $p < 0.01$) but significantly smaller decreases in mean right atrial pressure (−3.1 mm Hg versus −5.3 mm Hg, $p < 0.01$) than did nitroprusside. Changes in mean pulmonary artery pressure with both drugs were similar (−9.3 mm Hg with captopril and −8.0 mm Hg with nitroprusside).

**Comparative responses at matched reductions in left heart filling pressures:** The doses of nitroprusside which produced decreases in left ventricular filling pressures similar to those observed with captopril in each patient ranged from 67 to 330 μg/min (mean 180 ± 43), a dose significantly larger than that needed to produce captopril-like decreases in systemic vascular resistance ($p < 0.01$). As a result, these larger doses of nitroprusside produced significantly greater decreases in systemic vascular resistance than did captopril (−44 versus −34%, $p < 0.01$).

Despite this greater decrease in systemic resistance with nitroprusside, mean arterial pressure decreases similarly with both drugs; this reflected the substantially smaller increase in cardiac index with captopril than was seen with nitroprusside (+0.31 versus +0.90 liters/min/$m^2$, $p < 0.01$). The different effects on cardiac index were the result of both a decrease in heart rate seen with captopril (but not seen with nitroprusside) and a greater increase in stroke volume index with this higher dose of nitroprusside than was seen with captopril (+10.5 versus +6.3 ml/beat/$m^2$, respectively, $p < 0.01$).

Although (with these larger doses of nitroprusside) left ventricular filling pressure decreased similarly with both drugs, nitroprusside produced significantly greater decreases in mean right atrial pressure (−5.9 versus −3.1, $p < 0.01$) and in mean pulmonary artery pressure (−11.6 versus 9.3 mm Hg, $p < 0.01$) than did captopril.

## Discussion

The hemodynamic responses to captopril in our patients with severe chronic heart failure differed from those observed with nitroprusside with respect to 3 variables: (1) heart rate, (2) pulmonary arteriolar resistance, and (3) right and left ventricular filling pressures.

**Effects of captopril on heart rate:** Heart rate decreased significantly with captopril in our patients but did not change after the administration of nitroprusside. Hence, when doses of both drugs were matched so as to produce similar decreases in systemic vascular resistance, cardiac index increased less and mean arterial pressure decreased more with captopril than with nitroprusside. Although decreases in heart rate have been noted by other investigators after captopril administration to patients with heart failure,[11,13] such changes might have been a nonspecific effect of therapy, since heart rate frequently slows after the administration of any vasodilator drug that improves cardiac performance, and thereby leads to a withdrawal of reflex adrenergic activity.[18,19] In the present study, captopril and nitroprusside both produced marked improvements in stroke volume and left ventricular filling pressure, but a decrease in heart rate was observed only with captopril, and thus, must have been the consequence of a negative chronotropic effect of the drug independent of its peripheral vasodilator actions. Such effects are likely mediated by inhibition of the direct cardioaccelerating effects of angiotensin.[20,21]

When captopril is administered to hypertensive patients, the negative chronotropic effects of the drug are offset by baroreceptor-mediated reflex tachycardia, and thus little change in heart rate is observed.[22] In contrast, in patients with heart failure, autonomic reflexes are attenuated,[23] and thus the negative chronotropic actions of captopril are left unopposed and heart rate slows. A similar explanation has been proposed to account for the responses seen with the peripheral vasodilator drug, prazosin, which directly slows the sinus node.[24] Like captopril, prazosin produces no change in heart rate in hypertensive patients but may decrease heart rate in patients with heart failure; in doing so, prazosin produces relative changes in cardiac index, mean arterial pressure, and systemic vascular resistance similar to those observed in the present study with captopril.[16]

**Effects of captopril on pulmonary arteriolar resistance:** Captopril exerted minimal effects on pulmonary arteriolar resistance and right heart filling pressures in our patients with severe heart failure. This is consistent with experimental evidence that angiotensin has no direct effects on the pulmonary vasculature or the limb venous circulation,[25–28] and with clinical evidence that angiotensin inhibition produces little change in pulmonary vascular resistance[12,15,29–31] or systemic limb venous capacitance.[15,29] It is likely that both of these factors contribute to the modest decreases in mean right atrial pressure we observed with captopril, since right ventricular filling pressures are determined both by systemic venous return and by the impedance to right ventricular ejection. Accordingly, because of its marked effects on systemic limb venous capacitance and on pulmonary arteriolar resistance,[14] nitroprusside produced greater decreases in mean right atrial pressure than did captopril. The minimal effects of captopril on pulmonary arteriolar resistance may explain why arterial oxygen content does not decrease in patients with heart failure after converting-enzyme inhibition[32] but does decrease significantly with drugs that possess direct pulmonary vasodilating actions (such as nitroprusside).[33]

**Effects of captopril on ventricular filling pressures:** Despite *smaller* decreases in right heart filling pressures, captopril produced *greater* decreases in left ventricular filling pressure than did nitroprusside. This was an unexpected finding. Since captopril exerts minimal effects on systemic venous capacitance and right heart filling pressures, we would have expected a smaller decrease in central blood volume (volume of the circulation from the pulmonary valve to the aortic valve[34]) and hence in pulmonary capillary wedge pressure with captopril than with nitroprusside at doses matched to produce similar decreases in systemic vascular resistance. Even if we attributed the more modest decreases in mean right atrial pressure with captopril

entirely to its lesser reduction of right ventricular afterload (thus assuming that decreases in central blood volume with both drugs were similar), we would have anticipated that left heart filling pressure would have decreased similarly with captopril and nitroprusside. Our observation, however, that left ventricular filling pressure decreased *more* with captopril suggests that this drug must act to lower left heart pressure by a mechanism independent of changes in the peripheral arterial or venous circulations, possibly by a direct effect on pulmonary vascular compliance or by changing the pressure-volume relations in the left ventricle.[2] The latter hypothesis is supported by the work of Alderman and Glantz,[5] who noted that angiotensin shifts the pressure-volume relations of the human left ventricle so as to make the ventricle less compliant; antagonism of this shift by captopril could contribute to the marked decrease in left ventricular filling pressure we observed.

**Limitations of the study:** We tried to explain the observed differences between the effects of captopril and nitroprusside in our patients with severe heart failure by attributing to captopril actions opposite of those characteristic of angiotensin. However, since we only measured a limited number of central hemodynamic variables, our hypotheses are based on several assumptions. Although both drugs were titrated to produce similar decreases in systemic vascular resistance, direct measurements of ventricular afterload (wall stress and aortic impedance[35,36]) were not performed; if these loading variables were affected differently by nitroprusside and captopril, this might have contributed to some of the differences we observed between them. We attributed observed differences in the effects of the 2 drugs on left heart filling pressure to hypothesized differences in their effects on ventricular compliance; yet, we did not measure ventricular volumes, and we assumed that the effects of nitroprusside were entirely attributable to peripheral vasodilation. However, nitroprusside may also alter ventricular pressure-volume relations, although such effects appear quantitatively less marked than those exerted by angiotensin.[5] Finally, we assumed that observed differences in the effects of the 2 drugs on heart rate were the result of a direct negative chronotropic effect of captopril, but since both drugs affected right and left ventricular filling pressures differently, differences in degree of reflex stimulation of intracardiac mechanoreceptors[37] might also have accounted for the observed heart rate responses; captopril-induced decreases in heart rate may also be secondary to its effects on the sympathetic nervous system.[38] Further work needs to be done to confirm by direct measurement the hypotheses suggested by our observations.

**Clinical implications:** The differences we observed in the circulatory effects of captopril and nitroprusside in our patients with severe heart failure have important clinical implications. Although captopril's negative chronotropic effects could be clinically beneficial in patients with underlying coronary artery disease, the decrease in heart rate could potentiate the profound hypotension that is occasionally seen with initial doses of the drug[11,12]; indeed, the decreases in mean arterial pressure with captopril in heart failure patients are greater than those observed with most other vasodilator agents. Furthermore, patients with sick sinus syndrome may experience severe symptomatic bradycardias with the use of antihypertensive agents that possess direct negative chronotropic effects,[39] and caution should be exercised in the use of captopril in these patients. Of 54 patients with severe chronic heart failure that we have treated with captopril, 2 manifested asymptomatic but recurrent episodes of severe sinus bradycardia (heart rates <40 beats/min), which were shown to be directly attributable to treatment with the drug by rechallenge studies. Both patients had a history compatible with sick sinus syndrome before institution of captopril therapy.

Our findings that captopril has minimal effects on pulmonary arteriolar resistance also has clinical importance. The lack of a significant pulmonary vasodilator action suggests that captopril has limited usefulness in patients with marked impairment of right ventricular function, whereas most other systemic vasodilator drugs used in the management of heart failure possess marked effects on the pulmonary vasculature and can improve right heart performance.[40] As a result, the use of captopril should probably be avoided in patients with severe pulmonary vascular disease, regardless of whether it is structurally fixed or due to active vasoconstriction. In such patients, the failure of captopril to reduce transpulmonary resistances is likely to limit any increases in cardiac output that might otherwise be expected to accompany drug-induced systemic vasodilation, and this might result in profound systemic hypotension. This hypothesis requires further study.

**Conclusion:** Our comparative study of the responses to captopril and nitroprusside in patients with severe heart failure indicates that captopril exerts hemodynamic effects independent of its systemic vasodilator actions. These effects are consistent with the concept that the responses to captopril are mediated by inhibition of angiotensin, which has direct arterial vasoconstrictive and positive chronotropic actions and alters ventricular compliance, but has minimal direct effects on the limb venous circulation and on the pulmonary vasculature.

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## References

1. **Packer M, Le Jemtel TH.** Physiologic and pharmacologic determinants of vasodilator response: a conceptual framework for rational drug therapy for chronic heart failure. Prog Cardiovasc Dis 1982;24:275–292.
2. **Zelis R, Flaim SF, Moskowitz RM, Nellis SH.** How much can we expect from vasodilator therapy in congestive heart failure? Circulation 1979; 59:1092–1097.
3. **Khatri I, Uemura N, Notargiacom A, Freis E.** Direct and reflex cardiostimulatory effects on hydralazine. Am J Cardiol 1977;40:38–42.
4. **Leier CV, Desch CE, Magorien RD, Triffon DW, Unverferth DV, Boudoulas H, Lewis RP.** Positive inotropic effects of hydralazine in human subjects:

comparison with prazosin in the setting of congestive heart failure. Am J Cardiol 1980;46:1039–1044.
5. **Alderman EL, Glantz SA.** Acute hemodynamic interventions shift the diastolic pressure-volume curve in man. Circulation 1976;54:662–671.
6. **Brodie BR, Grossman W, Mann T, McLaurin LP.** Effects of sodium nitroprusside on left ventricular diastolic pressure-volume relations. J Clin Invest 1977;59:59–68.
7. **Cohn PF, Maddox D, Holman BL, Markis JE, Adams DF, See JR.** Effect of sublingually administered nitroglycerin on regional myocardial blood flow in patients with coronary artery disease. Am J Cardiol 1977;39:672–678.
8. **Ferguson RK, Turnini GA, Brunner HR, Gavras H.** A specific orally active inhibitor of angiotensin-converting enzyme in man. Lancet 1977;1:775–778.
9. **Davis R, Ribner HS, Keung E, Sonnenblick EH, Le Jemtel TH.** Treatment of chronic congestive heart failure with captopril, an oral inhibitor of angiotensin-converting enzyme. N Engl J Med 1979;301:117–121.
10. **Turnini GA, Brunner HR, Gribic M, Waeber B, Gavras H.** Improvement of chronic congestive heart failure by oral captopril. Lancet 1979;1:1213–1215.
11. **Ader R, Chatterjee K, Ports T, Brundage B, Hiramatsu B, Parmley W.** Immediate and sustained hemodynamic and clinical improvement in chronic heart failure by an oral angiotensin-converting enzyme inhibitor. Circulation 1980;61:931–937.
12. **Levine TB, Franciosa JA, Cohn JN.** Acute and long-term response to an oral converting-enzyme inhibitor, captopril, in congestive heart failure. Circulation 1980;62:35–41.
13. **Dzau VJ, Colucci WS, Williams GH, Curfman G, Meggs L, Hollenberg N.** Sustained effectiveness of converting-enzyme inhibition in patients with severe chronic heart failure. N Engl J Med 1980;302:1373–1379.
14. **Miller RR, Mason DT, Zelis R, Amsterdam EA, Mason DT.** Clinical use of sodium nitroprusside in chronic ischemic heart disease: effects on peripheral vascular resistance and venous tone and on ventricular volume, pump and mechanical performance. Circulation 1975;57:328–336.
15. **Faxon DP, Halperin JL, Creager MA, Gavras H, Schick EC, Ryan TJ.** Angiotensin inhibition in severe heart failure: acute central and limb hemodynamic effects of captopril with observations on sustained therapy. Am Heart J 1981;101:548–556.
16. **Packer M, Meller J, Gorlin R, Herman MV.** Differences in the hemodynamic effects of nitroprusside and prazosin in severe chronic heart failure. Evidence for a direct negative chronotropic effect of prazosin. Am J Cardiol 1979;44:310–317.
17. **Duncan DB.** T tests and intervals for comparisons suggested by the data. Biometrics 1975;31:339–359.
18. **Cohn JN, Taylor N, Vrobel T, Moskowitz R.** Contrasting effect of vasodilators on heart rate and plasma catecholamines in patients with hypertension and heart failure (abstr). Clin Res 1978;26:547A.
19. **Packer M, Meller J, Medina N, Yushak M, Gorlin R.** Determinants of drug response in severe chronic heart failure. I. Activation of vasoconstrictor forces during vasodilator therapy. Circulation 1981;64:506–514.
20. **Heyndrickx GR, Boettcher DH, Vatner SF.** Effects of angiotensin, vasopressin and methoxamine on cardiac function and blood flow distribution in conscious dogs. Am J Physiol 1976;231:1579–1587.
21. **Nishith SD, Davis LD, Youman WB.** Cardio-acceleration action of angiotensin. Am J Physiol 1962;202:237–240.
22. **Faggard R, Amery A, Reybrouck T, Lijnen P, Billiet L.** Acute and chronic systemic and pulmonary hemodynamic effects of angiotensin converting enzyme inhibition with captopril in hypertensive patients. Am J Cardiol 1980;46:295–300.
23. **Higgins CB, Vatner SF, Eckberg DL, Braunwald E.** Alterations in the baroreceptor reflex in conscious dogs with heart failure. J Clin Invest 1972;51:715–724.
24. **Schwartz KM, Urthaler F, James TN.** Direct effects of prazosin on the canine sinus node (abstr). Am J Cardiol 1981;47:389.
25. **Rose JC, Kot P, Cohn JN, Freis ED, Eckert GE.** Comparison of effects of angiotensin and norepinephrine on pulmonary circulation, systemic arteries and veins, and systemic vascular capacity in the dog. Circulation 1962; 25:247–252.
26. **DePasquale NP, Burch GE.** Effect of angiotensin II on the intact forearm veins of man. Circ Res 1963;13:239–245.
27. **Scroop GC, Walsh JA, Whelan RF.** A comparison of the effect of intra-arterial and intravenous infusions of angiotensin and noradrenaline on the circulation in man. Clin Sci 1965;29:315–320.
28. **Cohn JN.** Relationship of plasma volume changes to resistance and capacitance vessel effects of sympathomimetic amines and angiotensin in man. Clin Sci 1966;30:267–278.
29. **Faxon DP, Creager MA, Halperin JL, Gavras H, Coffman JD, Ryan TJ.** Central and peripheral hemodynamic effects of angiotensin inhibition in patients with refractory congestive heart failure. Circulation 1980;61: 925–930.
30. **Curtiss C, Cohn JN, Vrobel T, Franciosa JA.** Role of the renin-angiotensin system in the systemic vasoconstriction of chronic congestive heart failure. Circulation 1978;58:763–770.
31. **Gavras H, Faxon DP, Berkoben J, Brunner HR, Ryan TJ.** Angiotensin converting enzyme inhibition in patients with congestive heart failure. Circulation 1978;58:770–776.
32. **Vrobel TR, Cohn JN.** Comparative hemodynamic effects of converting enzyme inhibitor and sodium nitroprusside in severe heart failure. Am J Cardiol 1980;45:331–336.
33. **Moorkerjee S, Keighley J, Warren RA, Bowser MA, Obeid AT.** Hemodynamic, ventilatory and blood gas changes during infusion of sodium nitroferricyamide (nitroprusside): studies in patients with congestive heart failure. Chest 1977;72:273–278.
34. **Pouleur H, Covell JW, Ross J Jr.** Effects of nitroprusside on venous return and central blood volume in the absence and presence of acute heart failure. Circulation 1980;61:328–337.
35. **Pouleur H, Covell JW, Ross J Jr.** Effects of alteration of aortic input impedance on the force-velocity-length relationship in the intact canine heart. Circ Res 1979;45:126–136.
36. **Nichols WW, Pepine CJ.** Left ventricular afterload and aortic input impedance: implications of pulsatile blood flow. Prog Cardiovasc Dis 1982;24: 293–306.
37. **Mancia G, Shepard JT, Donald DE.** Role of cardiac, pulmonary and carotid mechanoreceptors in the control of hind-limb and renal circulation in dogs. Circ Res 1975;37:200–208.
38. **Clough DP, Collis MG, Conway J, Hatton R, Keddie JR.** Interaction of angiotensin-converting enzyme inhibitors with the function of the sympathetic nervous system. Am J Cardiol 1982;49:1410–1414.
39. **Scheinman MM, Strauss HC, Evans GT, Ryan C, Massie B. Wallace A.** Adverse effects of sympatholytic agents in patients with hypertension and sinus node dysfunction. Am J Med 1978;64:1013–1020.
40. **Colucci WS, Holman BL, Wynne J, et al.** Improved right ventricular function and reduced pulmonary vascular resistance during prazosin therapy of congestive heart failure. Am J Med 1981;71:75–80.

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Each packet (2.8 g) provides 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, and L-lysine monohydrochloride 0.913 g.

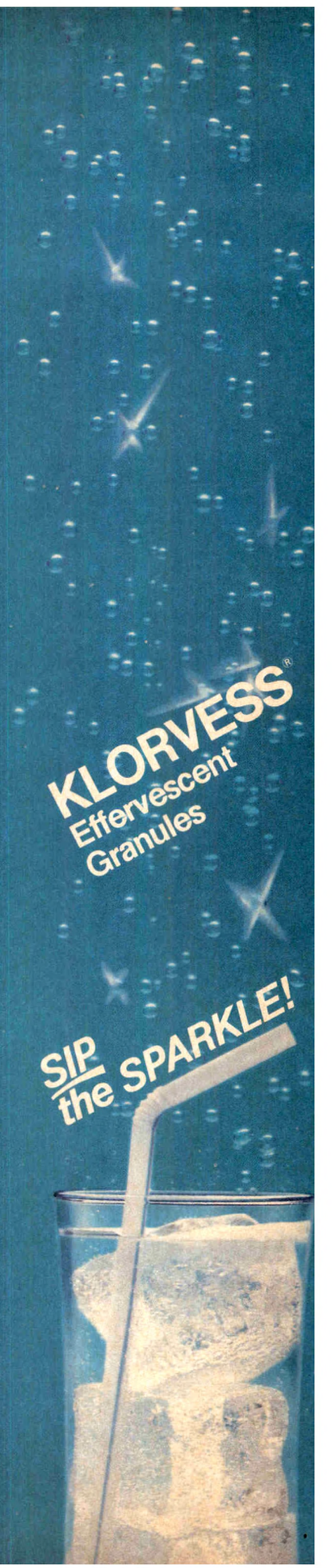
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Please see brief summary of prescribing information on adjoining page.

KLR-582-1



# Give your patients the KLORVESS® sparkle

## Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

*Brief summary of prescribing information*

**DESCRIPTION:** *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

*Klorvess (potassium chloride) 10% Liquid:* Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

**INDICATIONS:** For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

**CONTRAINDICATIONS:** Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

**PRECAUTIONS:** In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

**ADVERSE REACTIONS:** Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

**DOSAGE AND ADMINISTRATION:** *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

*Klorvess (potassium chloride) 10% Liquid:* Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

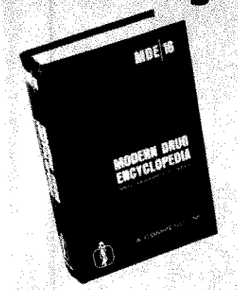
**OVERDOSAGE:** Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

**HOW SUPPLIED:** *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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# Announcing NEW cardizem™ (diltiazem HCl)



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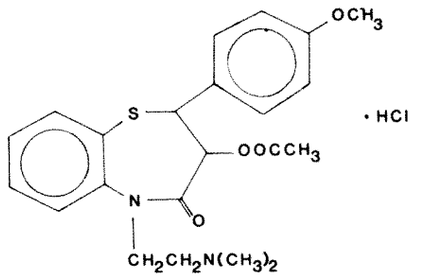
# PROFESSIONAL USE INFORMATION

## cardizem™ (diltiazem HCl)

**30 mg and 60 mg tablets**

## DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-,monohydrochloride,(+) -cis-. The chemical structure is:




Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

## CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

**Mechanism of Action.** Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

**Hemodynamic and Electrophysiologic Effects.** Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

**Pharmacokinetics and Metabolism.** Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels 2 to 3 hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

## INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

## CONTRAINDICATIONS

CARDIZEM is contraindicated in 1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, 2) patients with second- or third-degree AV block, and 3) patients with hypotension (less than 90 mm Hg systolic).

## WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

No other similar liver injury has been reported in clinical trials, but marketing experience in l resulted in a rechallenge confirmed instance of hepatocellular injury. However, it should be noted have been further episodes of raised transaminases in the absence of diltiazem in this patient, relationship to diltiazem of the abnormalities is not completely clear. Other instances of tra elevation have been reported in Europe, but their relationship to drug is uncertain.

## PRECAUTIONS

**General.** CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. A new drug given over prolonged periods, laboratory parameters should be monitored at regular interval should be used with caution in patients with impaired renal or hepatic function. In subacute and chron rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also with hepatic changes; however, these changes were reversible with continued dosing.

**Drug Interaction.** Pharmacologic studies indicate that there may be additive effects in prolonging AV when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-l digitalis is currently being investigated in well-controlled studies.

**Carcinogenesis, Mutagenesis, Impairment of Fertility.** A 24-month study in rats and a 21-month st showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial intrinsic effect on fertility was observed in rats.

**Pregnancy.** Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Adm of doses ranging from 5 to 10 times greater (on a mg/kg basis) than the daily recommended therapeuti resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cau abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup w survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant wor the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers.** It is not known whether this drug is excreted in human milk. Because many excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if benefits are thought to outweigh its potential risks in this situation.

**Pediatric Use.** Safety and effectiveness in children have not been established.

## ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized th with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZE was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relat CARDIZEM has not been established. The most common occurrences, as well as their frequency of pre are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), a (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of pr corresponds to the relative frequency of occurrence.

| | |
|---|---|
| Cardiovascular: | Flushing, congestive heart failure, bradycardia, hypotension, syncope, heart |
| Central Nervous System: | Drowsiness, dizziness, lightheadedness, nervousness, depression, wea somnia, confusion, hallucinations |
| Gastrointestinal: | Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis |
| Dermatologic: | Pruritus, petechiae, urticaria |
| Other: | Photosensitivity, nocturia, thirst, paresthesia, polyuria, osteoarticular p |

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes asso symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued an normalized within 1 week.

## OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, a supportive measures should be employed in addition to gastric lavage. The following measure considered:

| | |
|---|---|
| Bradycardia | Administer atropine (0.60 to 1.0 mg). If there is no response to vagal administer isoproterenol cautiously. |
| High-Degree AV Block | Treat as for bradycardia above. Fixed high-degree AV block should be tr cardiac pacing. |
| Cardiac Failure | Administer inotropic agents (isoproterenol, dopamine or dobutamine) and |
| Hypotension | Vasopressors (eg, dopamine or levarterenol bitartrate). |

Actual treatment and dosage should depend on the severity of the clinical situation and the judg experience of the treating physician.

The oral $LD_{50}$'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respec intravenous $LD_{50}$'s in these species were 60 and 38 mg/kg, respectively. The oral $LD_{50}$ in dogs is consic in excess of 50 mg/kg while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not k blood levels in excess of 800 ng/ml have not been associated with toxicity.

## DOSAGE AND ADMINISTRATION

**Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at R Coronary Artery Spasm.** Dosage must be adjusted to each patient's needs. Starting with 30 mg four ti before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses th times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and dosages exceeding 240 mg per day are currently being investigated. There are no available data concerni requirements in patients with impaired renal or hepatic function. If the drug must be used in such patient should be carried out with particular caution.

**Concomitant Use With Other Antianginal Agents.**

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM the
2. **Prophylactic Nitrate Therapy** — CARDIZEM may be safely co-administered with short- and l nitrates, but there have been no controlled studies to evaluate the antianginal effectivene combination.
3. **Beta-blockers** (See WARNINGS and PRECAUTIONS).

## HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is eng MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the

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# Relation of Electrocardiographic Abnormalities and Patterns of Left Ventricular Hypertrophy Identified by 2-Dimensional Echocardiography in Patients With Hypertrophic Cardiomyopathy

BARRY J. MARON, MD, JAMES K. WOLFSON, ELISABETTA CIRÓ, MD, and PAOLO SPIRITO, MD

**Distribution of left ventricular (LV) hypertrophy was assessed by wide-angle, 2-dimensional (2-D) echocardiography in 153 patients with hypertrophic cardiomyopathy and compared with the scalar electrocardiogram in the same patients. The most common electrocardiographic alterations were S-T segment changes and T-wave inversion (61%), LV hypertrophy (47%), abnormal Q waves (25%), and left atrial enlargement (24%). LV hypertrophy on the electrocardiogram was significantly more common in patients with the most extensive distribution of LV hypertrophy on 2-D echocardiogram involving substantial portions of both the ventricular septum and LV free wall (type III; 51 of 69, 74%) than in those with more limited distribution of LV hypertrophy (21 of 84, 25%; $p < 0.001$). Most patients with hypertrophic cardiomyopathy and *normal* electrocardiograms (13 of 23) had localized (type I) hypertrophy, but only 4 had the extensive type III pattern of hypertrophy.**

**Abnormal Q waves were significantly more common in those patients without hypertrophy of the anterior, basal septum (type IV; 15 of 27, 56%) than in those with basal septal hypertrophy (23 of 126, 18%; $p < 0.001$); abnormal Q waves were uncommon in extensive type III distribution of hypertrophy (13 of 69, 19%).**

**Thus, although no single electrocardiographic abnormality is characteristic of hypertrophic cardiomyopathy, 2-D echocardiography clarifies the significance of certain electrocardiographic patterns: (1) LV hypertrophy on the electrocardiogram, although present in only about half of the study group, was a relatively sensitive (74%) marker for extensive (type III) LV hypertrophy; (2) abnormal Q waves cannot be explained by ventricular septal hypertrophy alone; and (3) a normal electrocardiogram was most commonly a manifestation of localized LV hypertrophy.**

A variety of abnormalities may be present in the 12-lead electrocardiogram in patients with hypertrophic cardiomyopathy.[1–5] Electrocardiographic changes in such patients have been reported to show little relation to the morphologic and functional changes identified by M-mode echocardiography.[2–5] Recent studies with wide-angle, 2-D echocardiography in patients with hypertrophic cardiomyopathy[6,7] have demonstrated a variety of patterns of distribution of hypertrophy, not appreciated by M-mode echocardiography alone. Hence, we examined the relation between the extent and distribution of LV hypertrophy assessed by 2-D echocardiography and abnormalities on the 12-lead electrocardiogram in a large group of patients with hypertrophic cardiomyopathy, in an attempt to clarify the significance of electrocardiographic patterns in this disease.

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## Selection of Patients

Between February and November 1979, 186 patients with a diagnosis or a suspected diagnosis of hypertrophic cardiomyopathy (by virtue of personal or family history, physical examination, or M-mode echocardiographic or hemodynamic and angiographic studies) at the National Heart, Lung, and Blood Institute were studied with 2-D echocardiography. Of the 186 patients, 125 were selected for the study group because they were considered to have undergone technically satisfactory

2-D echocardiographic examination; that is, there was acceptable recognition of the endocardial and epicardial borders of the LV free wall, and delineation of the boundaries of the ventricular septum was obtained in at least the short- and long-axis views.[6] In addition, 28 other patients with hypertrophic cardiomyopathy not surgically treated and with a technically satisfactory 2-D echocardiogram were added to the study group: (1) 13 patients in the 2 echocardiographically defined morphologic groups[6,7] with the smallest number of patients (types I and IV as described later) evaluated after November 1979; and (2) 15 patients with no abnormality on any recorded 12-lead electrocardiogram. These 15 patients and 9 others with a normal electrocardiogram (who are included in the consecutive group of 125 patients just described) constitute the total number of 24 patients with hypertrophic cardiomyopathy and a normal electrocardiogram evaluated at the National Heart, Lung, and Blood Institute.

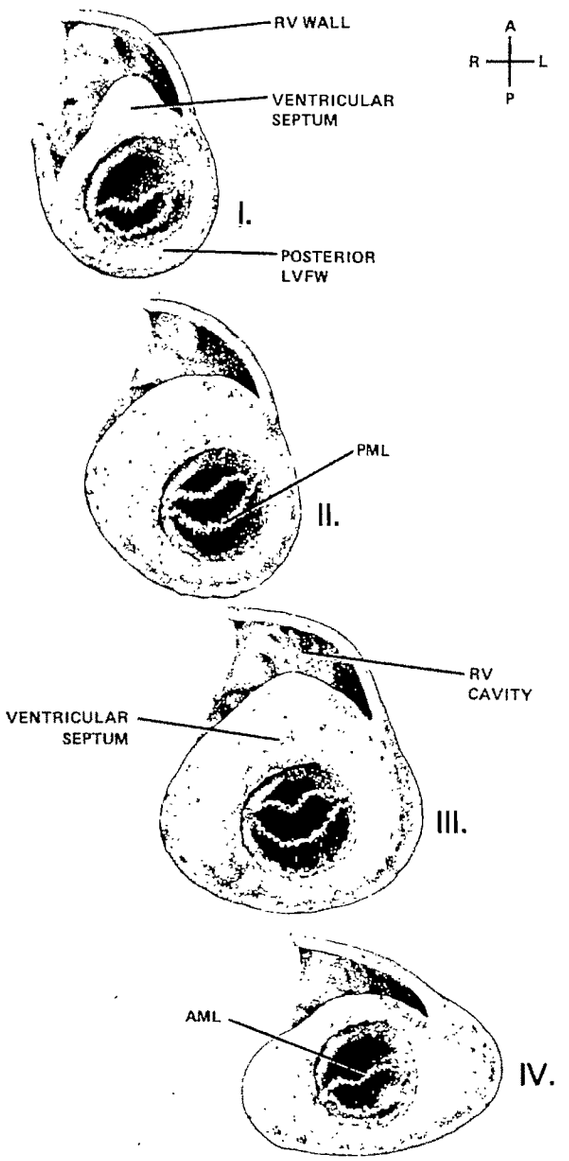



**FIGURE 1.** Artistic representation of the 4 patterns of hypertrophy identified by wide-angle 2-D echocardiography in 153 patients with hypertrophic cardiomyopathy. Shown only in cross-sectional (short-axis) planes at the level of the mitral valve. A = anterior; AML = anterior mitral leaflet; L = (patient's) left; LVFW = left ventricular free wall; P = posterior; PML = posterior mitral leaflet; R = (patient's) right; RV = right ventricular.

Hence, 153 patients with hypertrophic cardiomyopathy comprised the overall study group. In these patients, the diagnosis of hypertrophic cardiomyopathy was established with either M-mode or 2-D echocardiography by the demonstration of a nondilated, hypertrophied left ventricle in the absence of another cardiac or systemic disease which itself could produce left ventricular hypertrophy.[8] Specifically, no study patient was known to have coronary heart disease, systemic hypertension, or valvular heart disease.

## Characterization of Patients

The 153 study patients ranged in age from 5 to 69 years (mean 36). Ninety patients (59%) were male and 63 (41%) were female. Of the 153 patients, 48 (31%) had no functional limitation (New York Heart Association class I[9]), 41 (27%) had mild symptoms (functional class II), and 64 (42%) had moderate to severe functional limitation (classes III and IV).

The magnitude of LV outflow tract obstruction under basal conditions was assessed at cardiac catheterization (97 patients) or was estimated from the M-mode echocardiogram based on the magnitude and duration of systolic anterior motion of the anterior mitral leaflet (56 patients).[10] Outflow obstruction (gradient ≥30 mm Hg) was present at rest in 51 patients and was minimal (<30 mm Hg) or absent in the other 102 patients. Ninety-five of the 153 patients were taking cardioactive medication at the time of electrocardiographic study, including 66 receiving propranolol, 14 verapamil, 9 digitalis, and 6 quinidine.

## Methods

**M-mode echocardiography:** M-mode echocardiography was performed with use of a 2.25 MHz, 1.25 cm diameter unfocused Aerotech transducer and a Hoffrel 201 ultrasonic receiver interfaced with a Honeywell 1856 strip chart recorder. The methods utilized for imaging the ventricular septum and posterior LV free wall have previously been described.[11] Maximal thickness of the ventricular septum was measured just before atrial systole with the ultrasonic beam directed through or slightly below the caudal margins of the mitral leaflets. Thickness of the posterior LV free wall was measured during the same phase of the cardiac cycle, with the ultrasonic beam passing through the mitral leaflet tips.

**Two-dimensional echocardiography:** A Varian (V-3400) real-time, phased-array, 80° ultrasonic sector scanner with hand-held 2.25 MHz transducer was used to perform 2-D echocardiographic studies. The 2-D echocardiographic examination included the imaging of a number of cross-sectional planes through the heart. Serial short-axis views of the left ventricle were obtained by initially orienting the sector plane perpendicular to the long axis of the left ventricle from a standard transducer placement on the chest. The "short-axis sweep" was performed by maintaining the transducer in a fixed location on the chest wall and slowly angling the image plane from aorta (cephalad) to apex (caudad).[12] However, in the short-axis view, ultrasonic beam angulation from a single fixed transducer location prohibits imaging multiple cross-

sectional planes that are truly perpendicular to the cephalad-caudad axis. The apical portions of the anterior regions of the LV wall (that is, the anterior ventricular septum and anterior free wall) that are not well visualized in the short-axis plane are, however, often visualized in the long-axis and apical views.

The long-axis view was obtained by orienting the sector plane 90° to the short-axis plane and parallel to the longitudinal axis of the left ventricle, taking care to avoid improper angulation of the scan plane tangentially through the ventricle. The apical 4-chamber view was obtained with the transducer placed at the cardiac apex and the tomographic plane directed perpendicular to the ventricular and atrial septa and through the plane of the mitral and tricuspid valve orifices to permit simultaneous display of both atria and ventricles, atrioventricular valves, and cardiac septa.[13]

The location of regions of hypertrophy was identified in 2 cross-sectional planes according to previously described criteria.[6,7] In the anteroposterior plane, hypertrophy was designated as involving either the ventricular septum or the LV free wall. The ventricular septum was divided into 2 approximately equal-sized segments: anterior and posterior. The LV free wall was divided into 3 segments: the anterior, lateral, and posterior. In the cephalad-caudad plane the left ventricle was divided into 2 segments: the basal portion that extends from cardiac base to the inferior margins of the mitral leaflets, and the apical portion which included that portion of the left ventricle imaged caudal to the mitral leaflets.

**Echocardiographic classification of morphologic types:** Four basic patterns of distribution of LV hypertrophy were identified by 2-D echocardiography in the study patients. This classification has previously been described in detail,[6] but for the purposes of this study is also described briefly here.

In *type I* hypertrophy was confined to the anterior segment of the ventricular septum, usually the basal region alone but often both the basal and apical portions; the LV free wall and posterior portion of ventricular septum appeared essentially normal. In *type II*, hypertrophy involved both the anterior and posterior segments of the ventricular septum; the left ventricular free wall appeared essentially normal. In *type III*, hypertrophy involved substantial portions of both the ventricular septum and anterolateral LV free wall; the predominant region of hypertrophy was usually in the anterior or posterior segment of the ventricular septum, and often the only region of the LV wall free of hypertrophy was the posterior free wall. In *type IV*, hypertrophy involved regions of the LV wall, other than the anterior basal ventricular septum, that is, the posterior segment of the septum, anterolateral free wall, or the ventricular septum in its apical half. In each patient with type IV, M-mode echocardiography failed to show evidence of hypertrophy because LV wall thickening was situated in regions of the left ventricle that were inaccessible to the path of the conventional M-mode ultrasonic beam. However, 2-D echocardiography did permit identification of these regions of LV hypertrophy not visualized by M-mode echocardiography.[7] Patients with type IV hypertrophy were usually suspected clinically of having hypertrophic cardiomyopathy because of a distinctly abnormal scalar electrocardiogram (which most often showed deep Q waves, T-wave inversion, or right ventricular hypertrophy) and a family history of hypertrophic cardiomyopathy.

**Electrocardiographic procedure and criteria:** Standard 12-lead electrocardiography was performed with patients in the supine position during quiet respiration. Either a Sanborn heat-sensitive paper or a Marquette ink-writer electrocardiographic machine was used. The electrocardiogram was recorded on the same day the 2-D echocardiogram was performed in 122 (80%) of the patients, within 1 week of the echocardiogram in 15 (10%) other patients, within 5 months in 13 patients (8%), and within 12 or 18 months in the remaining 3 patients (2%).

The electrocardiograms were interpreted using criteria similar to those previously described in detail,[4] but with certain modifications. In particular, LV hypertrophy was diagnosed using the point-score system of Romhilt and Estes[14] for patients over 16 years of age; 5 or more points were considered indicative of LV hypertrophy. For the 22 study patients under 16 years of age, the criteria of Davignon et al,[15] Liebman and Plonsey,[16] and Cassels and Ziegler[17] were used.

Q or QS waves were considered abnormal if they were ≥0.04 second in duration or ≥3 mm deep, and were present in ≥2 leads. Q or QS waves present only in leads $V_1$ and $V_2$ were not considered abnormal. S-T segment and T-wave alterations that were judged secondary effects of digitalis administration were not tabulated as true abnormalities. Patterns suggestive of right ventricular hypertrophy were rightward mean QRS axis in the frontal plane (between +110° and +180°) or an R/S ratio ≥1 in lead $V_1$.

**Statistical analyses:** When appropriate, Student's *t* test or the chi-square test was used to assess statistical significance.

**TABLE I Electrocardiographic Abnormalities and Their Relation to the Distribution of Left Ventricular Hypertrophy (LVH) in 153 Patients With Hypertrophic Cardiomyopathy**

| Morphologic Type* | Patients | Electrocardiographic Abnormalities | | | | | | | | Normal ECG |
|---|---|---|---|---|---|---|---|---|---|---|
| | | LVH | RVH | Abn Q | ST-T Abn | LAE | RAE | AF | Conduction Abnormality† | |
| I | 33 | 7 (21%) | 1 (3%) | 4 (12%) | 12 (36%) | 4 (12%) | 1 (3%) | 2 (6%) | 7 (21%) | 13 |
| II | 24 | 9 (38%) | 0 (0%) | 6 (25%) | 17 (71%) | 2 (8%) | 2 (8%) | 1 (4%) | 6 (25%) | 3 |
| III | 69 | 51 (74%)‡ | 0 (0%) | 13 (19%) | 48 (70%) | 27 (39%)¶ | 7 (10%) | 4 (6%) | 16 (23%) | 4 |
| IV | 27 | 5 (19%) | 5 (19%)§ | 15 (56%)‖ | 16 (59%) | 3 (11%) | 3 (11%) | 0 (0%) | 3 (11%) | 3 |
| Total | 153 | 72 (47%) | 6 (4%) | 38 (25%) | 93 (61%) | 36 (24%) | 13 (8%) | 7 (5%) | 32 (21%) | 23 |

* As assessed by 2-D echocardiography.

† Includes patients with left-axis deviation, intraventricular conduction defect, left anterior hemiblock, left bundle branch block, first-degree atrioventricular block, right bundle branch block, and right ventricular conduction abnormality.

‡ Prevalence of LVH in type III is significantly greater than for each other morphologic type individually and in combination ($p < 0.005$).

§ Prevalence of RVH in type IV is significantly greater than for all other morphologic types combined and for type III individually ($p < 0.005$).

‖ Prevalence of abnormal Q waves in type IV is significantly greater than for all other morphologic types combined and for types I and III individually ($p < 0.001$).

¶ Prevalence of left atrial enlargement in type III is significantly greater than for all other morphologic types combined ($p < 0.001$) and types I, II, and IV individually ($p < 0.025$).

Abn = abnormal; AF = atrial fibrillation; ECG = electrocardiogram; LAE = left atrial enlargement; RAE = right atrial enlargement; LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy; ST-T = S-T segment and T wave.

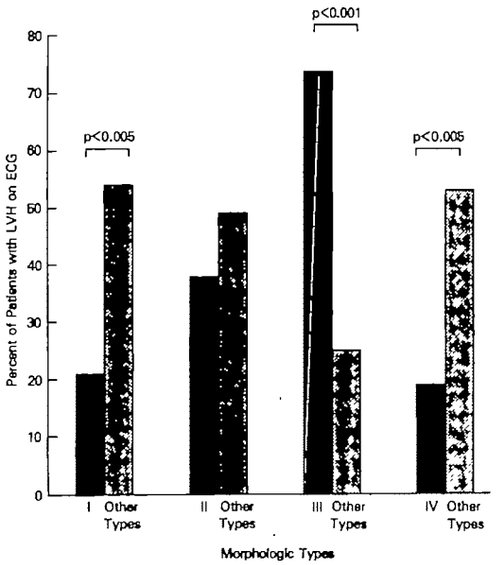



**FIGURE 2.** Prevalence of left ventricular hypertrophy (LVH) on electrocardiography (ECG) in the 4 morphologic types identified by 2-D echocardiography in 153 patients with hypertrophic cardiomyopathy.

## Results

**Electrocardiography:** Twelve-lead electrocardiograms were abnormal in 130 patients (85%). A wide variety of electrocardiographic abnormalities were present, although no particular pattern was characteristic of the study group (Table I). The most common abnormalities were S-T segment changes or T-wave inversion (93 patients, 61%), or both, LV hypertrophy (72 patients, 47%, including 36 patients with "strain" pattern), Q waves (38 patients, 25%), and left atrial enlargement (36 patients, 24%). Patients with obstruction to LV outflow under basal conditions more commonly demonstrated LV hypertrophy on electrocardiography (38 of 51, 75%) than did patients without obstruction to outflow (34 of 102, 33%; $p < 0.001$).

**M-mode echocardiography:** Ventricular septal thicknesses ranged from 6 to 41 mm (mean 21); posterior LV free wall thickness ranged from 6 to 17 mm (mean 12). In 123 patients (80%) the septal to free wall thickness ratio was $\geq 1.3$, meeting our criterion for asymmetric septal hypertrophy.[10] Concentric (symmetric) LV wall thickening (septal-free wall thickness ratio $< 1.3$) was present in 3 (2%) of the patients; the remaining 27 patients (18%) had both normal septal-free wall ratio and ventricular wall thicknesses.[7] Ventricular septal thickness, posterior free wall thickness, and septal-free wall thickness ratio were significantly greater in patients with LV hypertrophy on electrocardiography ($24 \pm 0.8$ mm, $13 \pm 0.3$ mm, and $1.9 \pm 0.1$, respectively) than in patients without LV hypertrophy on electrocardiography ($18 \pm 0.8$ mm, $12 \pm 0.3$ mm, $1.5 \pm 0.5$; $p < 0.005$).

**Two-dimensional echocardiography:** Four patterns of distribution of LV hypertrophy were identified.[6] The largest subgroup of patients (69 of 153, 45%) showed extensive hypertrophy involving substantial portions of both ventricular septum and anterolateral LV free wall (that is, type III) (Fig. 1). Thirty-three other patients had hypertrophy localized to only the

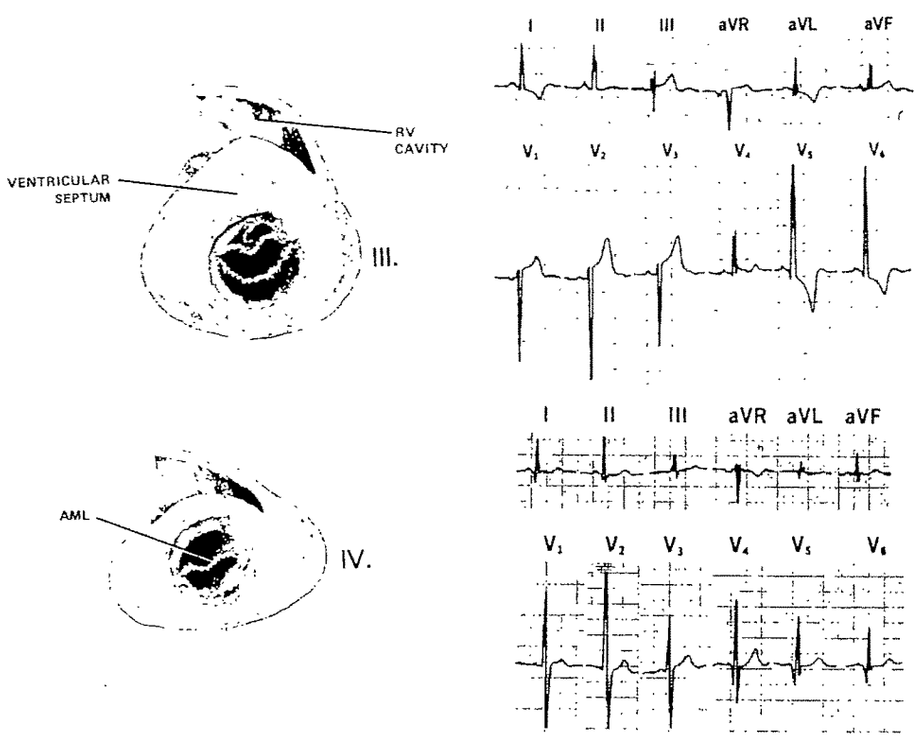



**FIGURE 3.** Typical electrocardiographic patterns that occur in patients with morphologic types III and IV. **Top,** electrocardiogram in a patient with morphologic type III showing LV hypertrophy with a "strain" pattern as well as T-wave abnormalities in standard leads. **Bottom,** electrocardiogram in a patient with morphologic type IV showing deep Q waves in the left precordial leads and a pattern consistent with right ventricular hypertrophy in the right precordial leads. AML = anterior mitral leaflet; RV = right ventricular.

anterior (and usually basal) portion of ventricular septum (type I); in these patients the LV free wall and other portions of the ventricular septum did not appear thickened. Twenty-four patients had substantial hypertrophy involving most or all of the ventricular septum (type II); the LV free wall did not appear thickened. The remaining 27 patients had unusually located regions of hypertrophy involving portions of the left ventricle other than the anterobasal ventricular septum (usually the posterior segment of septum, anterolateral free wall, or septum in the apical region (type IV). Conventional M-mode echocardiography failed to show evidence of hypertrophy in the latter patients since the M-mode beam could not traverse those regions of the LV wall that were thickened, and hence the diagnosis of hypertrophic cardiomyopathy could be established only by 2-D echocardiography.[7]

**Relation of electrocardiographic and 2-D echocardiographic abnormalities:** The electrocardiographic diagnosis of LV hypertrophy was present in patients with each of the 4 patterns of hypertrophy identified by 2-D echocardiography. However, left ventricular hypertrophy on electrocardiography was significantly more common in patients with morphologic type III (51 of 69, 74%) than in each of the other 3 morphologic types individually or in combination (21 of 84, 25%; $p < 0.001$; Fig. 2 and 3). In addition, left atrial enlargement (27 of 69, 39%) was significantly more common in patients with type III than in all other morphologic types (9 of 84, 11%; $p < 0.001$).

Abnormal Q waves were significantly more common in patients with morphologic type IV (15 of 27, 56%) than in patients with the other 3 types combined (23 of 126, 18%; $p < 0.001$; Fig. 3 and 4). Of the 15 patients with type IV and Q waves in the electrocardiogram, LV hypertrophy was present either in the anterolateral free wall (8 patients), the posterior segment of the septum (1 patient), both the posterior septum and anterolateral free wall (5 patients), or the ventricular septum in its apical portion (1 patient). Abnormal Q waves were uncommon in patients with extensive type III distribution of hypertrophy (13 of 69, 19%).

The electrocardiographic pattern of right ventricular hypertrophy was uncommon (6 of 153 patients, 4%), but occurred almost exclusively in the patients with type IV distribution of hypertrophy (5 of 27, 19%; $p < 0.005$) (Fig. 3). Right atrial enlargement, atrial fibrillation, and conduction abnormalities in the electrocardiogram did not show a statistically significant predilection for any of the morphologic types identified by 2-D echocardiography.

**Patients with normal electrocardiograms:** The subgroup of 23 patients with hypertrophic cardiomyopathy and normal electrocardiogram included at least 1 patient with each pattern of LV hypertrophy. Type I, which was the most common morphologic pattern, occurred in 13 patients; 3 patients had type II, 4 had type III, and 3 had type IV (Fig. 5). Hence, the prevalence of a normal electrocardiogram in patients with type I (13 of 33, 39%) was significantly greater than in the other 3 morphologic types combined (10 of 120, 8%; $p < 0.001$).

Patients with a normal electrocardiogram ranged in age from 13 to 67 years (mean 45); 7 patients were asymptomatic, but 16 had cardiac symptoms (including 7 who were in functional class III or IV). Seventeen patients had no evidence of subaortic obstruction under basal conditions, although 6 had outflow gradients >50 mm Hg measured at cardiac catheterization under basal conditions or with provocative maneuvers.

## Discussion

The results of this study confirm that patients with hypertrophic cardiomyopathy exhibit a wide variety of electrocardiographic patterns[1-5] and that no single electrocardiographic abnormality is characteristic of patients with this disease. However, by utilizing 2-D echocardiography to define the distribution of LV hypertrophy in patients with hypertrophic cardiomyopathy, it became apparent that certain electrocardiographic patterns reflected particular patterns of hy-

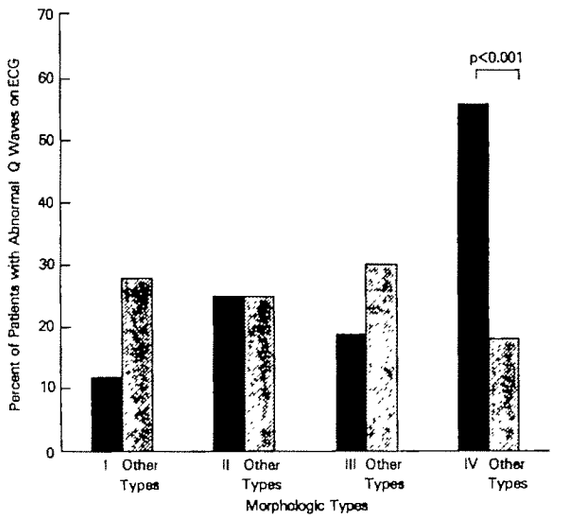



**FIGURE 4.** Prevalence of abnormal Q waves on electrocardiography (ECG) in the 4 morphologic types identified by 2-D echocardiography.

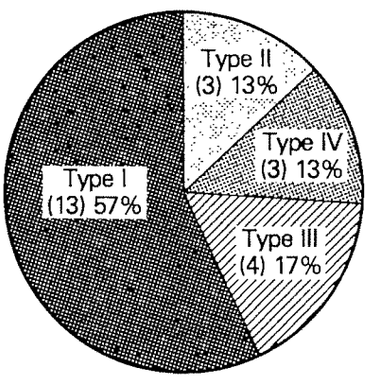



**FIGURE 5.** Frequency of 4 morphologic types identified by 2-D echocardiography in 23 patients with hypertrophic cardiomyopathy and *normal* scalar electrocardiograms.

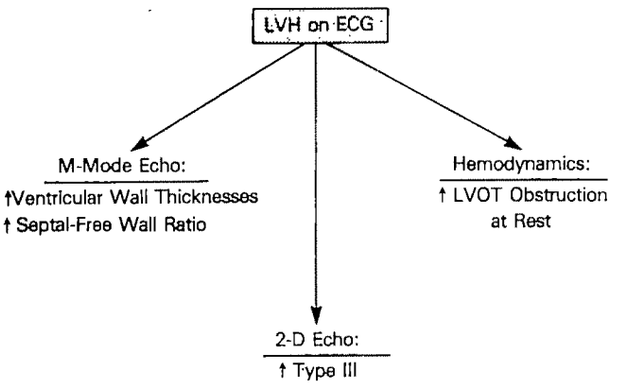



**FIGURE 6.** Clinical and echocardiographic (Echo) variables associated with left ventricular hypertrophy (LVH) on electrocardiography (ECG). **Arrow,** increase in, or increased frequency of variables shown. LVOT = left ventricular outflow tract.

pertrophy on the 2-D echocardiogram. For example, patients with the widespread hypertrophy involving substantial portions of both the ventricular septum and the LV free wall (type III) most commonly manifest LV hypertrophy on electrocardiography (that is, 74%), as well as left atrial enlargement (39%). Conversely, those patients with hypertrophy limited to only the anterior ventricular septum (type I) have electrocardiograms that uncommonly exhibit LV hypertrophy (that is, 21%) and frequently show no abnormalities. Patients with LV hypertrophy on the electrocardiogram also have significantly greater ventricular septal and posterior free wall thicknesses and septal-free wall ratio than do patients without electrocardiographic evidence of LV hypertrophy (Fig. 6). In addition, obstruction to LV outflow under basal conditions is more commonly associated with LV hypertrophy on the electrocardiogram (Fig. 6).

A substantial number of patients with hypertrophic cardiomyopathy have electrocardiograms that either fail to show LV hypertrophy or are entirely normal.[2,4,5] Several factors may be responsible for this finding. First, the relatively poor intrinsic sensitivity of the electrocardiogram for detecting LV hypertrophy is well documented.[14,18–22] Second, the fact that hypertrophy may be localized to particular portions of the LV wall could have been responsible, in part, for "false-negative" electrocardiograms in some patients. For example, we found that the majority of our patients with a normal electrocardiogram had localized type I hypertrophy. Such patients with morphologic type I uncommonly meet electrocardiographic criteria for LV hypertrophy because the hypertrophy is localized in distribution and overall LV mass is only slightly increased over normal. Such a mild degree of LV hypertrophy is less likely to be reflected by increased voltages in the electrocardiogram.

Other investigators have concluded that Q waves, when present in patients with hypertrophic cardiomyopathy, originate from increased initial depolarization of the markedly hypertrophied ventricular septum.[23–27] However, our data indicate that Q waves were present in only about 20% of those patients showing the most substantial involvement of the ventricular septum (that is, morphologic types II and III). Furthermore, abnormal Q waves were most common in those patients with hypertrophy involving regions of the left ventricle other than the anterior basal septum (type IV). Hence, while our study can not define the precise origin of Q waves in hypertrophic cardiomyopathy, our data do suggest that these Q waves in the electrocardiogram are not simply related to depolarization of the greatly thickened ventricular septum.

## References


1. **Frank S, Braunwald E.** Idiopathic hypertrophic subaortic stenosis: clinical analysis of 126 patients with emphasis on the natural history. Circulation 1968;37:759–788.
2. **Joye J, DeMaria AN, Neumann A, Miller RR, Vismara LA, Mason DT.** Electrocardiographic abnormalities in hypertrophic cardiomyopathy: relation to cardiac hypertrophy and intraventricular obstruction (abstr). Circulation 1976;54:Suppl II:II–209.
3. **Halpern SW, Mandel WJ, Allen HN, Kraus R, Charuzi Y.** Disparity between echocardiographic and electrocardiographic findings in asymmetric septal hypertrophy (abstr). Clin Res 1977;25:89A.
4. **Savage DD, Seides SF, Clark CE, Henry WL, Maron BJ, Robinson FC, Epstein SE.** Electrocardiographic findings in patients with obstructive and nonobstructive hypertrophic cardiomyopathy. Circulation 1978;58:402–408.
5. **Engler RL, Smith P, LeWinter M, Gosink B, Johnson A.** The electrocardiogram in asymmetric septal hypertrophy. Chest 1979;75:167–173.
6. **Maron BJ, Gottdiener JS, Epstein SE.** Patterns and significance of the distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a wide-angle, two-dimensional echocardiographic study of 125 patients. Am J Cardiol 1981;48:418–428.
7. **Maron BJ, Gottdiener JS, Bonow RO, Epstein SE.** Hypertrophic cardiomyopathy with unusual locations of left ventricular hypertrophy undetectable by M-mode echocardiography: identification by wide-angle two-dimensional echocardiography. Circulation 1981;63:409–418.
8. **Maron BJ, Epstein SE.** Hypertrophic cardiomyopathy: a discussion of nomenclature. Am J Cardiol 1979;43:1242–1244.
9. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of The Heart and Great Vessels. 6th ed. Boston: Little, Brown, 1964;112–113.
10. **Henry WL, Clark CE, Glancy DL, Epstein SE.** Echocardiographic measurement of left ventricular outflow gradient in idiopathic hypertrophic subaortic stenosis. N Engl J Med 1973;288:989–993.
11. **Henry WL, Clark CE, Epstein SE.** Asymmetric septal hypertrophy (ASH): echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. Circulation 1973;47:225–233.
12. **Kisslo J, von Ramm OT, Thurstone FL.** Cardiac imaging using phased array ultrasound system. II. Clinical technique and application. Circulation 1976;52:262–267.
13. **Silverman NH, Schiller NB.** Apex echocardiography. A two-dimensional technique for evaluation of congenital heart disease. Circulation 1978; 57:503–511.
14. **Romhilt DW, Estes EH.** A point-score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 1969;73:752–758.
15. **Davignon A, Rautaharju P, Boisselle E, Soumis F, Megelas M, Choquette A.** Normal ECG standards for infants and children. Pediatr Cardiol 1979; 1:123–131.
16. **Liebman J, Plonsey R.** Electrocardiography. In: Moss A, Adams F, Emmanoulides G, eds. Heart Disease in Infants, Children and Adolescents. Baltimore: Williams & Wilkins, 1977:18–61.
17. **Cassels DE, Ziegler RF.** Electrocardiography in Infants and Children. New York: Grune & Stratton, 1966:352–359.
18. **Grieg AH.** Pitfalls in the electrocardiographic diagnosis of left ventricular hypertrophy: a correlative study of 200 autopsied patients. Circulation 1959;20:30–34.
19. **McPhie J.** Left ventricular hypertrophy: electrocardiographic diagnosis. Austral Ann Med 1959;7:317–327.
20. **Scott RC.** The correlation between the electrocardiographic patterns of ventricular hypertrophy and the anatomic findings. Circulation 1960;21: 256–291.
21. **Allenstein BJ, Mori H.** Evaluation of electrocardiographic diagnosis of ventricular hypertrophy based on autopsy comparison. Circulation 1960; 21:401–412.
22. **Romhilt DW, Bove KE, Norris RJ, Conyers E, Conradi S, Rowlands DT, Scott RC.** A critical appraisal of the electrocardiographic diagnosis of left ventricular hypertrophy. Circulation 1969;40:185–195.
23. **Prescott R, Quinn JS, Littman D.** Electrocardiographic changes in hypertrophic subaortic stenosis which simulate myocardial infarction. Am Heart J 1963;66:43–48.
24. **Braudo M, Wigle ED, Keith JD.** Distinctive electrocardiogram in muscular subaortic stenosis due to ventricular septal hypertrophy. Am J Cardiol 1964;14:599–607.
25. **Wigle ED, Baron RH.** The electrocardiogram in muscular subaortic stenosis: effect of a left septal incision and right bundle-branch block. Circulation 1966;34:585–594.
26. **Bahl OP, Walsh TJ, Massie E.** Electrocardiography and vectorcardiography in idiopathic hypertrophic subaortic stenosis. Am J Med Sci 1970;259: 262–271.
27. **Cosio FG, Moro C, Alonso M, De La Calzada CS, Llovet A.** The Q waves of hypertrophic cardiomyopathy: an electrophysiologic study. N Engl J Med 1980;302:96–99.

# Comparative Effects of Nifedipine, Verapamil, and Diltiazem On Experimental Pulmonary Hypertension

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**The role of calcium-channel blocking agents in the treatment of pulmonary hypertension is not well defined. Consequently, the effects of diltiazem, nifedipine, and verapamil were compared in 3 groups of anesthetized dogs (n = 6 for each group). In each group, normoxic hemodynamic variables were recorded before and after increasing doses of diltiazem, nifedipine, and verapamil ($5 \times 10^{-8}$ *M*/kg, low; $10^{-7}$ *M*/kg, medium; and $10^{-6}$ *M*/kg, high dose; given intravenously over 2 minutes). In addition, the effect of these doses on the pulmonary pressor responses to hypoxia (fractional inspired oxygen concentration [$FIO_2$] 12%) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (5 μg/kg/min, intravenously for 4 minutes) was measured.**

**During normoxia, high-dose nifedipine and verapamil decreased mean aortic pressure and systemic vascular resistance while increasing cardiac output in all dogs in both groups ($p < 0.01$). Pulmonary vascular resistance, however, remained unchanged. High-dose diltiazem did not significantly alter cardiac output or pulmonary vascular resistance. During acute hypoxic pulmonary hypertension, verapamil decreased cardiac output by 30% ($p < 0.01$) without appreciably altering pulmonary arterial pressure; thus pulmonary vascular resistance increased slightly (4.9 ± 0.6 to 6.4 ± 1.0 mm Hg/liter/min, difference not significant [NS]). Nifedipine decreased hypoxic pulmonary vascular resistance to normoxic values ($p < 0.01$). Cardiac output increased 71% while pulmonary arterial pressure remained unchanged. Diltiazem administration produced no change in hypoxic pulmonary hemodynamic variables.**

**The responses to diltiazem, nifedipine, and verapamil during acute pulmonary vasoconstriction induced by $PGF_{2\alpha}$ were similar to those induced by hypoxia. After verapamil, pulmonary vascular resistance tended to increase (7.3 ± 1.3 to 8.1 ± 1.4 mm Hg/liter/min, NS). Nifedipine, however, completely blocked pulmonary vasoconstriction by decreasing pulmonary vascular resistance to pre-$PGF_{2\alpha}$ levels ($p < 0.01$). This was accompanied by a 157% increase in cardiac output and only a small increase in pulmonary arterial pressure (7 mm Hg). Again, diltiazem produced no change in pulmonary hemodynamic variables. In these acute studies, nifedipine appeared to be a more effective pulmonary vasodilator than verapamil or diltiazem.**

Vasodilator agents used in the treatment of pulmonary hypertension may be classified into 4 groups: beta-adrenergic agonists,[1,2] alpha-adrenergic blockers,[3] calcium-channel blockers,[4,5] and finally, those that act directly on vascular smooth muscle such as diazoxide[6,7] and hydralazine.[8] No single drug has been found effective in all patients with pulmonary hypertension, and most drugs have potentially serious adverse effects. As a result, new vasodilators are tried empirically as they become available. Hemodynamically, the most adverse potential effect of a vasodilator agent is systemic vasodilatation and hypotension in the absence of pulmonary vasodilatation.[9] The ideal drug for the treatment of pulmonary hypertension should produce pulmonary vasodilatation with little or no change in systemic pressure.

Different calcium-channel blocking agents have been reported effective[4,5,10] or relatively ineffective[11] in the treatment of pulmonary hypertension, but clinical experience is limited. The calcium antagonists that have been most extensively studied—diltiazem, nifedipine, and verapamil—vary considerably in their pharmaco-

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logic characteristics.[12] Consequently, we compared their acute effects on the pulmonary and systemic vascular circuits in 2 experimental models of pulmonary hypertension, produced by hypoxia or $PGF_{2\alpha}$ in the anesthetized dog.

## Methods

Eighteen mongrel dogs of both sexes (mean weight 22 ± 1 kg) were anesthetized with pentobarbital sodium (30 mg/kg intravenously), paralyzed with succinyl choline (2 mg/kg intravenously), intubated with an endotracheal tube, and ventilated on room air with a Harvard respirator (Harvard Apparatus, Millis, Massachusetts). Additional doses of pentobarbital sodium (15 mg/kg intravenously) were given during the experiment to maintain anesthesia. The respirator was adjusted initially to maintain a systemic arterial pH of approximately 7.39. Ventilation was therefore maintained constant throughout the experiment. Care was taken to "sigh" the dogs at regular intervals and to maintain an esophageal temperature of 38.0 to 39.5°C. Polyethylene catheters were placed into the superior and inferior vena cavae and in the descending aorta. A Swan-Ganz balloon tipped catheter was advanced into a branch of the pulmonary artery. Pulmonary artery, pulmonary artery wedge, and aortic pressures were measured using Statham P23 transducers (Statham Instruments, Oxnard, California) and a Hewlett-Packard 8-channel recorder (Hewlett-Packard, Waltham, Massachusetts). Cardiac output was determined by injecting 1.25 mg indocyanine-green dye into the inferior vena cava and withdrawing blood from the aorta at 20 ml/min through a Waters cuvette densitometer (Waters Instruments, Rochester, Minnesota). Pulmonary vascular resistance was calculated as mean pulmonary arterial pressure minus the wedge pressure (mm Hg) divided by the cardiac output (liters/min). Systemic arterial oxygen and carbon dioxide tensions and pH were measured with a Corning model 168 pH blood gas analyzer (Corning Glass Works, Medfield, Massachusetts).

In all dogs, pulmonary and systemic hemodynamic variables (pressures, cardiac output, and systemic blood gases) were recorded in the control state (normoxia) and after 8 and 15 minutes of hypoxia (12% $FIO_2$). For presentation and calculation of statistics, the hemodynamic values recorded during hypoxia at 8 and 15 minutes were averaged to give 1 hypoxic value. After hypoxia, the pressures were allowed to return to baseline level, where recontrol normoxic hemodynamic variables were recorded. $PGF_{2\alpha}$ (5 μg/kg/min) was then infused into the superior vena cava and hemodynamic values were recorded after 4 minutes. Once again, the pressures were allowed to return to baseline level and recontrol hemodynamic values recorded.

At this point, 6 dogs (Group 1) were treated with diltiazem, 6 dogs (Group 2) with nifedipine, and 6 dogs (Group 3) with verapamil in equimolar doses ($5 \times 10^{-8}$ *M*/kg intravenous bolus, low dose). Solutions of diltiazem and verapamil were made daily by dissolving the drug in saline solution. Nifedipine solution was prepared by dissolving the agent in absolute ethyl alcohol, then combining this with polyethylene glycol as the vehicle. Ten minutes after administration of low-dose drug, hemodynamic data were recorded. All groups were then challenged with hypoxia, followed by administration of $PGF_{2\alpha}$ as before.

In order to examine any hemodynamic effect of the vehicle, hemodynamics were recorded immediately before and 5 minutes after the administration of the vehicle (saline solution in Groups 1 and 3, polyethylene glycol in Group 2) without the drug. At this point, the whole protocol including normoxia, hypoxia, and $PGF_{2\alpha}$ was repeated after the administration of diltiazem, nifedipine, and verapamil in increasing equimolar doses ($10^{-7}$ *M*/kg, medium dose; and $10^{-6}$ *M*/kg, high dose).

**Statistical analysis:** The data are given as means ± standard error of the mean. Statistical analyses were performed using one-way analysis of variance (ANOVA) for repeated measurements within individual groups. The least significant difference[13] was employed to assess the significance of differences between groups. A p value <0.05 was considered statistically significant.

## Results

**Normoxia:** Figure 1 illustrates the systemic and pulmonary vascular effects of an equimolar dose ($10^{-6}$ *M*/kg, high dose) of diltiazem, nifedipine, or verapamil during normoxic conditions. Diltiazem caused a small decrease in aortic pressure (133 ± 5 to 125 ± 5 mm Hg) but no significant change in pulmonary hemodynamics. In contrast, nifedipine and verapamil produced marked changes in hemodynamic values. Both nifedipine and verapamil produced a decrease in aortic pressure and a concomitant increase in cardiac output ($p < 0.01$). Pulmonary arterial pressure increased ($p < 0.05$), and the calculated pulmonary vascular resistance showed a small, statistically insignificant decrease. Both nifedipine and verapamil resulted in similar pulmonary and systemic hemodynamic changes; however, the changes associated with nifedipine were more pronounced.

Figure 2 shows the relation between cardiac output and pulmonary arterial pressure in Groups 1, 2, and 3 with low-, medium-, and high-dose drug during normoxia. With the use of vectors to represent the cumulative effect, it can be seen that in equimolar doses the

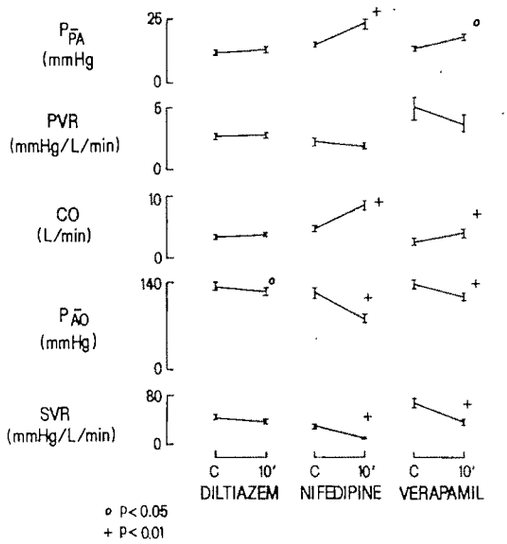



**FIGURE 1.** Comparative effects of equimolar high dose ($10^{-6}$ *M*/kg) drug during normoxia. Hemodynamic effects were measured before (C) and 10 minutes (10') after infusion of the drug. The statistical comparison is between the data obtained at these 2 times. **Bars** represent standard error of the mean. CO = cardiac output; $P_{\bar{AO}}$ = mean aortic pressure; $P_{\bar{PA}}$ = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

**TABLE I Hemodynamic Effects of Hypoxia and Hypoxia Plus High-Dose Drug**

| | $P_{\overline{AO}}$ (mm Hg) | $P_{\overline{PA}}$ (mm Hg) | CO (liters/min) | SVR (mm Hg/ liter/min) | PVR (mm Hg/ liter/min) |
|---|---|---|---|---|---|
| | | | Group 1 (Diltiazem) | | |
| Normoxia | 141 ± 4 | 12 ± 1 | 3.3 ± 0.4 | 46 ± 6 | 2.4 ± 0.3 |
| Hypoxia | 160 ± 3* | 21 ± 2* | 4.0 ± 0.3 | 41 ± 3 | 4.5 ± 0.6* |
| Hypoxia + high-dose drug | 146 ± 6† | 22 ± 2 | 4.0 ± 0.3 | 37 ± 2 | 4.7 ± 0.6 |
| | | | Group 2 (Nifedipine) | | |
| Normoxia | 152 ± 9 | 15 ± 1 | 3.5 ± 0.3 | 46 ± 5 | 2.5 ± 0.2 |
| Hypoxia | 168 ± 10* | 26 ± 2* | 4.2 ± 0.3 | 41 ± 4 | 5.2 ± 0.8* |
| Hypoxia + high-dose drug | 84 ± 5† | 24 ± 1 | 7.2 ± 0.7† | 12 ± 1† | 2.5 ± 0.2† |
| | | | Group 3 (Verapamil) | | |
| Normoxia | 152 ± 6 | 16 ± 1 | 4.2 ± 0.6 | 42 ± 9 | 3.1 ± 0.4 |
| Hypoxia | 167 ± 9* | 25 ± 2* | 4.7 ± 0.6 | 40 ± 7 | 4.9 ± 0.6* |
| Hypoxia + high-dose drug | 135 ± 5† | 22 ± 1 | 3.3 ± 0.6† | 47 ± 7 | 6.4 ± 1.0 |

Values are expressed as mean ± standard error of the mean. * $p < 0.05$ for differences between normoxia and hypoxia; † $p < 0.05$ for differences between hypoxia and hypoxia plus high-dose drug.

CO = cardiac output; $P_{\overline{AO}}$ = mean aortic pressure; $P_{\overline{PA}}$ = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

3 drugs behaved quite differently. The length of the added vectors as well as the angle of the vectors differs for each drug. Nifedipine caused an increase in pulmonary arterial pressure and a very marked increase in cardiac output with increasing doses, in a linear relation ($r = 0.98$). On the other hand, with increasing doses, verapamil decreased cardiac output as well as pulmonary arterial pressure. Diltiazem produced very little change in either pulmonary arterial pressure or cardiac output with increasing doses, as evidenced by the small magnitude of its combined vector.

**Hypoxia:** The hypoxic challenge induced a marked increase in pulmonary arterial pressure ($p < 0.01$) and pulmonary vascular resistance ($p < 0.01$) in each group (Table I).

Figure 3 illustrates the systemic and pulmonary hemodynamic effects of equimolar doses of diltiazem, nifedipine, and verapamil during hypoxia. Hemody-

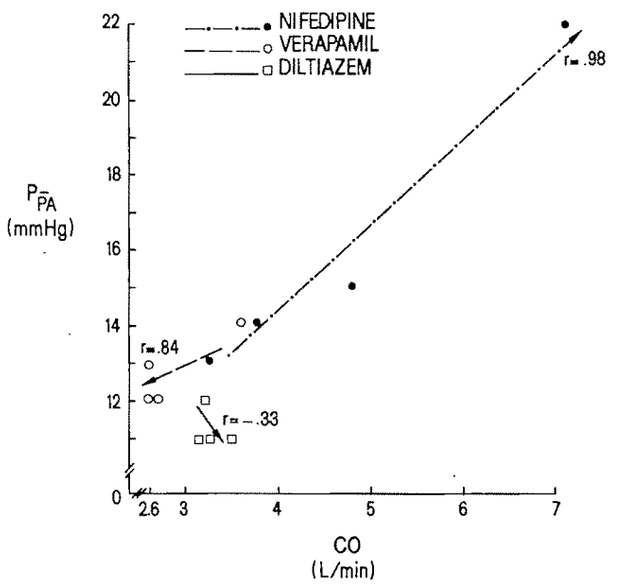



**FIGURE 2.** Comparative effects of increasing dose of diltiazem, nifedipine, and verapamil on the relation of cardiac output to pulmonary arterial pressure during normoxia. In each drug group there are 4 points: the control, followed by values obtained 15 minutes after low-, medium-, and high-dose drug. The magnitude and the angle between each 2 successive points for each group were measured and converted into a vector, and the resulting 3 vectors were added to give a single combined vector for that group, shown by the **lines with arrows.** CO = cardiac output; $P_{\overline{PA}}$ = mean pulmonary arterial pressure.

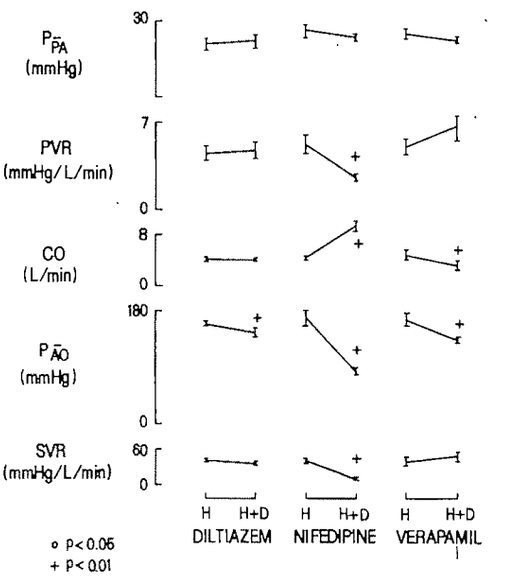



**FIGURE 3.** Comparative effects of equimolar high-dose ($10^{-6}$ *M*/kg) drug during hypoxic ($FIO_2$ 12%) pulmonary vasoconstriction. Hemodynamic affects were measured during hypoxia (H) and during hypoxia with high-dose drug (H + D). The statistical comparison is between the data obtained at these 2 times. **Bars** represent standard error of the mean. Abbreviations as in Figure 1.

**TABLE II Hemodynamic Effects of $PGF_{2\alpha}$ and $PGF_{2\alpha}$ Plus High-Dose Drug**

| | $P_{\overline{AO}}$ (mm Hg) | $P_{\overline{PA}}$ (mm Hg) | CO (liters/min) | SVR (mm Hg/liter/min) | PVR (mm Hg/liter/min) |
|---|---|---|---|---|---|
| | | | Group 1 (Diltiazem) | | |
| Normoxia | 138 ± 5 | 12 ± 1 | 3.2 ± 0.3 | 45 ± 4 | 2.3 ± 0.2 |
| $PGF_{2\alpha}$ | 144 ± 3 | 23 ± 1* | 3.3 ± 0.3 | 46 ± 5 | 5.5 ± 0.2* |
| $PGF_{2\alpha}$ + high-dose drug | 137 ± 6 | 22 ± 1 | 3.7 ± 0.3 | 38 ± 2 | 5.3 ± 0.4 |
| | | | Group 2 (Nifedipine) | | |
| Normoxia | 145 ± 9 | 13 ± 1 | 3.3 ± 0.3 | 47 ± 6 | 2.5 ± 0.3 |
| $PGF_{2\alpha}$ | 154 ± 9 | 22 ± 2* | 3.3 ± 0.3 | 48 ± 5 | 5.0 ± 0.8* |
| $PGF_{2\alpha}$ + high-dose drug | 85 ± 4† | 29 ± 2† | 8.5 ± 0.7† | 10 ± 1† | 2.7 ± 0.2† |
| | | | Group 3 (Verapamil) | | |
| Normoxia | 143 ± 6 | 14 ± 1 | 3.6 ± 0.6 | 49 ± 12 | 3.5 ± 0.7 |
| $PGF_{2\alpha}$ | 157 ± 7* | 25 ± 2* | 3.3 ± 0.5 | 54 ± 9 | 7.3 ± 1.5* |
| $PGF_{2\alpha}$ + high-dose drug | 128 ± 4† | 21 ± 2† | 2.6 ± 0.4 | 54 ± 7 | 8.1 ± 1.4 |

Values are expressed as mean ± standard error of the mean. * $p < 0.05$ for differences between normoxia and $PGF_{2\alpha}$; † $p < 0.05$ for differences between $PGF_{2\alpha}$ and $PGF_{2\alpha}$ + high-dose drug.
Abbreviations as in Table I.

namic values were recorded during the initial hypoxic challenge before treatment (see Methods) and the data were compared with recordings made during hypoxia after administration of high-dose drug. Diltiazem had no significant effect on pulmonary hemodynamic function. However, systemic arterial pressure did decrease (160 ± 3 to 146 ± 6 mm Hg) ($p < 0.01$). Nifedipine, in contrast to diltiazem, markedly blunted the hypoxic vasoconstrictor response. During the hypoxic challenge nifedipine increased cardiac output by 71%; at the same time pulmonary arterial pressure was, if anything, slightly decreased, thus suggesting pulmonary vasodilatation, as indicated by the 52% decrease in pulmonary vascular resistance. Systemic hemodynamic effects were also altered by nifedipine. Aortic pressure and systemic vascular resistance both decreased considerably ($p < 0.01$ for both). The administration of verapamil did not alter pulmonary arterial pressure. However, cardiac output showed a small decrease and consequently pulmonary vascular resistance tended to increase.

**$PGF_{2\alpha}$:** $PGF_{2\alpha}$ was used as a second independent agent to provoke pulmonary hypertension. In each group of dogs, the $PGF_{2\alpha}$ challenge induced a marked increase in pulmonary arterial pressure ($p < 0.01$) and pulmonary vascular resistance ($p < 0.01$), without a change in cardiac output (Table II). The hemodynamic effects of diltiazem, nifedipine, and verapamil on $PGF_{2\alpha}$-induced pulmonary vasoconstriction are compared in Figure 4.

Diltiazem had no effect on hemodynamic function and did not blunt the $PGF_{2\alpha}$ vasoconstriction. With high-dose nifedipine there was a remarkable increase in cardiac output of 156%. This was associated with a relatively small increase in pulmonary arterial pressure of 32% or 7 mm Hg. This resulted in a calculated decrease in pulmonary vascular resistance of 46%, or nearly half. Medium-dose nifedipine increased cardiac output 55%. Pulmonary arterial pressure was not significantly altered at this dose, but pulmonary vascular resistance again decreased significantly.

The response of the pulmonary hypertension induced by $PGF_{2\alpha}$ to verapamil was nearly identical to that of hypoxia-induced pulmonary hypertension. Verapamil reduced cardiac output by 21%, although this was not statistically significant. There was an associated reduction in pulmonary arterial pressure. Pulmonary vascular resistance tended to increase, but not significantly.

**Effect of vehicle:** Hemodynamic measurements were recorded 5 minutes after the administration of the vehicle (saline solution in Groups 1 and 3 and polyethylene glycol in Group 2) alone without the drug. In no case in any group was any change in hemodynamic function noted.

**Dose response of pulmonary vascular resistance to nifedipine:** The response of pulmonary vascular resistance to increasing doses of nifedipine in both models of acute pulmonary vasoconstriction, hypoxia, and $PGF_{2\alpha}$ is illustrated in Figure 5. As the dose of nifedipine was increased, pulmonary vascular resistance decreased in a linear fashion. At the high dose of nifedipine, pulmonary vascular resistance decreased to the control normoxic values, indicating complete blunting of the pulmonary vasoconstrictor effect of hypoxia and $PGF_{2\alpha}$

## Discussion

The pathophysiology of the various forms of clinical pulmonary hypertension is largely unknown. This is true whether the initial stimulus is hypoxia, high flow, or idiopathic, as in primary pulmonary hypertension. It is logical to consider the therapeutic potential of calcium-channel blocking agents, since they are known to relax vascular smooth muscle and inhibit platelet aggregation.[14] Verapamil has been observed to inhibit the pulmonary pressor response to acute hypoxia in the isolated rat lung,[15] the awake calf,[16] and the anesthetized dog.[17] However, disappointing results have been reported by Landmark et al,[11] who injected verapamil into the pulmonary artery of 12 patients with pulmonary hypertension. Only 3 of their patients had a sig-

nificant decrease in pulmonary vascular resistance, while 10 had a reduction in cardiac output.

Because of the differences in the systemic hemodynamic effects[18] and mechanisms of action[19] observed with several calcium-channel blocking agents, we compared the effectiveness of verapamil, diltiazem, and nifedipine in reducing pulmonary hypertension caused by hypoxia or $PGF_{2\alpha}$. The latter stimulus acts primarily by pharmacomechanical excitation contraction coupling, while the mechanism of hypoxic pulmonary vasoconstriction is unknown. The hemodynamic effect of verapamil during hypoxic pulmonary hypertension in the anesthetized dog mimicked the findings described in patients with pulmonary hypertension. Thus, cardiac output and pulmonary artery pressure decreased slightly while pulmonary vascular resistance was unchanged, compared with the preverapamil hypoxic values. The experiments of Tucker et al[17] in the anesthetized dog,[17] using the same dose of verapamil as our high dose, demonstrated a reduction in hypoxic pulmonary vascular resistance, whereas we found an insignificant increase. This difference seems to reflect the fact that in their series cardiac output increased after verapamil administration, whereas in our study it tended to decrease. It is not clear whether these discrepancies are related to the different hemodynamic responses to hypoxia of highland and lowland dogs,[20] or to the fact that their dogs breathed spontaneously while ours were mechanically ventilated. We observed that the absolute pulmonary arterial pressure attained during an infusion of $PGF_{2\alpha}$ was decreased after verapamil, although pulmonary vascular resistance was unchanged. Tucker et al found that verapamil caused no change in pulmonary perfusion pressure after a bolus of $PGF_{2\alpha}$, but did not measure cardiac output.

While diltiazem decreased aortic pressure during both normoxia and hypoxia, it had no effect on pulmonary vascular hemodynamic function during any of the interventions. Administration of diltiazem (0.2 mg/kg intravenously) in open-chest anesthetized dogs has also been reported to decrease systemic pressures significantly.[21]

The most marked effect of nifedipine under normoxic conditions was a decrease in aortic pressure and a concomitant increase in cardiac output. During normoxia, when the pulmonary vasculature is almost fully dilated, this increased flow was associated with an increase in pulmonary arterial pressure but no change in resistance. When the pulmonary vasculature was preconstricted by hypoxia, administration of nifedipine did not increase pulmonary pressure and the calculated resistance returned to normoxic control values because of the increased cardiac output. In the clinical management of pulmonary hypertension, the ideal response to therapy is both a reduction in pulmonary arterial pressure and an increase in cardiac output to normal levels. However, as in these nifedipine studies, it is more common for vasodilators to increase cardiac output with little or no reduction in pulmonary arterial pressure. Patients with primary pulmonary hypertension whose cardiac outputs are in the normal range have been reported to have a better prognosis than those whose cardiac output is diminished.[22] However, an increase in cardiac output induced by vasodilators, without a reduction in pulmonary arterial pressure, increases right ventricular work and it is not known whether the net effect is beneficial in terms of longevity.

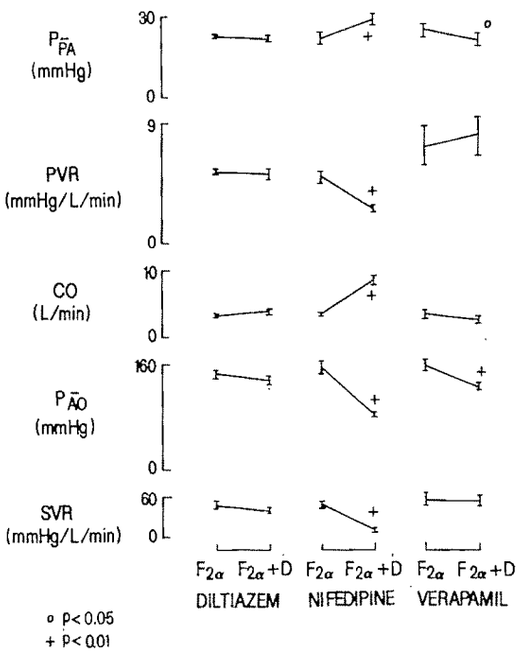



**FIGURE 4.** Comparative effects of equimolar high-dose ($10^{-6}$ *M*/kg) drug during $PGF_{2\alpha}$-induced pulmonary vasoconstriction. Hemodynamic effects were measured during $PGF_{2\alpha}$ vasoconstriction and during $PGF_{2\alpha}$ plus high-dose drug ($F_{2\alpha}$ + D). The statistical comparison is between the data obtained at these 2 times. Abbreviations as in Figure 1.

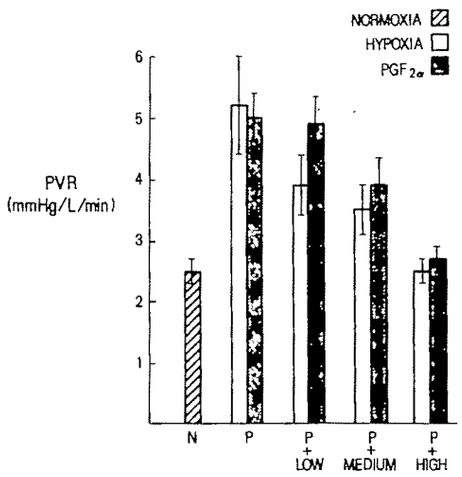



**FIGURE 5.** The effect of increasing doses of nidefipine on pulmonary vasoconstriction stimulated with hypoxia (12% $FIO_2$) or $PGF_{2\alpha}$. N represents pulmonary vascular resistance (PVR) during normoxia for Group 2 dogs before any intervention. P represents the PVR during pressor stimulation. P + LOW, P + MEDIUM, and P + HIGH represent PVR during pressor stimulation plus low-, medium-, or high-dose nifedipine, respectively. **Bars** represent standard error of the mean.

The major problem in the clinical use of vasodilators to treat pulmonary hypertension is that there is no pulmonary hypotensive agent which does not also affect the systemic vasculature. The lack of a selective pulmonary vasodilator gives rise to 2 problems. If the pulmonary vasculature is relatively unresponsive, systemic vasodilatation without an increase in cardiac output may lead to systemic hypotension. Alternately, if cardiac output increases, pulmonary arterial pressure may also increase. In 1 patient with primary pulmonary hypertension reported by Camerini et al,[4] sublingual nifedipine (20 mg) increased cardiac output 90% and decreased pulmonary and systemic vascular resistances by 56 and 49%, respectively.[4] In that patient, pulmonary arterial pressure also decreased. She improved clinically and hemodynamically over the subsequent 3 months on nifedipine and anticoagulants. In this instance the chronic effect of the vasodilator followed the same pattern as the acute response, but frequently this is not the case. Consequently, it is important to be cautious when extrapolating from an acute effect to long-term treatment. Equally, a vasodilator given during acute pulmonary hypertension in the dog may not give the same hemodynamic result when administered to a patient with chronic pulmonary vascular disease. Despite these caveats, the fact that nifedipine returned pulmonary vascular resistance to control levels during hypoxia and $PGF_{2\alpha}$ infusion in the dog, and causes acute pulmonary vasodilatation in patients with respiratory failure,[5] makes it a logical candidate for evaluation in the chronic treatment of clinical pulmonary hypertension.

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## References

1. **Lee TD, Rovell GC, Ross RS.** The hemodynamic effects of isoproterenol in pulmonary hypertension in man. Am Heart J 1963;65:361–367.
2. **Daoud FS, Reeves JT, Kelly DB.** Isoproterenol as a potential pulmonary vasodilator in primary pulmonary hypertension. Am J Cardiol 1978;42: 817–822.
3. **Ruskin JN, Hutter AM.** Primary pulmonary hypertension treated with oral phentolamine. Ann Intern Med 1979;90:772–774.
4. **Camerini F, Alberti E, Klugmann S, Salvi A.** Primary pulmonary hypertension: effects of nifedipine. Br Heart J 1980;44:352–356.
5. **Simonneau G, Escourrou P, Duroux P, Lockhart A.** Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. N Engl J Med 1981;304: 1582–1585.
6. **Honey M, Cotter L, Davies N, Denison D.** Clinical and haemodynamic effects of diazoxide in primary pulmonary hypertension. Thorax 1980;35: 269–276.
7. **Klinke WP, Gilbert JAL.** Diazoxide in primary pulmonary hypertension. N Engl J Med 1980;302:91–92.
8. **Rubin LJ, Peter RH.** Oral hydralazine therapy for primary pulmonary hypertension. N Engl J Med 1980;302:69–73.
9. **Rubino J, Schroeder J.** Diazoxide in treatment of primary pulmonary hypertension. Br Heart J 1979;42:362–363.
10. **Kambara H, Fujimoto K, Wakabayashi A, Kawai C.** Primary pulmonary hypertension: beneficial therapy with diltiazem. Am Heart J 1981;101: 230–231.
11. **Landmark K, Refsum AM, Simonsen S, Storstein O.** Verapamil and pulmonary hypertension. Acta Med Scand 1978;204:299–302.
12. **Henry PD.** Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. Am J Cardiol 1980;46:1047–1058.
13. **Sokal RR, Rohlf FJ.** Analysis of variance I: the one-way classification. In: Biometry: Principles and Practice of Statistics. San Francisco: WH Freeman, 1969:99–106.
14. **Ono H, Kimura M.** Effect of $Ca^{2+}$-antagonistic vasodilators, diltiazem, nifedipine, perhexiline and verapamil on platelet aggregation in vitro. Arzneimittelforsch 1981;31:1131–1134.
15. **McMurtry IF, Davidson BS, Reeves JT, Grover RF.** Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs. Circ Res 1976;38:99–104.
16. **McMurtry IF, Reeves JT, Will DH, Grover RF.** Reduction of bovine pulmonary hypertension by normoxia, verapamil and hexaprenaline. Experientia 1977;33:1192–1194.
17. **Tucker A, McMurtry IF, Grover RF, Reeves JT.** Attenuation of hypoxic pulmonary vasoconstriction by verapamil in intact dogs. Proc Soc Exp Biol Med 1976;151:611–614.
18. **Walsh RA, Badke RF, O'Rourke RA.** Differential effects of systemic and intracoronary calcium channel blocking agents on global and regional left ventricular function in conscious dogs. Am Heart J 1981;102:341–350.
19. **Zelis R, Flaim SF.** "Calcium influx blockers" and vascular smooth muscle: do we really understand the mechanisms? Ann Intern Med 1981;94: 124–126.
20. **Weir EK, Tucker A, Reeves JT, Grover RF.** Increased pulmonary vascular pressor response to hypoxia in highland dogs (39615). Proc Soc Exp Biol Med 1977;154:112–115.
21. **Bourassa MG, Cote P, Theroux P, Tabau JF, Genain C, Waters DD.** Hemodynamics and coronary flow following diltiazem administration in anesthetized dogs and in humans. Chest 1980;78:224–230.
22. **Kanemoto N, Sasamoto H.** Pulmonary hemodynamics in primary pulmonary hypertension. Jpn Heart J 1979;20:395–405.

# Compensatory Cardiac Mechanisms Evoked by Septal Ischemia in Dogs

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**To examine the cardiac responses to selective septal ischemia, the septal artery was occluded intermittently in anesthetized open-chest dogs. Myocardial segment length was recorded continuously by an ultrasonic technique in the interventricular septum and the right and left ventricular free walls. At left ventricular end-diastolic pressure of 3.0 ± 0.6 mm Hg, occlusion of the septal artery increased left ventricular end-diastolic segment length by 3.0 ± 0.9% and stroke volume was maintained. After blood volume expansion to a left ventricular end-diastolic pressure of 7.2 ± 1.4 mm Hg, occlusion of the septal artery did not increase end-diastolic dimensions and stroke volume decreased significantly but by <10%. At all levels of blood volume expansion, occlusion of the septal artery did not alter significantly the end-systolic segment length of the free wall of the left ventricle and the dimensions of the free wall of the right ventricle. The distance between the septum and the right ventricular free wall was unchanged in end-diastole and reduced in end-systole after occlusion of the septal artery. These observations indicate paradoxical movement of the ischemic septum. The ischemic septum seems to act as a passive diaphragm pump on the right ventricle without activation of the Frank-Starling mechanism in uninjured areas. In the left ventricle, the Frank-Starling mechanism is fully exploited with unaltered end-systolic dimensions of the uninjured myocardium because of the systolic bulging of the ischemia septum.**

In man, about 80% of the blood supply to the septum is provided by branches from the left anterior descending coronary artery[1] and the rest from short branches of the posterior descending coronary artery. Septal ischemia, therefore, usually occurs together with ischemic lesions of variable extent in the free walls of either ventricle. In contrast, in dogs a separate septal artery originates from the left coronary artery and supplies approximately 75% of the septal myocardium.[2–4] Thus, the anatomy of the coronary circulation in dogs offers a unique possibility to examine the effect of isolated septal ischemia on the pump function of either ventricle.

Septal ischemia might influence the function of both ventricles as blood pumps, but experiments in dogs have shown that ligation of the septal artery has no effect on stroke volume.[5] The compensatory mechanisms which contribute to the maintenance of stroke volume during septal ischemia have not been previously investigated. The objective of the present study was to examine the acute changes in cardiac dynamics induced by intermittent occlusions of the septal artery.

One possibility is that septal ischemia leads to reduced ejection and that the increase in end-diastolic ventricular blood volume increases the activation of the Frank-Starling mechanism in the nonischemic parts of the myocardium. This response has been demonstrated in dogs in the free wall of the left ventricle during acute occlusion of the left anterior descending coronary artery.[6–8] Another possibility is that the ischemic septum bulges into the right ventricular cavity during systole. This paradoxical movement may maintain right ventricular emptying and reduce the end-systolic afterload of the left ventricle.

To examine the compensatory responses to septal ischemia, pairs of ultrasonic elements were inserted into the septum and the free walls of both ventricles of anesthetized open-chest dogs. The distance between the elements—the segment length—was recorded continuously before, during, and after occlusion of the septal artery. These examinations were supplemented by re-

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cordings of the distance between the septum and the right ventricular free wall.

The ability of the Frank-Starling mechanism to compensate for myocardial ischemia is reduced during blood volume expansion.[9] Occlusions of the septal artery were therefore repeated at increasing levels of blood volume expansion. This experimental procedure permitted comparisons of right and left ventricular dynamic function with and without septal ischemia at equal end-diastolic segment lengths in the free wall of the left ventricle.

## Methods

**Animal preparation:** Six mongrel dogs of both sexes weighing 17.8 ± 2.2 kg were anesthetized with sodium pentobarbital, 25 mg/kg body weight intravenously initially, followed by 50 mg intravenously as required to maintain anesthesia. The dogs were kept on a positive pressure respirator (Cyclator Mk II, British Oxygen). Throughout the experiments, appropriate measures were taken to keep blood gases and the acid-base balance normal. The heart was exposed by a bilateral thoracotomy and suspended in a pericardial cradle. The septal artery originated either from the brief left main coronary artery at the point of branching or from the left anterior descending coronary artery 1 to 2 mm distal to its origin. After isolation, a thin silicon rubber snare was looped around the septal artery for later occlusion. Care was taken not to obstruct the left anterior descending coronary artery or the circumflex artery.

**Hemodynamic and dimensional measurements:** Right and left ventricular pressures were measured with Statham P23Db and P23Gb transducers connected to short polyethylene catheters introduced into the right ventricle through the outflow tract and into the left ventricle through the apex. Aortic flow was measured electromagnetically with a flow probe (Nycotron, model 376) around the ascending aorta. Left ventricular stroke volume (minus coronary flow) was determined by electronic beat-to-beat integration of the aortic flow curve. Local myocardial dimensions (segment length) were measured ultrasonically.[10] Pairs of piezoelectric crystals were inserted into the free walls of the left and right ventricles. A third pair of crystals was inserted blindly with curved needles through the left ventricle into the septum. The position of the crystals permitted recordings along the long axis of the septum.

The amplified pulses from the receiver crystals were continuously monitored on an oscilloscope. Segment length is maximal in end-diastole and is reduced during systole until end-systolic segment length is attained when aortic blood flow is reduced to zero. The difference between end-diastolic and end-systolic segment length is called systolic myocardial shortening. Any further reduction in segment length because of changes in the shape of the ventricle does not contribute to ejection and is not included in the measurement of systolic myocardial shortening. To record the septum to free wall distance, 1 ultrasonic crystal was inserted into the middle part of the septum and the other into the overlying right ventricular free wall in the inflow area.

Throughout the experiments pressures, flow, segment lengths, and the distance between the septum and the right ventricular free wall were continuously recorded on a Sanborn multichannel oscillograph.

**Experimental procedure:** After control observations, the septal artery was occluded with the snare. Recordings were continued until a new steady state had been reached during

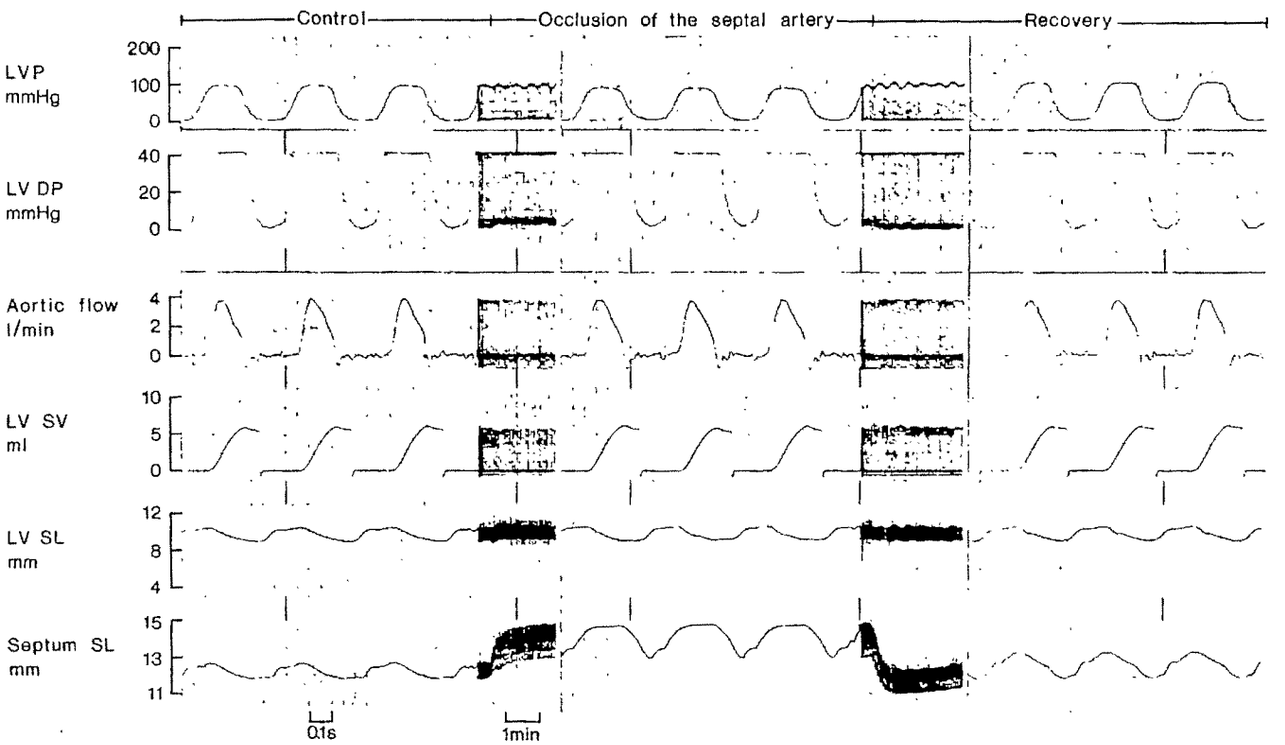



**FIGURE 1.** Hemodynamic effects of occluding the septal artery. Tracings from an experiment in a dog weighing 15 kg. LV DP = left ventricular diastolic pressure; LVP = left ventricular pressure; LV SL = left ventricular segment length (nonischemic free wall); LV SV = left ventricular stroke volume; Septum SL = septal segment length.

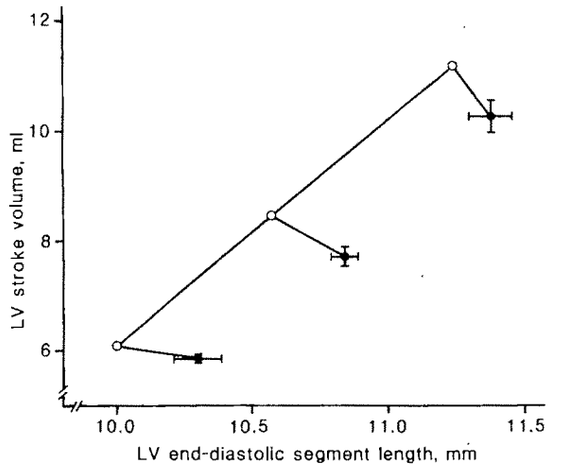



**FIGURE 2.** Relation between left ventricular (LV) stroke volume and end-diastolic segment length in the nonischemic free wall. End-diastolic segment lengths were normalized to 10.0 mm in the control period before blood volume expansion with infusion of saline solution and dextran; the individual numerical values ranged from 8.5 to 13.2 mm. **Open circles** = mean values obtained in 6 dogs (body weight 17.8 ± 2.2 kg, same dogs as in Table I) at 3 levels of blood volume when LV end-diastolic pressure increased from 3.0 ± 0.6 to 7.2 ± 1.4 mm Hg. **Closed circles** = changes (mean ± standard error of the mean) induced by occlusion of the septal artery.

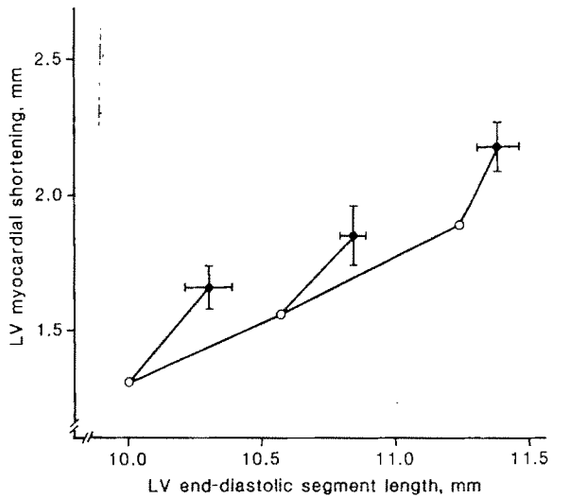



**FIGURE 3.** Relation between myocardial shortening and end-diastolic segment length in the left ventricular (LV) nonischemic free wall. **Open circles** = mean values obtained at 3 levels of blood volume. **Closed circles** = change (mean value ± standard error of the mean) induced by occlusion of the septal artery. Same dogs and experiments as in Figure 2.

septal ischemia. The duration of the ischemic period was usually 3 to 4 minutes. After release of the occlusion, the hemodynamic variables returned to control levels in 1 to 2 minutes. Occlusion of the septal artery was repeated at increasing levels of blood volume expansion induced by infusion with saline solution and dextran.

After terminating the experiment, the dogs were killed and the position of the ultrasonic crystals was examined. No signs of myocardial or coronary artery injury were observed in any of the experiments.

**Statistics:** The data are expressed as mean ± standard error of the mean. Each dog served as its own control, and Wilcoxon's test for paired comparisons was used to calculate probability values.[11] A probability value $<0.05$ was regarded as statistically significant.

## Results

Occlusion of the septal artery immediately increased end-diastolic and end-systolic segment length of the septum, and a new steady state was reached within 2 to 3 minutes. Figure 1 shows tracings from 1 representative experiment. Most of the increase in segment length of the ischemic septum occurred as ventricular pressure increased during the isovolumic period. During ejection there was a small reduction in segment length (positive systolic myocardial shortening) in 3 experiments and a further dilation (negative systolic myocardial shortening) in the 3 other experiments.

Before blood volume expansion, occlusion of the septal artery increased left ventricular end-diastolic pressure from 3.0 ± 0.6 to 4.0 ± 0.6 mm Hg, but had no effect on left ventricular peak systolic and end-systolic pressure; right ventricular pressure did not change significantly. Stroke volume averaged 6.1 ± 0.5 ml before and 5.9 ± 0.5 ml during occlusion of the septal artery ($p = 0.13$). Thus, septal ischemia did not reduce systolic ventricular pressure and stroke volume before blood volume expansion.

To examine the role of the Frank-Starling mechanism in the maintenance of the stroke volume, saline solution and dextran were infused intravenously, and occlusion of the septal artery was repeated at left ventricular end-diastolic pressures averaging 4.8 ± 0.8 and 7.2 ± 1.4 mm Hg. Although 4 to 6 intermittent occlusions were undertaken in the course of 1 experiment, the recovery time did not increase. There were no signs of deterioration as judged from the segment length recordings after release of the occlusion.

In contrast to the findings before infusion with saline solution and dextran, stroke volume decreased during occlusion of the septal artery by 9.3 ± 2.2% and 7.5 ± 2.1% at the 2 levels of blood volume expansion. Figure 2 illustrates that the reduction in stroke volume during occlusion of the septal artery was associated with a compensatory increase in left ventricular end-diastolic segment length.

Occlusion of the septal artery was associated with a marked increase in myocardial shortening of the free wall of the left ventricle (Fig. 3). The increase in myocardial shortening was similar at all levels of ventricular expansion and averaged 25 ± 8% of control values.

To further examine the change in ventricular dynamics, we compared the response to occlusion of the septal artery and the response to infusion with saline solution and dextran at similar end-diastolic segment lengths of the free wall of the left ventricle. The results of experiments in 6 dogs are summarized in Table I. Although stroke volume decreased, end-systolic segment length was significantly smaller and myocardial shortening accordingly larger in the free wall of the left ventricle during occlusion of the septal artery than during blood volume expansion. Despite the difference in end-systolic dimensions, the end-systolic pressure

**TABLE I Hemodynamic Effects of Constriction of the Septal Artery: Comparison at Similar End-Diastolic Segment Length in the Nonischemic Left Ventricular Free Wall During Blood Volume Expansion and During Septal Ischemia**

| | Blood Volume Expansion | Septal Ischemia | Difference | p |
|---|---|---|---|---|
| Right ventricle | | | | |
| End-diastolic segment length (mm) | 11.73 ± 0.79 | 11.42 ± 0.76 | −0.32 ± 0.13 | NS |
| End-systolic segment length (mm) | 9.41 ± 0.57 | 9.42 ± 0.64 | 0.01 ± 0.14 | NS |
| Myocardial shortening (mm) | 2.33 ± 0.34 | 2.00 ± 0.24 | −0.33 ± 0.15 | NS |
| Peak systolic pressure (mm Hg) | 30.5 ± 1.7 | 30.2 ± 2.2 | −0.3 ± 1.2 | NS |
| End-diastolic pressure (mm Hg) | 4.7 ± 1.3 | 4.5 ± 1.1 | −0.2 ± 0.4 | NS |
| Septum | | | | |
| End-diastolic segment length (mm) | 12.31 ± 0.87 | 12.88 ± 0.86 | 0.57 ± 0.15 | <0.02 |
| End-systolic segment length (mm) | 11.25 ± 0.79 | 12.73 ± 0.91 | 1.48 ± 0.21 | <0.02 |
| Myocardial shortening (mm) | 1.06 ± 0.21 | 0.14 ± 0.27 | −0.92 ± 0.25 | <0.05 |
| Left ventricle | | | | |
| End-diastolic segment length (mm) | 11.95 ± 0.84 | 11.98 ± 0.86 | 0.03 ± 0.03 | NS |
| End-systolic segment length (mm) | 10.01 ± 0.65 | 9.74 ± 0.55 | −0.27 ± 0.11 | <0.05 |
| Myocardial shortening (mm) | 1.94 ± 0.20 | 2.24 ± 0.31 | 0.30 ± 0.13 | <0.05 |
| Peak systolic pressure (mm Hg) | 98 ± 5 | 97 ± 4 | −1 ± 3 | NS |
| End-systolic pressure (mm Hg) | 70 ± 5 | 71 ± 4 | 1 ± 3 | NS |
| End-diastolic pressure (mm Hg) | 6.7 ± 1.2 | 7.0 ± 1.6 | 0.3 ± 0.6 | NS |
| Stroke volume (ml) | 10.4 ± 1.0 | 8.9 ± 0.9 | −1.5 ± 0.2 | <0.02 |

Data are mean ± standard of the mean in 6 dogs (body weight 17.8 ± 2.2 kg). NS = not significant.

was the same during the 2 procedures. In the right ventricle, myocardial shortening and end-diastolic segment length did not differ significantly during occlusion of the septal artery and blood volume expansion. Hence the free wall of the right ventricle did not participate in the compensatory response.

This observation together with increased myocardial shortening of the free wall of the left ventricle was compatible with paradoxical movement of the septum. This possibility was examined in 2 supplementary experiments by measuring the distance between the septum and the right ventricular wall. Occlusion of the septal artery had no significant effect on the end-diastolic distance but reduced the end-systolic distance as expected for paradoxical movement of the septum. Figure 4 shows tracing from 1 of the experiments, and Figure 5 shows that the systolic excursions during occlusion of the septal artery increased at all levels of ventricular expansion.

## Discussion

This study shows that acute occlusion of the septal artery in dogs immediately leads to deterioration of contractility of the septum. At a low level of blood volume expansion there is no reduction in stroke volume, partly because of increased activation of the Frank-Starling mechanism in the uninjured left ventricular myocardium. Our data also suggest that paradoxical movement of the ischemic septum compensates to some extent for the normal function of the septum in the emptying of the right ventricle.

**Septum:** After occlusion of the septal artery, the septum immediately attains an ischemic pattern with loss of contractility. This pattern is the same as observed during ischemia of the free ventricular wall.[6,7,10,12] Most of the dilation occurred during the isovolumic period. There was no significant reduction in segment length during the ejection period. Myocardial dimensions were reduced in early diastole, but end-diastolic control values were not regained.

Because of the localization of the septum, ischemia influences the emptying of both ventricles. Normally, the septum moves toward the center of the left ventricle during systole despite a large transseptal pressure difference. A bellows function is induced because the free wall of the right ventricle moves more than the septum towards the left. When the septum becomes ischemic, it behaves in a passive fashion, and the transseptal pressure gradient may cause a paradoxical movement toward the right. The extent of the movement would depend on the degree of ischemia.

Despite marked systolic bulging, occlusion of the septal artery may not render the septum completely ischemic, since collateral blood flow from the left and right coronary artery has been demonstrated.[4,13] Fixler et al[5] measured myocardial blood flow in dogs with a microsphere technique and found that as much as 54% of the blood flow to the septum remained afer ligation of the septal artery. In our study, occlusion of the septal artery probably led to a more profound reduction in blood supply. By occlusion of the left anterior descending coronary artery, 40% of the myocardial shortening may remain in the ischemic area despite the reduction in myocardial blood flow to 20% of control values.[12] Provided the nutritional requirements of the left ventricular free wall and septum are similar, the remaining blood flow to the septum should be <20% of control value since no significant myocardial shortening remained. In our study ischemic changes in the septum were reversible, and there were no signs of progressive deterioration of myocardial function in the course of several ischemic periods of 3 to 4 minutes' duration. Except for a few irregular beats immediately after occlusion of the septal artery (probably mechanically induced), no arrhythmia or conduction disturbance was observed. Evidently, longer periods of septal ischemia are required to produce arrhythmia.[3]

**Left ventricle:** Occlusion of the septal artery reduced stroke volume only after blood volume expansion, suggesting compensatory activation of the Frank-

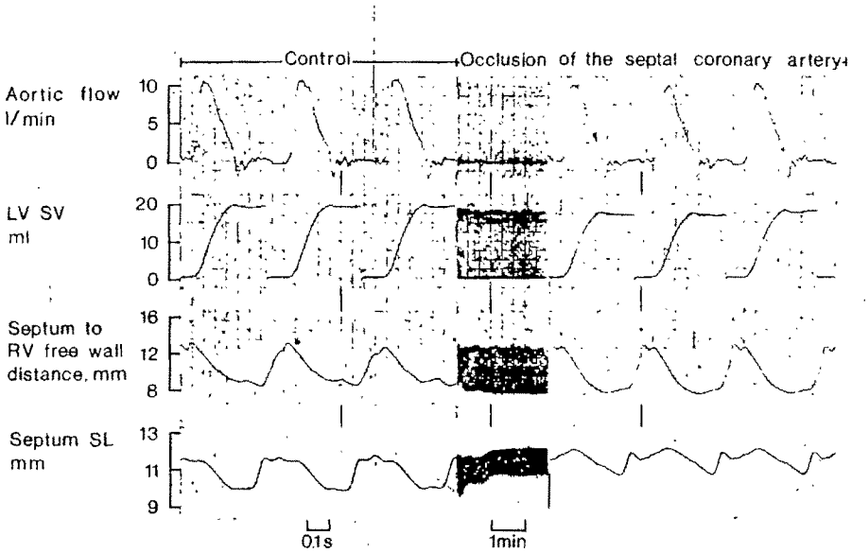



**FIGURE 4.** Effects of occluding the septal artery on the distance from the septum to the right ventricular (RV) free wall. Tracings from an experiment in a dog weighing 16 kg. LV SV = left ventricular stroke volume; Septum SL = septal segment length.

Starling mechanism after septal ischemia. The Frank-Starling mechanism, characterized by increased end-diastolic segment length and myocardial shortening, is operative up to left ventricular end-diastolic pressures of 12 to 15 mm Hg, but the response to a constant stimulus such as infusion of a certain amount of saline solution decreases as end-diastolic pressure is increased.[9] Similarly, occlusion of the septal artery might activate the Frank-Starling mechanism more at low than at high end-diastolic pressures. An interesting observation was that septal ischemia consistently modified the dynamic response of the free wall of the left ventricle. An increase in preload is usually associated with an increase in afterload because the ventricle dilates and end-systolic wall tension increases. Therefore, blood volume expansion results in increased end-diastolic and end-systolic dimensions. An isolated papillary muscle exposed to constant afterload contracts to the same end-systolic length when the end-diastolic length is varied over a wide range.[14] During occlusion of the septal artery, the nonischemic myocardium of the left ventricle contracted to the same end-systolic length as before occlusion. Thus, the intact myocardium behaved as the isolated muscle, suggesting no increase in left ventricular afterload after occlusion of the septal artery.

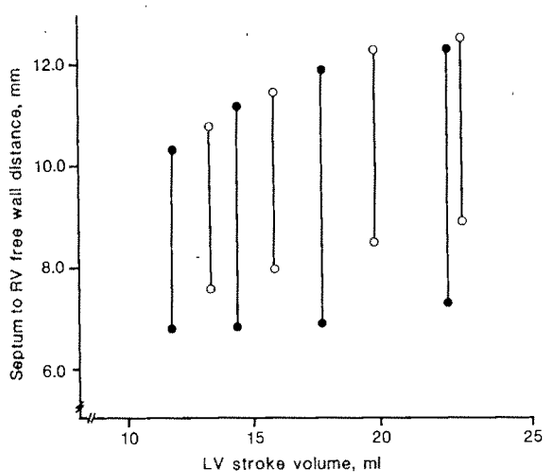



**FIGURE 5.** Relation between the distance from the septum to the right ventricular (RV) free wall and left ventricular (LV) stroke volume. Measurements were performed at 4 levels of blood volume. **Open circles** = control; **closed circles** = occlusion of the septal artery. The **vertical lines** connecting end-diastolic and end-systolic distances are systolic excursions which increased with occlusion of the septal artery.

The sequence of events may be that septal ischemia reduces stroke volume because a fraction of the ventricular blood volume is displaced toward the bulging ischemic septum rather than ejected through the aortic orifice. Myocardial shortening in the nonischemic area proceeded to the same end-systolic segment length as before occlusion of the septal artery. Comparisons at similar end-diastolic segment lengths during occlusion of the septal artery and expansion of the blood volume show that left ventricular contraction stopped at an end-systolic pressure of about 70 mm Hg but at widely different end-systolic dimensions (Table I).

**Right ventricle:** The dynamics of the free wall of the right ventricle were not changed by occlusion of the septal artery. In contrast, blood volume expansion was associated with proportional increments in end-diastolic segment length and myocardial shortening at all sites of recordings.[15] Unaltered dynamics of the free wall of the right ventricle and no reduction in stroke volume before blood volume expansion despite marked septal ischemia strongly suggest another compensatory mechanism. In addition to the ischemic contraction pattern of the septum, further evidence for bulging of the ischemic septum into the right ventricular cavity was provided by measurements of the distance between the septum and the right ventricular free wall. Increased systolic excursion to a smaller end-systolic distance than before occlusion of the septal artery strongly suggests

that the ischemic septum behaves as a passive diaphragm pump. This paradoxical movement may to some extent replace the normal contraction of the septum in right ventricular pump function.

Fixler et al[5] were first to claim that they had detected changes in right ventricular function during septal ischemia. In their study stroke volume was not reduced, and they found a reduction in systolic right ventricular pressure from 28 to 25 mm Hg. They attributed this small decrease in systolic pressure to reduced right ventricular contractility, but reduced pulmonary vascular resistance is an equally acceptable explanation since stroke volume did not decrease. To our knowledge, a reduction in stroke volume during occlusion of the septal artery has not previously been observed.

**Clinical considerations:** In man, ischemia of the septal region is usually associated with ischemia of the free walls in which systolic bulging would only have a deleterious effect. However, in principle, septal ischemia may elicit similar compensatory mechanisms in dog and man. Lesions of the left anterior descending coronary artery which reduce the blood supply to the septum either reduce septal excursion during systole or induce a paradoxical movement of the septum. This has been shown in several ventriculocardiographic and echocardiographic observations in patients with coronary artery disease.[16,17] It should be noted that the function of the ischemic septum as a diaphragm pump may be transitory because the distensibility of the septum changes during development of infarction. However, as long as paradoxical movement of the ischemic septum persists, it would support right ventricular emptying.

**Conclusion:** Our study shows that septal ischemia alters the dynamics of both ventricles. Stroke volume was not significantly reduced by occlusion of the septal artery in the unexpanded heart of a dog. Because of increased compliance of the ischemic septum, end-diastolic dilation of the left ventricle is not associated with an increase in afterload counteracting contraction. The compensatory effects of the Frank-Starling mechanism can therefore be fully exploited. However, even at moderate degrees of blood volume expansion this salutary function of the uninjured myocardium becomes insufficient and stroke volume decreases. In the right ventricle, paradoxical movement of the ischemic septum would contribute to the ejection, explaining why no compensatory changes are induced in the free wall of the right ventricle.

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## References

1. **James TN, Burch GE.** Blood supply of the human interventricular septum. Circulation 1958;17:391–396.
2. **Planetto MB.** The coronary arteries of the dog. Am Heart J 1939;18: 403–410.
3. **Donald DE, Essex HE.** The canine septal coronary artery. An anatomic and electrocardiographic study. Am J Physiol 1954;176:143–154.
4. **Blair E.** Anatomy of the ventricular coronary arteries in the dog. Circ Res 1961;9:333–341.
5. **Fixler DE, Monroe GA, Wheeler JM.** Hemodynamic alterations during septal or right ventricular ischemia in dogs. Am Heart J 1977;93:210–215.
6. **Lekven J, Mjøs OD, Kjekshus JK.** Compensatory mechanisms during graded myocardial ischemia. Am J Cardiol 1973;31:467–473.
7. **Lekven J, Kiil F.** Myocardial function in general and regional left ventricular ischaemia in dogs at control and high aortic blood pressure. Cardiovasc Res 1975;9:373–383.
8. **Theroux P, Franklin D, Ross J Jr, Kemper WS.** Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. Circ Res 1974;35:896–908.
9. **Lekven J, Bugge-Asperheim B, Kiil F.** Relationship between local myocardial dimensions and left ventricular volume in dogs. Scand J Clin Lab Invest 1972;29:5–14.
10. **Bugge-Asperheim B, Leraand S, Kiil F.** Local dimensional changes of the myocardium measured by ultrasonic technique. Scand J Clin Lab Invest 1969;24:361–371.
11. **Snedecor GW, Cochran WG.** Statistical Methods. 6th ed. Ames, IA: Iowa State University Press, 1967:59–62.
12. **Miller MM, Thorvaldson J, Ilebekk A, Lekven J.** Myocardial ischemia. Relationship between local flow, function and ST-segment elevation. Eur J Cardiol 1979;10:7–18.
13. **Sostman HD, Kelley MJ, Langou RA.** Perfusion of the canine interventricular septum: significance of right coronary artery supply. Am Heart J 1977; 94:611–617.
14. **Sonnenblick EH.** Instantaneous force-velocity-length determinants in the contraction of heart muscle. Circ Res 1965;16:441–451.
15. **Molaug M, Stokland O, Ilebekk A, Lekven J, Kiil F.** Myocardial function of the interventricular septum. Effects of right and left ventricular pressure loading before and after pericardiotomy in dogs. Circ Res 1981;49:52–61.
16. **Gordon MJ, Kerber RE.** Interventricular septal motion in patients with proximal and distal left anterior descending coronary artery lesions. Circulation 1977;55:338–341.
17. **Kollbash AJ, Beaver BM, Fulkerson PK, Khullar S, Leighton RF.** The relationship between abnormal echocardiographic septal motion and myocardial perfusion in patients with significant obstruction of the left anterior descending artery. Circulation 1977;56:780–785.

# Mechanisms of Spontaneous and Induced Ventricular Arrhythmias in the 24-Hour Infarcted Dog Heart

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**The incidence and types of ventricular arrhythmias were evaluated in 14 dogs, 24 hours after occlusion of the left anterior descending coronary artery. After induction of anesthesia and left thoracotomy, standard electrocardiographic leads and electrograms from the His bundle and the left ventricular endocardium and epicardium (both infarct and normal zones) were recorded. Spontaneous ventricular tachycardia presumably due to abnormal automaticity was consistently observed (average rate 154 ± 26 beats/min). These arrhythmias were irregular and multiform. In this same group of dogs 3 ventricular paced beats at rates above 300 beats/min induced rapid and uniform reentrant ventricular tachycardias (average rate 345 ± 17 beats/min) that were difficult to terminate by premature beats or overdrive pacing. During this sustained ventricular tachycardia, continuous electrical activity was recorded from composite electrodes on the epicardial surface overlying the infarcted zone. Such interectopic activity was not observed during the spontaneous, automatic arrhythmias. Two of the 14 dogs showed only ventricular fibrillation in response to the provocative stimuli. These data confirm previous findings that 24 hours after acute myocardial infarction in the dog heart multiform ventricular rhythms can result from enhanced automaticity. In addition, it was found that ventricular tachycardia can be induced in the same dog heart by a standard ventricular pacing procedure. Continuous electrical activity bridging the interectopic intervals only during the latter tachycardia provides strong evidence for the reentrant basis of these induced arrhythmias. These experimental findings are comparable to the 2 different forms of ventricular arrhythmias described clinically, at the same stage of myocardial infarction. The direct myocardial recordings also provide new insights into the phenomenon of entrainment of tachyarrhythmias by overdrive pacing.**

Previous studies have described various phases of ventricular ectopy occurring after the onset of myocardial ischemia and infarction in the dog heart.[1–4] Evidence compiled from experiments in vivo and in vitro indicates that the spontaneous ventricular ectopic beats and ventricular tachycardias seen in dogs 24 to 48 hours after coronary artery occlusion are primarily due to abnormal automaticity.[3,5–7] In the present study 2 different forms of ventricular tachycardia were found in the 24-hour infarcted dog heart; the mechanism of tachycardia—either abnormal automaticity or reentry—could be determined by rate, QRS morphology, and direct recordings from the myocardium. Moreover, through attempts to terminate the rapid, reentrant ventricular tachycardias with overdrive pacing, the direct recordings provided new evidence on the phenomenon of entrainment described in recent experimental[8] and clinical reports.[9,10]

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## Methods

Experiments were performed in 14 adult mongrel dogs weighing 10 to 20 kg. Each was anesthetized with intravenously administered sodium pentobarbital, 30 mg/kg. Under controlled ventilation, thoracotomy was performed in the fourth intercostal space and the left atrium reflected in order to dissect the proximal left anterior descending coronary artery from the epicardial surface of the heart. The artery was ligated distal to the anterior septal branch by silk sutures passed around it and subsequently tied in 2 stages as described by Harris.[2] After repair of the thoracotomy, the animals were allowed to recover for 24 hours.

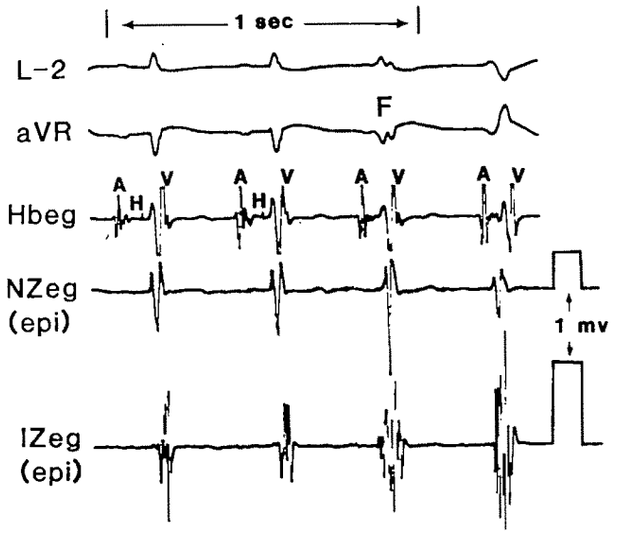



**FIGURE 1.** Spontaneous occurrence of ectopic beats in the 24-hour infarcted dog heart. Traces are lead II (L-2) and aVR electrocardiograms; His bundle electrogram (Hbeg); and composite electrogram from the normal zone of the posterior left ventricular epicardium (NZeg) and anterior epicardium overlying the infarct zone (IZeg). The first 2 beats are sinus beats and the last 2 are a fusion beat (F) and a ventricular ectopic beat. Note the disappearance of His bundle potential (H). Also the IZ composite electrogram shows various fractionated potentials but no delayed activity beyond the QRS complex.

Twenty-four hours later, after induction of anesthesia with sodium pentobarbital, standard electrocardiographic leads I through $V_6$ were monitored and transmural myocardial infarction was confirmed by the presence of Q-S patterns in the anterolateral precordial leads, mainly $V_2$ through $V_6$. The left thoracotomy incision was reopened and the pericardium split to expose the left atrium and ventricle. A large multipolar composite electrode[11] was placed over the epicardial surface of the infarct zone (anteroapical wall) and held in place by the overlying pericardium. A similar composite electrode was positioned on the posterior wall to record from the normal, noninfarcted portion of the left ventricle. Another electrode catheter passed through a carotid artery was positioned by electrographic monitoring on the endocardial surface in the infarct zone. This was determined by the marked diminution or fractionation, or both, of the electrograms recorded at this site in comparison with the normal appearance of electrograms: high amplitude, nonfractionated, within a few millimeters of this site.

A common carotid artery was exposed in the neck and a 5 or 6Fr electrode catheter with ring electrodes 10 mm apart was advanced into the aortic root to record His bundle activity.[12] Vagal-induced slowing of the heart rate was utilized to unmask underlying ventricular automaticity. This was accomplished by delivery of 0.05 ms square wave pulses at 1 to 20 V at a frequency of 20 Hz through silver wires inserted into the cervical vagosympathetic trunks.[13] Electrocardiographic leads II and aVR were monitored continuously as was arterial blood pressure. Atrial and ventricular pacing was achieved by the use of an S-88 Grass stimulator and SIU-5 isolation unit. The stimulator output delivered pulses of 2 to 10 V amplitude and 2 ms duration through stainless steel wires (0.005 in diameter) inserted into the left atrial appendage for atrial pacing or into the right ventricular myocardium near the pulmonary conus for ventricular pacing.

All records were obtained on a multichannel oscilloscopic-photographic recorder (Electronics for Medicine VR-12) at paper speeds of 25 to 200 mm/s with filter frequencies of direct current to 250 Hz for electrocardiographic leads and 30 to 250 Hz for electrographic recordings. In addition, continuous recordings were made in each experiment on a multichannel magnetic tape recorder (Hewlett-Packard 8-channel) so that selected sections could be replayed and photographed at paper speeds as high as 500 mm/s for detailed analysis. Measurements were accurate up to ±5 ms at 100 mm/s, ±3 ms at 200 mm/s, and ±1.0 ms at 500 mm/s.

**Procedure:** Recordings were obtained during sinus rhythm. Vagal-induced slowing of the sinus pacemaker was used to determine the rate and morphology of underlying ventricular ectopic pacemakers. Initially, regular pacing, at rates up to those at which Wenckebach periodicity occurred, was used to induce ventricular arrhythmias. In addition, long-short cycles of atrial paced beats[14] as well as ventricular pacing were used in an attempt to induce repetitive ventricular responses, namely, sustained ventricular tachycardia. Ventricular pacing consisted of 3 paced beats introduced during sinus rhythm at pacing rates of 300 to 420 beats/min. Sustained ventricular

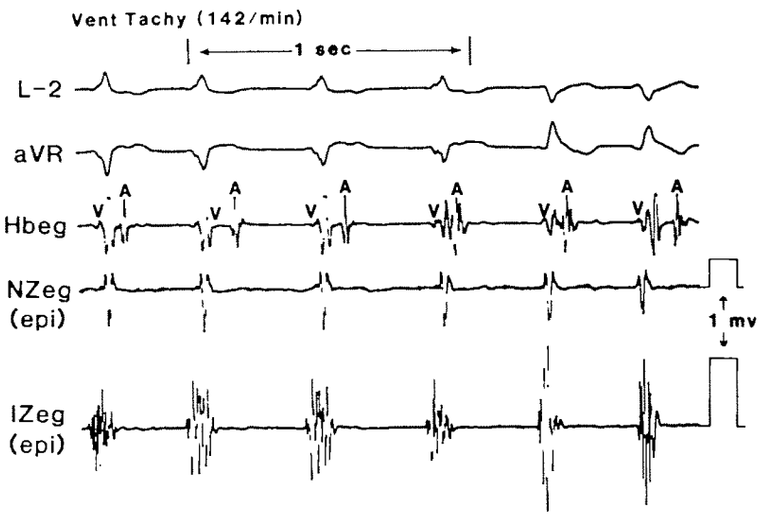



**FIGURE 2.** Spontaneous ventricular tachycardia (Vent Tachy) (approximately 142 beats/min) in the 24-hour infarcted dog heart. Traces and abbreviations are the same as in Figure 1. All the beats are ventricular ectopic in origin. Note the irregular rate and morphology of the ventricular tachycardia. As in Figure 1, the fractionated potentials are confined to the duration of the QRS and are seen only in the electrogram from the epicardium overlying the infarct zone (IZeg).

tachycardia was defined as ≥100 consecutive ectopic beats. During these pacing procedures, areas of maximal epicardial delay or diminished amplitude were sought within the infarct zone by changing the position of the composite electrode on the anteroapical wall.

## Results

In the 14 dogs studied 24 hours after coronary artery ligation, 2 distinct types of ventricular arrhythmias were consistently noted. One type of ventricular arrhythmia could be characterized as multiform ventricular rhythms at an average rate of 154 ± 26 beats/min. The ventricular beats appeared as fusion beats (Fig. 1) or were seen more commonly in the form of runs of ventricular tachycardia which were intermittent and displayed varying QRS morphologies. In order to determine the rate of the ventricular rhythm, vagal-induced slowing or arrest of the sinus rate was achieved over a period of 30 seconds to 1 minute, during which time ventricular ectopic beats were easily identified without interference of the sinus rate. Figure 1 shows 2 sinus beats with His bundle potentials (H) preceding ventricular activation (V). The last 2 beats are either fusion (F) or ventricular in origin.

The multiform nature of the observed ventricular rhythms is characterized in Figure 2. Note that during each different QRS morphology a His bundle deflection cannot be identified before ventricular activation. Also, ventricular activation in all electrograms was coincident with the QRS complex of that beat. Marked fractionation of the electrograms beyond the QRS complex was not observed.

The second type of ventricular arrhythmia was induced by 3 ventricular paced beats at rates between 300 and 420 beats/min. In the same dog as shown in Figures 1 and 2, 24 hours after coronary artery occlusion, sustained ventricular tachycardia was induced by 3 ventricular paced beats (stimuli 1, 2, and 3) at a rate of 360 beats/min. Note that in the first 2 ectopic beats preceding ventricular pacing, electrograms from the epicardium overlying the infarct zone (IZeg) are similar to those seen in the composite recordings shown in Figures 1 and 2. These electrogams show some degree of fractionation as compared with the composite electrogram over the normal zone (NZeg), but activation is confined to the duration of the QRS complex seen in leads II (L-2) and aVR. However during 3 ventricular paced beats (Fig. 3), the duration of ventricular activation increased markedly so that after the second and third beats, electrical activation in the subepicardium overlying the infarct zone extends into the S-T and T wave. At such time ventricular tachycardia at a rate of 360 beats/min was reproducibly induced. Note that during the sustained ventricular tachycardia a pattern of

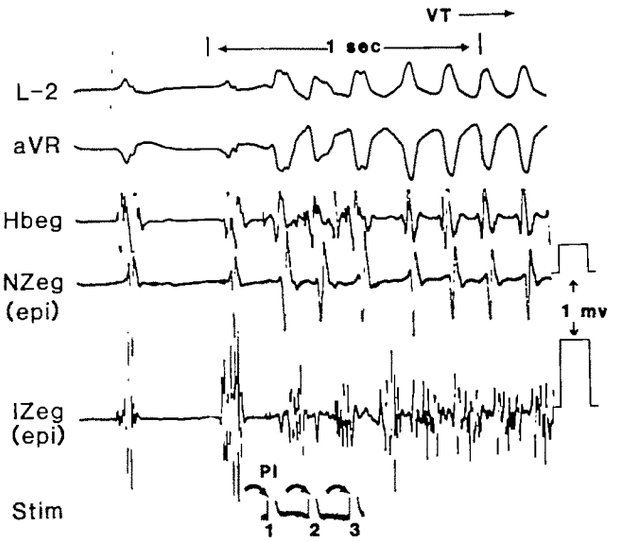



**FIGURE 3.** Induction of sustained ventricular tachycardia (VT) in the 24-hour infarcted dog heart. Traces are the same as in previous figures except for the bottom trace, which depicts stimuli (Stim) delivered to the ventricles to induce ventricular tachycardia. After 2 spontaneous ventricular ectopic beats, 3 ventricular paced beats at a rate of 360 beats/min induce a regular sustained ventricular tachycardia. Note the change in the composite recording from the IZeg, which shows continuous electrical activity during the ventricular tachycardia compared with that seen during the first ectopic beats. Note the lack of continuous activity in other leads during the induced tachycardia. Abbreviations as before.

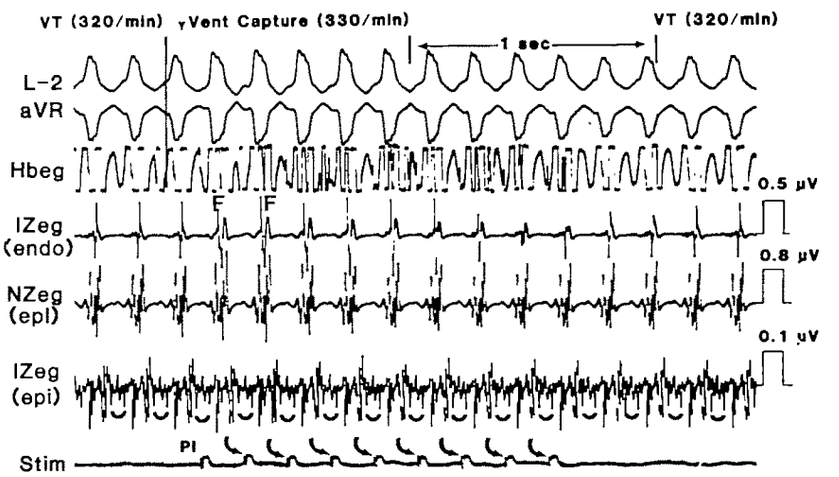



**FIGURE 4.** Overdrive pacing of sustained ventricular tachycardia (VT). Traces are the same as in Figure 3 except that the endocardial catheter recording in the area of the infarct zone (IZeg [endo]) is also shown. Ventricular (Vent) capture (**arrowhead**) by pacer impulses (PI) alters the rate (330 beats/min) and QRS morphology of the sustained ventricular tachycardia (rate 320 beats/min). Fusion beats (F) are shown in the endocardial electrograms. In the epicardial infarct zone (IZeg [epi]) no capture of the continuous electrical activity (**brackets**) occurs by the overdrive pacing, as indicated by its unchanged pattern. With cessation of pacing the sustained tachycardia continues. Abbreviations as before.

continuous electrical activity was recorded in the infarct zone electrogram but not in the normal zone electrogram.

Sustained ventricular tachycardia was induced in 12 of the 14 dogs. These sustained ventricular tachycardias were difficult to terminate using 1 or more ventricular paced beats at a rate faster than the induced tachycardia. In 8 cases it was not possible to terminate the induced sustained ventricular tachycardia by pacing, even though "capture of the QRS" was obtained. These were cardioverted by direct-current shock including 2 cases in which overdrive led to ventricular fibrillation. In the other 4 cases termination was possible with overdrive pacing. In 2 dogs ventricular fibrillation developed in response to 3 paced beats at rates between 300 to 420 beats/min rather than sustained ventricular tachycardia.

Figure 4 shows a sustained ventricular tachycardia (rate 320 beats/min) in which a reproducible pattern of continuous electrical activity was recorded only in the composite electrogram overlying the infarcted myocardium. Ventricular pacing (330 beats/min) from the right ventricular outflow tract caused ventricular capture as evidenced by the more rapid upstroke and greater amplitude of the QRS complex in both leads. Also, the electrogram from the endocardial electrode in the area of the infarct was similarly altered. However, no change in the pattern of continuous electrical activity was seen in the infarct zone electrogram. The lack of capture in the infarct zone allowed the ventricular tachycardia to continue on cessation of ventricular pacing.

However, Figure 5 shows the ability of overdrive pacing to alter the interectopic pattern without terminating tachycardia. Initially, sustained ventricular tachycardia was observed with a relatively reproducible pattern of continuous electrical activity during the interectopic intervals. After the third beat, pacing impulses (PI, curved arrows) were delivered to the ventricle at a faster rate (400 beats/min) than the spontaneous tachycardia (360 beats/min). Note that although the major portion of the ventricles has been captured, resulting in a changed QRS complex (vertical arrow) and alteration of the normal zone electrogram, the pattern of continuous electrical activation in the area overlying the infarct zone is only partly altered. The negative potential (slanted arrows), which was consistently activated at the end of the interectopic interval, just before the onset of the QRS complex is, during pacing, activated at various times within the interectopic interval. Note the changing relation of this potential (straight arrow) to the pacing impulse (PI, curved arrows). When ventricular pacing ceases the sustained ventricular tachycardia continues, and this negative potential resumes its previous position in the interectopic interval. Analysis of the QRS complex might support entrainment[10]; however, recordings from the epicardium in the infarct zone show that the reentrant circuit was only partly captured.

In Figure 6, after a more prolonged overdrive at 390 beats/min, the sustained ventricular tachycardia was terminated. Before termination there is capture of the entire heart including the reentrant circuit, but a different pattern of continuous activity is seen during the interectopic interval. In the trace labelled IZ eg (epi) the length of the interectopic interval is indicated with a black bar. Note that during the interval there is a progressive delay between the initial and the terminal deflections in a Wenckebach-like manner (from 53 to 75 ms). At the greatest delay the continuous activity ceases and an isoelectric period precedes each paced beat. When pacing stops the sustained ventricular tachycardia does not continue. These various forms of entrainment are discussed later.

Table I summarizes the results of this study. Spontaneous ventricular arrhythmias that were intermittent and multiform were found either during normal sinus rhythm or by slowing the sinus rate of vagosympathetic trunk stimulation. The average heart rate of these ectopic rhythms was 154 ± 26 beats/min. Continuous activity was not observed on any of the direct recordings from the ventricular surfaces. At pacing rates of 300 to

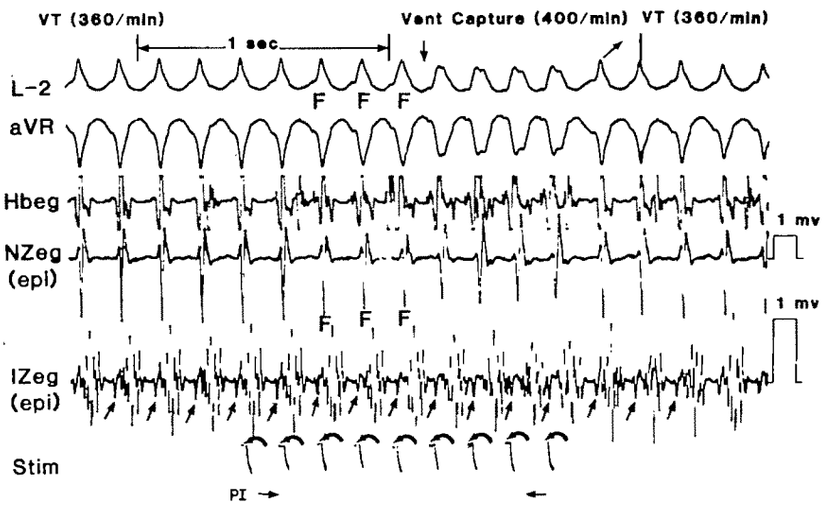



**FIGURE 5.** Attempt to terminate sustained ventricular tachycardia (VT) by ventricular pacing. In the first 6 beats there is a reproducible pattern of electrical activation that occupies most of the interectopic interval. The **slanted arrows** denote the potential that precedes each QRS complex. Ventricular pacing (400 beats/min) (PI = pacer impulse, **curved arrows**) at a rate faster than the induced ventricular tachycardia (360 beats/min) captures the ventricles (**vertical arrow**) as indicated by the change in the QRS complex after the fusion beats (F). Ventricular pacing fails to terminate the tachycardia. See text for details.

420 beats/min in 12 of 14 dogs sustained ventricular tachycardia resulted. These ventricular tachycardias are unifocal and regular at an average rate of 345 ± 17 beats/min. The difference between the average heart rates of these spontaneous and induced ventricular tachycardias was significant ($p < 0.01$). Furthermore, mean blood pressure was also significantly different during the automatic (98 ± 27) and reentrant (33 ± 18) arrhythmias ($p < 0.001$).

**TABLE I Comparisons of Automatic and Reentrant Tachycardias in the 24-Hour Infarcted Dog Heart**

| | Automatic | | Reentrant |
|---|---|---|---|
| Heart rate | 154 ± 26 | $p < 0.01$ | 345 ± 17 |
| QRS morphology | Multiform | | Uniform |
| Regularity | Irregular | | Regular, sustained |
| Mean blood pressure (mm Hg) | 98 ± 27 | $p < 0.001$ | 33 ± 18 |

## Discussion

**The 24-hour infarcted heart:** Several aspects of this experimental preparation should be emphasized. From a mechanistic viewpoint, this study shows that there are 2 distinct forms of arrhythmias seen in this setting: 1 due to abnormal automaticity and the other to a reentrant mechanism. In regard to the former, the present study confirms the previous findings of others[2–4,15] which provided evidence that multiform ventricular rhythms in the 24-hour infarcted dog heart were unmasked by vagal-induced slowing of the heart rate, easily overdriven by atrial pacing but not terminated by the paced beats. In vitro, surviving subendocardial Purkinje fibers have been found in the 24-hour infarct which showed enhanced diastolic depolarization.[5,6] This enhanced automaticity is not found in Purkinje fibers at the same sites after excision from normal hearts.[16] Some recent reports have suggested that triggered automaticity might be responsible for the abnormal automaticity seen in 24-hour infarcted hearts.[7]

The present study also demonstrates that ventricular pacing can be used to consistently induce sustained ventricular tachycardia (12 of 14 dogs). The induced tachycardias were always associated with fractionated electrical activity recorded from the subepicardium overlying the infarct. Moreover, this activity was found to form a continuous bridge between the beat initiating the tachycardia and the first ectopic beat and between subsequent ectopic beats. Although this evidence of slow conduction does not fulfill many of the previously established criteria for reentry, that is, unidirectional block and mapping of the circus movement(s), it represents strong presumptive evidence for reentry.[1,8,17–19] In this regard, electrograms taken from identical sites during the multiform ventricular rhythms never showed continuous or bridging electrical activity between ectopic beats (Fig. 1 and 2). In addition, a clear difference in the rate of the induced reentrant tachycardias and the automatic arrhythmias was observed (Table I). The former showed a regularity of rhythm and QRS morphology, whereas the latter were irregular and had multiform QRS complexes.

Previous reports have described the induction of sustained or protracted ventricular tachycardia in the 3 to 7 day infarcted dog heart.[8,20–24] The incidence of sustained ventricular tachycardia was as variable among these groups as were the techniques for producing their models of sustained ventricular tachycardia. All these reports had in common the conclusion that these tachycardias were well tolerated hemodynamically, easily induced and easily terminated by pacing, and probably caused by a reentrant mechanism. As such, the preparation of an infarcted dog heart 3 to 7 days after coronary artery occlusion[8,20,21,24] or after coronary artery occlusion and reperfusion[22,23] is similar to the patient with recurrent ventricular tachycardias.[25,26]

The 24-hour infarcted heart preparation described in the present study shows induced tachycardia which differed from those described in the subacute studies mainly by the hemodynamic and electrical instability

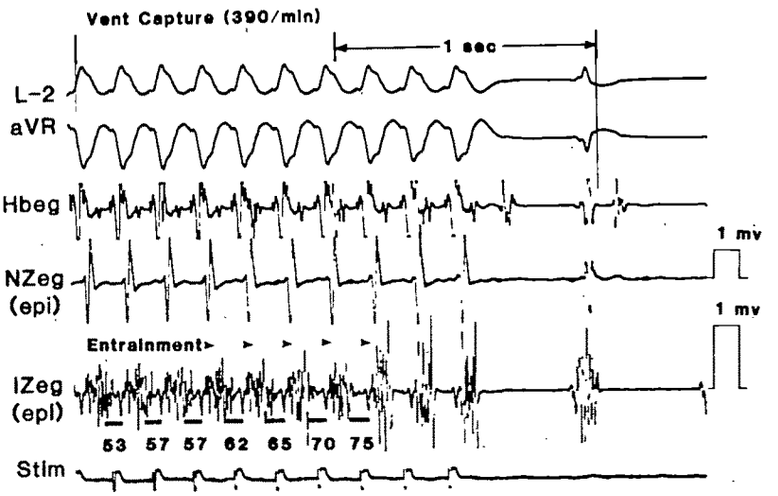



**FIGURE 6.** Successful termination of sustained ventricular tachycardia by prolonged overdrive pacing. Pacing changed the pattern of the interectopic activity (bars) compared with that seen during ventricular capture in Figure 5. During the period of entrainment the time between the initial and terminal interectopic activity (IZeg [epi]) increased from 53 to 75 ms in a Wenckebach fashion. Subsequently, an isoelectric period occurred concomitant with a change in the infarct zone electrogram. With cessation of pacing sustained tachycardia was abolished. See text for discussion. Abbreviations as before.

of the former preparation. In this respect, the sustained ventricular tachycardias induced in the 24-hour infarcted heart are similar to those induced in patients surviving out-of-hospital cardiac arrest.[27] Therefore the use of this preparation may be applicable in testing new antiarrhythmic agents against life-threatening arrhythmias in the experimental animal and eventually in the patient at risk for sudden death.

**Clinical implications:** With the advent of continuous electrocardiographic monitoring in the coronary care unit, it was found that paroxysmal ventricular tachycardia, rather than being rare, was a common occurrence in patients 24 to 48 hours after the onset of myocardial infarction. It has been reported that accelerated idioventricular rhythms occur fairly often in patients with acute myocardial infarction.[28,29] In man, these arrhythmias have been characterized by a relatively slow rate, 60 to 100 beats/min, a gradual onset, and termination with no adverse hemodynamic effect and no tendency to ventricular fibrillation. Enhanced automaticity of ectopic foci has been regarded as a primary causal mechanism because ventricular fusion beats are common. Except for the rate and multiformity, these clinical tachycardias are very similar to those occurring spontaneously in the 24-hour infarcted dog heart. The explanation for the faster rate and multiform character of the abnormal ventricular automaticity may be the high sympathetic tone in the open-chest, pentobarbital-anesthetized dog.

In contrast, Wellens et al[30] presented a series of patients studied 24 to 48 hours after acute myocardial infarction who manifested sustained ventricular tachycardias. Both atrial and ventricular paced beats failed to convert these arrhythmias to sinus rhythm. This is consistent with our findings in 24 infarcted dog hearts in which the induced ventricular tachycardias (rates averaging 345 beats/min) were interrupted only with difficulty and only after prolonged periods of overdive pacing (Fig. 4 and 5). Wellens et al[30] concluded that the ventricular tachycardias they observed were the result of an automatic mechanism because they could not be readily initiated and terminated by paced beats. However, there is no indication that the rhythms were overdriven; rather cardioversion was used to terminate the arrhythmia in 4 of the 6 patients. In only 2 of these patients could the tachycardia be terminated by 2 ventricular premature beats in close succession. In contrast to these patients with acute myocardial infarction, Wellens et al[30] found that the great majority of patients with chronic myocardial infarction, studied electrophysiologically, exhibited facile initiation and termination of tachycardias with ventricular premature or atrial premature beats.

Rothfeld et al[28] described 2 patients studied 24 to 48 hours after acute myocardial infarction. Each showed accelerated idioventricular rhythm (60 to 100 beats/min) which were intermittently interrupted by paroxysms of rapid ventricular tachycardia at rates at least 100 beats/min faster. This occurrence of 2 forms of ventricular tachycardia supposedly caused by 2 different mechanisms is closely analogous to that seen in our experimental preparation.

**Entrainment of ventricular tachycardia:** In the course of these studies several insights were made into the phenomenon of entrainment of ventricular tachycardia.[10] This process has been variously described as continuous concealed reentry,[8] concealed perpetuation,[26] and entrainment.[10] The last term has been the subject of detailed studies both in atrial[31] and ventricular tachyarrhythmias. MacLean et al[10] defined entrainment of a tachycardia by rapid pacing as "an increase in the rate of all tissue of a chamber being paced to a faster rate than the tachycardia, with resumption of the intrinsic rate upon either abrupt cessation of pacing or slowing of the pacing rate below the intrinsic rate of the tachycardia." This effect occurs within a narrow range of increased pacing rates above which the tachycardias are usually interrupted. The use of the composite electrogram in the infarct zone in the present study allowed observations not possible using electrocardiography alone. For example, our results demonstrate that entrainment of ventricular tachycardia or capture of the ventricles by pacing can occur while local electrograms in the infarct zone are unaltered in their pattern of activation (Fig. 3). Similarly, Josephson et al[9] showed transient entrainment of ventricular tachycardia during overdrive with concealed perpetuation of the intrinsic ventricular tachycardia. This was indicated by the unchanged activation of an electrogram recorded within a ventricular aneurysm during sustained ventricular tachycardia and during ventricular pacing. These investigators concluded that "the reentrant circuit must be small, electrocardiographically silent and relatively protected." MacLean et al,[10] on the other hand, proposed that transient entrainment occurs as a result of failure to achieve a critical ventricular rate. Our findings provide evidence for this view as well. In Figure 6 we showed that the pattern of continuous activity during "ventricular capture" at a rate of 390 beats/min was substantially different from the pattern during the intrinsic ventricular tachycardia at a rate of 360 beats/min (Fig. 5). That 390 beats/min was a critical rate is shown by the occurrence of a Wenckebach-like delay within the slow conducting portion of the reentrant circuit before actual capture and termination of the sustained tachycardia (last 3 paced beats in Figure 6).

In our studies the apparent protection of the reentrant circuit may be in part the result of the rapid rate of the ventricular tachycardia which leaves little interectopic time for the pacing impulse to enter the circuit, the distance from the pacing site to the area of reentry, and the small size of the reentrant circuit. A more systematic study of this phenomenon in the preparation we have decribed may provide a better understanding of entrainment of ventricular tachycardia.

In conclusion, in a preparation of myocardial infarction in the dog heart 24 hours after coronary artery occlusion, 2 types of ventricular arrhythmias can be consistently differentiated on the basis of the presence or absence of continuous electrical activity recorded from composite electrodes on the epicardial surface overlying the infarct zone. This preparation can be used

to study the mechanisms of sudden death, the effect of drugs in the prevention of life-threatening ventricular tachycardia, and the pathophysiologic mechanisms of ventricular tachycardia.

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## References

1. **Harris AS, Guevera Rojas A.** The initiation of ventricular fibrillation due to coronary occlusion. Exp Med Surg 1943;1:105–121.
2. **Harris AS.** Delayed development of ventricular ectopic rhythm following experimental coronary occlusion. Circulation 1950;1:1318–1328.
3. **Scherlag BJ, El-Sherif N, Hope R, Lazzara R.** Characterization and localization of ventricular arrhythmias resulting from myocardial ischemia and infarction. Circ Res 1974;35:372–383.
4. **Kaplinsky E, Ogawa S, Balke CW, Dreifus LS.** Ventricular reentry and automaticity in myocardial infarction. Chest 1978;74:66–71.
5. **Lazzara R, El-Sherif N, Scherlag BJ.** Electrophysiological properties of Purkinje cells in one-day-old myocardial infarction. Circ Res 1973;33: 722–734.
6. **Friedman PL, Stewart JR, Fenoglio JJ Jr, Wit AL.** Survival of subendocardial Purkinje fibers after extensive myocardial infarction in dogs; in vitro and in vivo correlation. Circ Res 1973; 33:597–611.
7. **El-Sherif N, Zeiler R, Gough WB.** Effects of catecholamines, verapamil and tetrodotoxin on triggered automaticity in canine ischemic Purkinje fibers (abstr). Circulation 1980;62:Suppl III:III-281.
8. **Hope RR, Scherlag BJ, El-Sherif N, Lazzara R.** Continuous concealed ventricular arrhythmias. Am J Cardiol 1977;40:733–738.
9. **Josephson ME, Horowitz LN, Farshidi A, Spielman SR, Michelson EL, Greenspan AM.** Sustained ventricular tachycardia: evidence for a protected localized reentry. Am J Cardiol 1978;42:416–424.
10. **MacLean WAH, Plumb VJ, Waldo AL.** Transient entrainment and interruption of ventricular tachycardia. PACE 1981;4:358–366.
11. **William DO, Scherlag BJ, Hope R, El-Sherif N, Lazzara R.** The pathophysiology of malignant ventricular arrhythmias during acute myocardial infarction. Circulation 1974;50:1163–1172.
12. **Scherlag BJ, Abelleira JL, Samet P.** Electrode catheter recording from the His bundle and left bundle in the intact dog. In: Kao FF, Kolzumi K, Vassalle M, eds. Research in Physiology. Bologna, Italy: Aulo Gaggi, 1971:223–238.
13. **Lazzara R, Scherlag BJ, Robinson MJ, Samet P.** Selective in situ parasympathetic control of the canine sinoatrial and atrioventricular nodes. Circ Res 1973A;32:393–401.
14. **Hope RR, Scherlag BJ, El-Sherif N, Lazzara R.** Ventricular arrhythmias in healing myocardial infarction: role of rhythm vs rate in reentrant activation. J Thorac Cardiovasc Surg 1978;75:458–466.
15. **Kerzner J, Wolf M, Kosowsky BD, Lown B.** Ventricular ectopic rhythms following vagal stimulation in dogs with acute myocardial infarction. Circulation 1973;47:44–50.
16. **Hope RR, Scherlag BJ, El-Sherif N, Lazzara R.** Hierarchy of ventricular pacemakers. Circ Res 1976;39:883–888.
17. **Waldo AL, Kaiser GA.** Study of ventricular arrhythmias associated with acute myocardial infarction in the canine heart. Circulation 1973;47:1222–1228.
18. **Wit AL, Biggers JT Jr.** Possible electrophysiological mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. Circulation 1975;51:96–115.
19. **El-Sherif N, Scherlag BJ, Lazzara R, Hope RR.** Reentrant ventricular arrhythmias in the late myocardial infarctin period. i. Conduction characteristics in the infarction zone. Circulation 1977;55:686–702.
20. **Wolff GA, Veith F, Lown B.** A vulnerable period for ventricular tachycardia following myocardial infarction. Cardiovasc Res 1968;2:111–121.
21. **Kaplinsky E, Yahini JH, Neufeld HN.** On the mechanism of sustained ventricular arrhythmias associated with acute myocardial infarction. Cardiovasc Res 1972;6:135–142.
22. **Karagueuzian HS, Fenoglio JJ Jr, Weiss MB, Wit AL.** Protracted ventricular tachycardia induced by premature stimulation of the canine heart after coronary artery occlusion. Circ Res 1979;44:833–846.
23. **Michelson EL, Spear JF, Moore EN.** Electrophysiologic and anatomic correlates of sustained ventricular tachyarrhythmias in a model of chronic myocardial infarction. Am J Cardiol 1980;45:583–590.
24. **Garan H, Falkon JT, Ruskin JN.** Sustained ventricular tachycardia in recent canine myocardial infarction. Circulation 1980;62:980–987.
25. **Wellens HJJ, Lie KI, Durrer D.** Further observations on ventricular tachycardia as studied by electrical stimulation of the heart. Chronic recurrent ventricular tachycardia and ventricular tachycardia during acute myocardial infarction. Circulation 1974;49:647–653.
26. **Josephson ME, Seides SF.** Clinical Cardiac Electrophysiology. Techniques and interpretation. Chap. 12. Philadelphia: Lea & Febiger, 1979:247–280.
27. **Ruskin JN, DiMarco JP, Garan H.** Out-of-hospital cardiac arrest. Electro-New Engl J Med 1980;303:607–613.
28. **Rothfeld EL, Zucker IR, Leff WA, Ritota MC.** Coexisting paroxysmal ventricular tachycardia and idioventricular rhythm in acute myocardial infarction. J Electrocardial 1973;6:149–152.
29. **Schamroth L.** Idioventricular tachycardia. J Electrocardiol 1968;1:205–212.
30. **Wellens HJJ, Durrer DR, Lie KI.** Observations on mechanisms of ventricular tachycardia in man. Circulation 1976;54:237–244.
31. **Waldo AL, MacLean WAH, Karp RB, Kouchoukos NT, James TN.** Entrainment and interruption of atrial flutter with atrial pacing: studies in man following open heart surgery. Circulation 1977;56:737–745.

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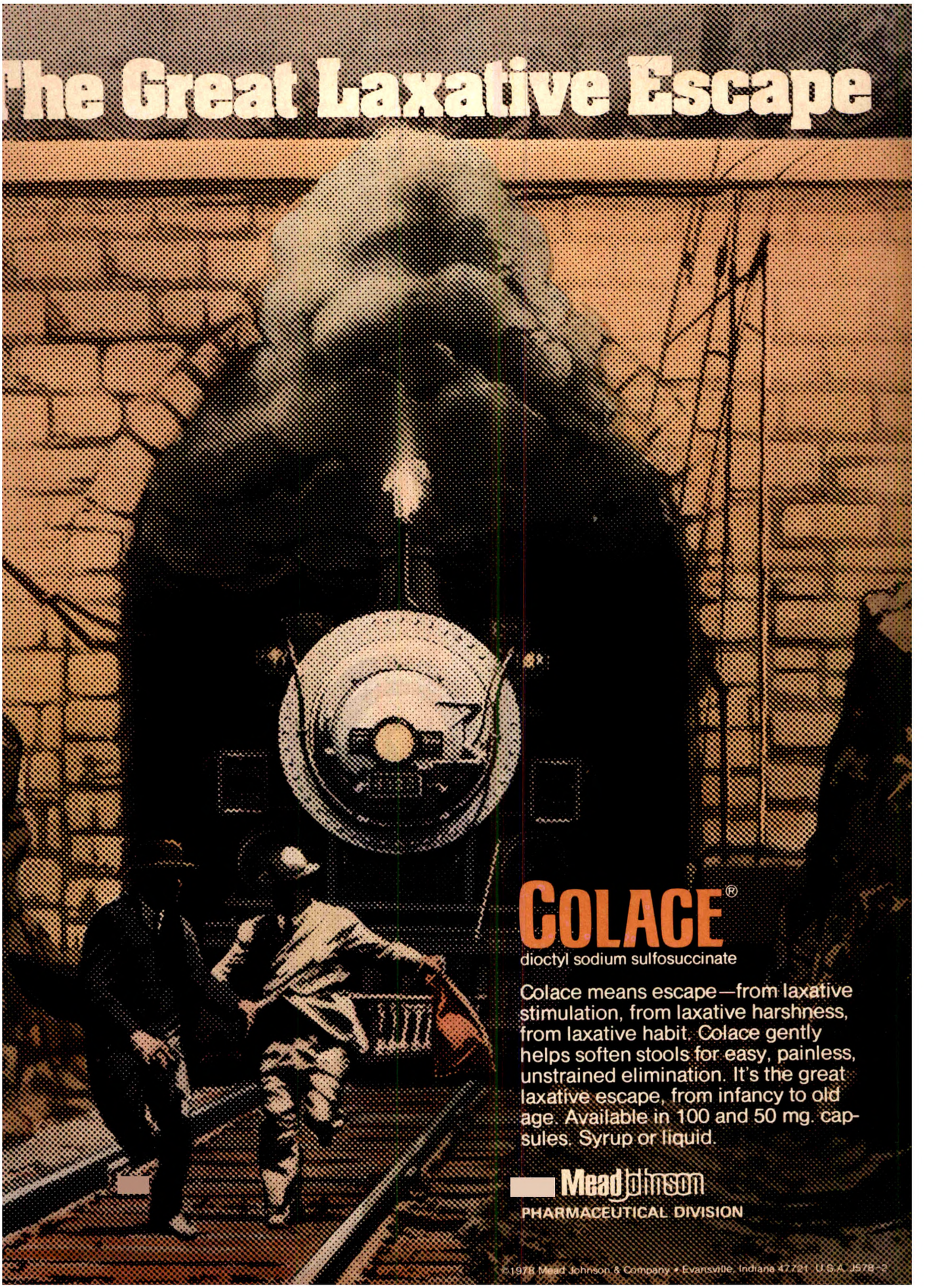
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> **Journal:** Vismara LA, Vera Z, Miller RR, Mason DT. Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. Am J Cardiol 1977; 39:1027–1034.
>
> **Chapter in Book:** Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. Heart Disease in Infants, Children and Adolescents. Baltimore: Williams & Wilkins, 1968: 134–139.
>
> **Book:** Berne E. Principles of Group Treatment. New York: Oxford University Press, 1966:26.

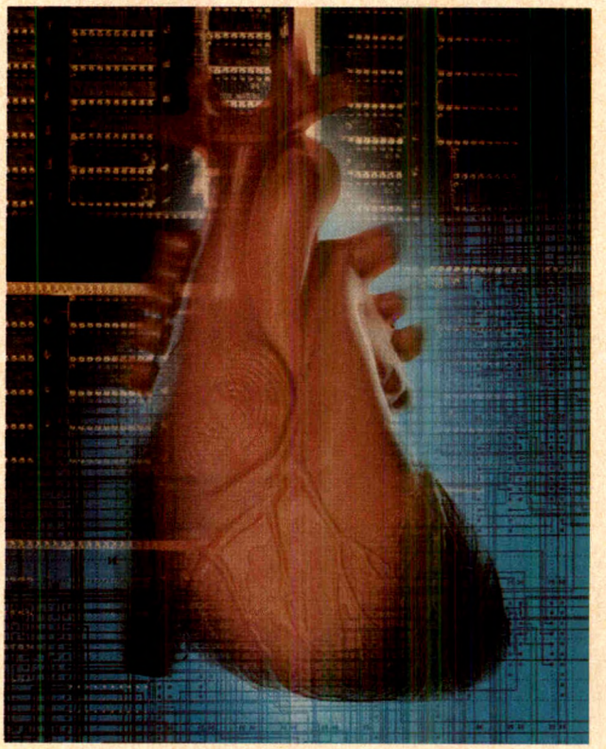
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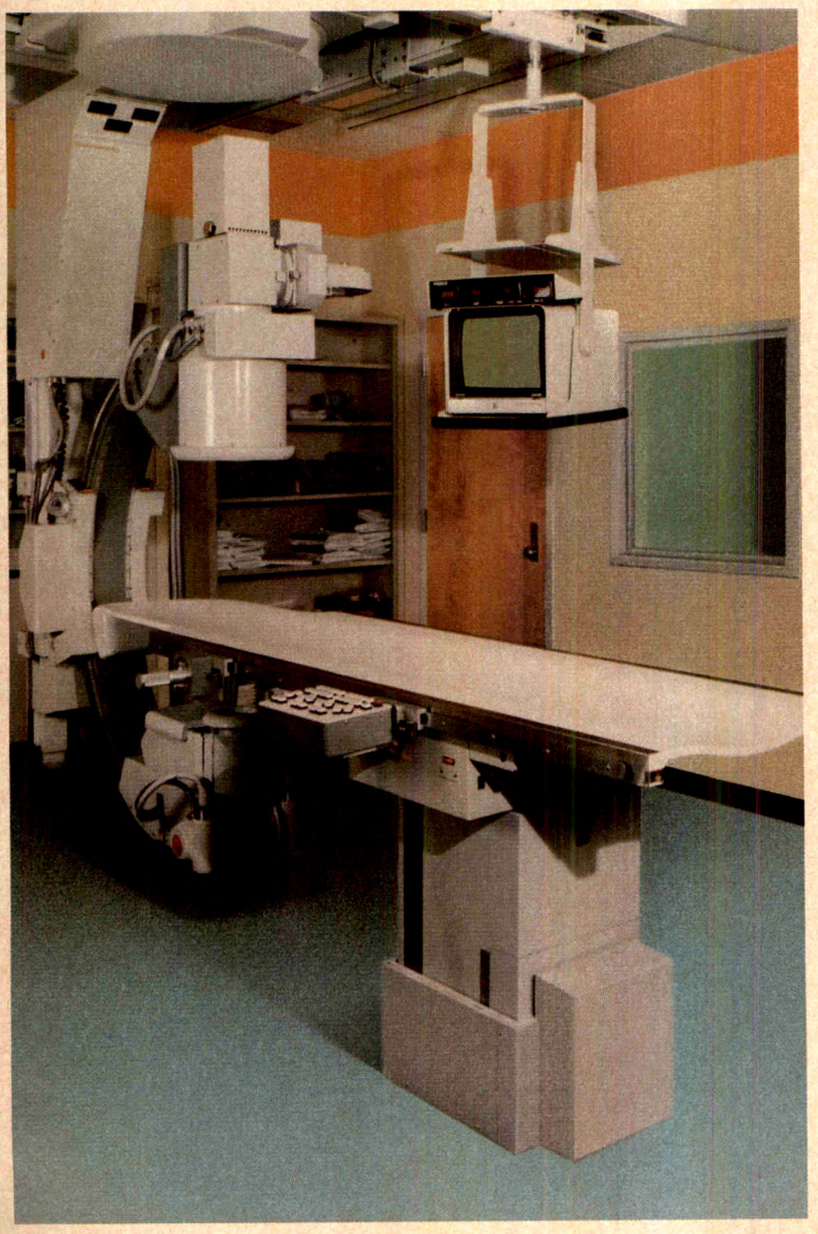
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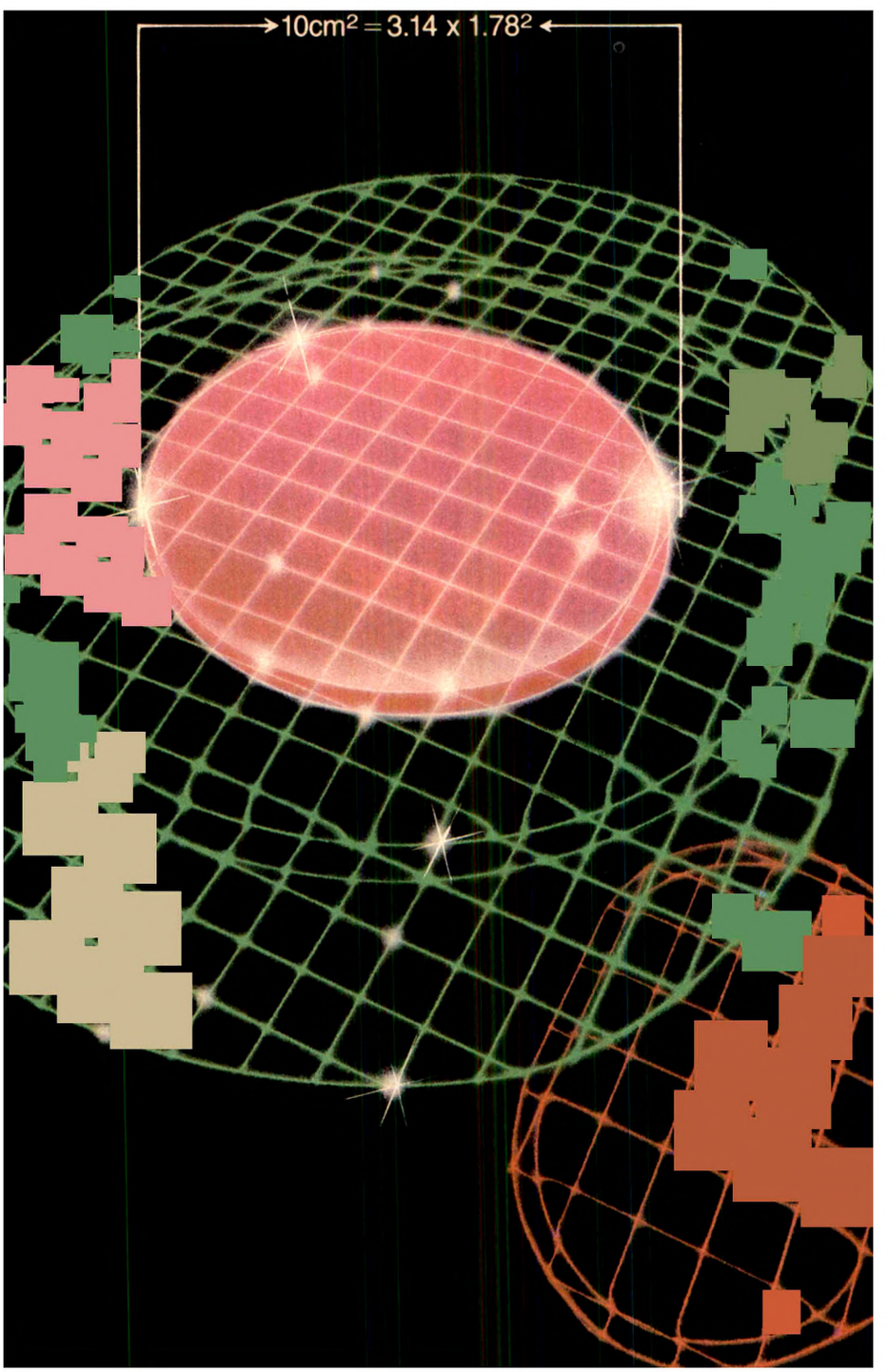
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10cm² = 3.14 x 1.78²

# Designed with the patient in mind.

**People move, bend, stretch, perspire.**
When we designed Nitro-Dur™ (nitroglycerin) Transdermal Infusion System, we designed it with features to accommodate these human factors. Because of the size of Nitro-Dur it has features that other nitroglycerin systems don't have.

**It's big because it's the only one with a wide adhesive strip.**
If angina patients were supine for 24 hours, adhesion would be a minor concern. But people move, bend, stretch, and turn while awake and asleep. A system has to stay put throughout all these movements.

In developing Nitro-Dur, we tested dozens of tapes before we settled on a microporous tape known for its excellent adhesion, one that doesn't leave the skin macerated and is relatively painless on removal.

The Nitro-Dur adhesive strip is wider than that on any other system. Wide enough to stay put during a 24-hour day of walking, showering, bending, standing or sleeping. Wide enough to prevent leaking or falling off.

**It's big because it's the only one with an absorbent pad.**
Because perspiration could affect adhesion, we added an absorbent pad behind the matrix. Nitro-Dur is the only system with this feature.

**Surface area determines the dose.**
The stratum corneum regulates the absorption of cutaneously applied nitroglycerin. Therefore, as the surface area of application is increased the dose of nitroglycerin also increases. To insure a fixed surface area, we offer a solid—a gel polymer matrix that contains the active drug.

**The only transdermal to offer you greater dosage flexibility.**
Nitro-Dur has four dosage strengths—5, 10, 15 and 20 $cm^2$. Other systems limit your options to two strengths.

**The only place it's smaller—the cost to your patients.**
Your patients can save up to $75 a year using Nitro-Dur rather than competitive products. Considering that they may be taking the product for years, that's a very important advantage.[1]

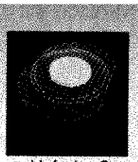
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**The most widely prescribed transdermal nitroglycerin system.**

**Nitro-Dur™**
(nitroglycerin)
Transdermal Infusion System

Please see next page for a summary of prescribing information.

# Nitro-Dur™
(nitroglycerin)
Transdermal Infusion System



**DESCRIPTION:** The Nitro-Dur Transdermal Infusion System contains nitroglycerin in a gel-like matrix composed of glycerin, water (purified), lactose, polyvinyl alcohol, povidone and sodium citrate to provide a continuous source of the active ingredient. Nitro-Dur is available in dosage sizes 5cm², 10cm², 15cm² and 20cm², containing 26 mg, 51 mg, 77 mg and 104 mg of nitroglycerin, respectively, thereby providing precise dosing levels of nitroglycerin. Nitro-Dur has a rated release *in vivo* of approximately 0.5mg/cm²/24 hours. Each unit is sealed in a polyester-foil-polyethylene laminate. The bandage portion consists of a medical grade non-woven, heat sealable, microporous tape.

**CLINICAL PHARMACOLOGY:** When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies[2] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

**INDICATIONS AND USAGE:** Prevention and treatment of angina pectoris due to coronary artery disease.

**CONTRAINDICATIONS:** Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

**WARNINGS:** The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

**PRECAUTIONS:** Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

**ADVERSE REACTIONS:** Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

**HOW SUPPLIED:** Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28.

**CAUTION:** Federal law prohibits dispensing without a prescription.

**PATIENT INSTRUCTIONS FOR APPLICATION:** Patient instructions are furnished with each unit dose package.

*For complete prescribing information, please see package insert.*

1082

**References**


1. Pharmacy acquisition cost (AWP), *Drug Topics Red Book*, 1982 (assuming a 50% markup).
2. Data on file: Key Pharmaceuticals, Inc.


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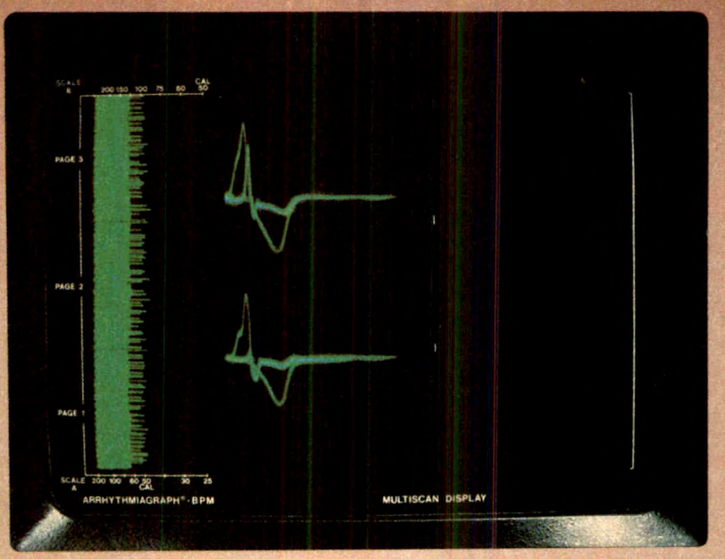
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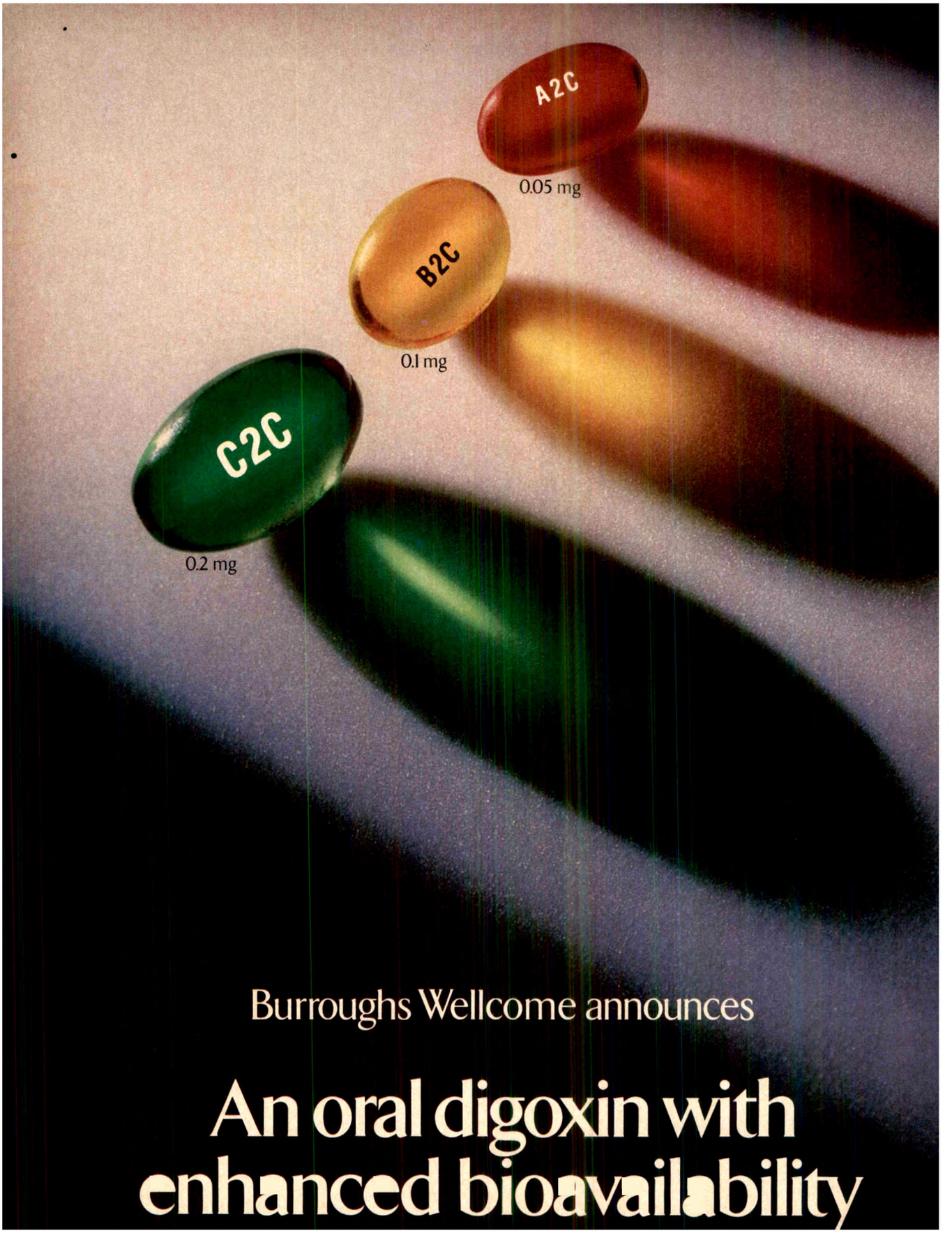
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|---|---|---|---|---|
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| Lanoxin® Elixir | 70-85% | 0.125 | 0.25 | 0.5 |
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| Lanoxin® Injection/IV | 100% | 0.1 | 0.2 | 0.4 |
| **LANOXICAPS®** Capsules | 90-100% | 0.1 | 0.2 | 0.4 |

*1 mg = 1,000 μg

Due to the more complete absorption of digoxin from Lanoxicaps, recommended oral doses are 80% of those for tablets, elixir, and IM injection.

Lanoxicaps may help make a smoother transition for patients who are being switched from intravenous to oral therapy. Also, consider Lanoxicaps for all your newly diagnosed patients.

Colors of Lanoxicaps are distinctive, for less confusion or misidentification by patients. Please see next page for brief summary of prescribing information.

# new LANOXICAPS®
## (digoxin solution in capsules)

50 μg (0.05 mg) I.D. Imprint A2C (red)
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LANOXICAPS® shown magnified four times actual size.

Wellcome / **Burroughs Wellcome Co.**
Research Triangle Park
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# new LANOXICAPS®
## (digoxin solution in capsules)

**LANOXICAPS®** brand DIGOXIN SOLUTION IN CAPSULES 50 μg (0.05 mg), 100 μg (0.10 mg), and 200 μg (0.20 mg)
*Brief Summary of Prescribing Information*

**INDICATIONS AND USAGE**
**Heart Failure:** The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma).

Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

**CONTRAINDICATIONS**
Digitalis glycosides are contraindicated in ventricular fibrillation.

Any untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin, as is hypersensitivity to digoxin itself. Allergy to digoxin, though rare, does occur. It may not extend to all preparations, and another digitalis glycoside may be tried with caution.

**WARNINGS**
The use of digoxin or other digitalis glycosides is unwarranted in the treatment of obesity.

Digoxin in soft capsules should be administered in divided daily doses to minimize any potential adverse reactions. Where compliance is considered a problem, single daily dosing may be appropriate.

Anorexia, nausea, vomiting, and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section in complete prescribing information).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary. Careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity. Note: Digitalis glycosides are an important cause of accidental poisoning in children.

**PRECAUTIONS**
**General:** Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section in complete prescribing information). More time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range," because potassium depletion sensitizes the myocardium to digoxin. Hypokalemia may result from diuretic, amphotericin B, or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see *Treatment of arrhythmias produced by overdosage*, in OVERDOSAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypocalcemia can nullify the effects of digoxin in man; digoxin may be ineffective until serum calcium is restored to normal.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine causes a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the quinidine dose. Because of the considerable variability of this interaction, digoxin dosage should be carefully individualized.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (eg, hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e., sick sinus syndrome), digoxin may worsen sinus bradycardia or sinoatrial block.

In patients with Wolff-Parkinson-White syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

**Drug Interactions:** Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias. *Quinidine* causes a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. *Antacids, kaolin-pectin, sulfasalazine, neomycin,* and *cholestyramine* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Thyroid* administration to a digitalized hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias, because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although *propranolol* and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

**ADVERSE REACTIONS**
The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5% to 20%, with 15% to 20% being considered serious (1% to 4% of patients receiving digoxin). Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

**Adults:**
*Cardiac*—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease. Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm, and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage.

Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances.

*Gastrointestinal*—Anorexia, nausea, vomiting, and, less commonly, diarrhea are common early symptoms of overdosage. Uncontrolled heart failure may also produce such symptoms.

*CNS*—Visual disturbances (blurred or yellow vision), headache, weakness, apathy, and psychosis can occur.

*Other*—Gynecomastia is occasionally observed.

**Infants and Children:**
Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea, and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular

arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

**OVERDOSAGE** Treatment of arrhythmias produced by overdosage

**Adults:**

Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe.

Potassium salts are commonly used, particularly if hypokalemia is present. Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in infants and children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 ml) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol, and phenytoin, although use of the latter must be considered experimental. In advanced heart block, temporary ventricular pacing may be beneficial.

**Infants and Children:**

See Adults section (immediately above) for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium.

If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

**DOSAGE AND ADMINISTRATION**

*Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions.* Diminished renal function is the most important factor requiring modification of recommended doses.

Due to the more complete absorption of digoxin from soft capsules, recommended oral doses are only 80% of those for tablets, elixir, and IM injection.

Because the significance of the higher peak serum concentrations associated with once-daily capsules is not established, divided daily dosing is presently recommended for:

1. infants and children under 10 years of age;
2. patients requiring a daily dose of 300 μg (0.3 mg) or greater;
3. patients with a previous history of digitalis toxicity;
4. patients considered likely to become toxic;
5. patients in whom compliance is not a problem.

Where compliance is considered a problem, once-daily dosing may be appropriate.

**Adults:**

*Adults: rapid digitalization with a loading dose*—Peak body digoxin stores of 8 to 12 μg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Larger stores (10 to 15 μg/kg) are often required for adequate control of ventricular rate in patients with atrial flutter or fibrillation. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 μg/kg [see PRECAUTIONS section]).

The loading dose should be based on the projected peak body stores and administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6- to 8-hour intervals, *with careful assessment of clinical response before each additional dose.*

If the patient's clinical response necessitates a change from the calculated dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

**Dosage for Previously Undigitalized Patients:**

In previously undigitalized patients, a single initial Lanoxicaps dose of 400 to 600 μg (0.4 to 0.6 mg) usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Additional doses of 100 to 300 μg (0.1 to 0.3 mg) may be given cautiously at 6- to 8-hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Lanoxicaps that a 70-kg patient requires to achieve 8 to 15 μg/kg peak body stores is 600 to 1000 μg (0.6 to 1.0 mg).

*Adults: gradual digitalization with a maintenance dose*—The following table provides average Lanoxicaps daily maintenance dose requirements for patients with heart failure based upon lean body weight and renal function:

Usual Lanoxicaps Daily Maintenance Dose Requirements (μg) for Estimated Peak Body Stores of 10 μg/kg

| Corrected Ccr (ml/min per 70 kg) | Lean body weight (kg/lbs) 50/110 | 60/132 | 70/154 | 80/176 | 90/198 | 100/220 | Number of days before steady-state achieved |
|---|---|---|---|---|---|---|---|
| 0 | 50 | 100 | 100 | 100 | 150 | 150 | 22 |
| 10 | 100 | 100 | 100 | 150 | 150 | 150 | 19 |
| 20 | 100 | 100 | 150 | 150 | 150 | 200 | 16 |
| 30 | 100 | 150 | 150 | 150 | 200 | 200 | 14 |
| 40 | 100 | 150 | 150 | 200 | 200 | 250 | 13 |
| 50 | 150 | 150 | 200 | 200 | 250 | 250 | 12 |
| 60 | 150 | 150 | 200 | 200 | 250 | 300 | 11 |
| 70 | 150 | 200 | 200 | 250 | 250 | 300 | 10 |
| 80 | 150 | 200 | 200 | 250 | 300 | 300 | 9 |
| 90 | 150 | 200 | 250 | 250 | 300 | 350 | 8 |
| 100 | 200 | 200 | 250 | 300 | 300 | 350 | 7 |

*Example*—Based on the above table, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 ml/min should be given 200 μg (0.2 mg) of Lanoxicaps per day, usually taken as a 100 μg (0.1 mg) capsule after the morning and evening meals. Steady-state serum concentrations should not be anticipated before 11 days.

**Digitalizing Dose for Children:**

Usual Digitalizing and Maintenance Dosages for Lanoxicaps in Children With Normal *Renal Function Based on Lean Body Weight*

| Age | Digitalizing* Dose (μg/kg) | *Daily*† Maintenance Dose (μg/kg) |
|---|---|---|
| 2-5 Years<br>5-10 Years<br>Over 10 Years | 25-35<br>15-30 | 25%-35% of the oral or IV loading dose‡ |

*IV digitalizing doses are the same as Lanoxicaps digitalizing doses.
†Divided daily dosing is recommended for children under 10 years of age.
‡Projected or actual digitalizing dose providing desired clinical response.

More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided above can be used in calculating this dose for patients with normal renal function. In children with renal disease, digoxin dosing must be carefully titrated based upon desired clinical response.

Long-term use of digoxin is indicated in many children who have been digitalized for acute heart failure, unless the cause is transient. Children with severe congenital heart disease, even after surgery, may require digoxin for prolonged periods.

*It cannot be overemphasized that both the adult and pediatric dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.*

**HOW SUPPLIED**

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 50 μg (0.05 mg): bottles of 100. Imprint A2C (red)

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 100 μg (0.10 mg)†: bottles of 100. Imprint B2C (yellow)

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 200 μg (0.20 mg)†: bottles of 100. Imprint C2C (green)

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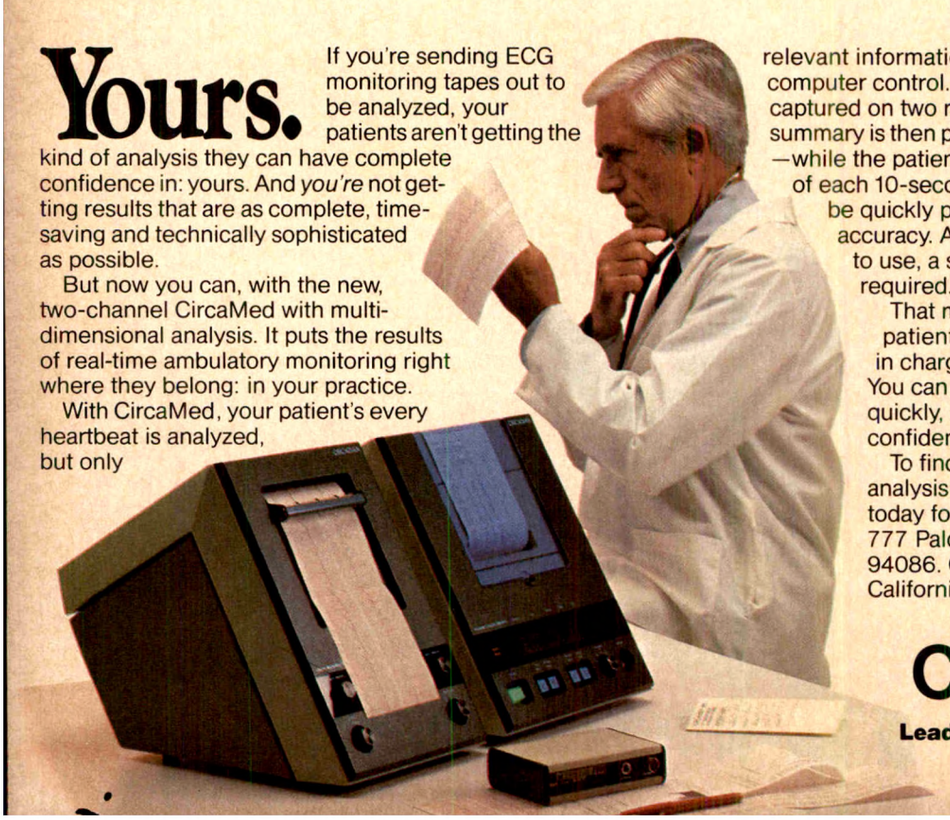
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# Can Tracking of Contrast Echocardiographic Targets Be Used to Measure Intracardiac Flow Velocities?

LILLIAM M. VALDES-CRUZ, MD, DAVID J. SAHN, MD, SUZANA HOROWITZ, BS, DANIEL C. FISHER, MD, STANLEY J. GOLDBERG, MD, and HUGH D. ALLEN, MD

**Recent studies suggest that the slopes of linearly moving echocardiographic contrast targets (microbubbles) can be used to predict flow velocities in the right heart. The purpose of this study was to assess the accuracy of velocities measured with contrast echocardiography by comparing them with those recorded with a previously calibrated quantitative range-gated 2-dimensional echocardiographic Doppler flow meter. Venous saline echocardiographic contrast injections and Doppler studies were performed in 10 patients, aged 6 months to 16 years, who had been operated on for lesions in the left side of the heart. Blood velocities were measured on a Doppler flow meter along the direction of flow in the main pulmonary artery just distal to the pulmonary valve in a short-axis plane. Immediately after the Doppler study, an M-mode echocardiogram of the pulmonary valve was derived from the same plane as that used for the preceding Doppler sample volume, passing through the pulmonary valve; 2 to 10 ml of normal saline solution was forcefully hand-injected through a previously positioned peripheral venous line and recorded on strip chart and videotape at a paper speed of 100 mm/s. Pulmonary flow velocities by contrast echocardiography were measured as the slopes of the moving contrast echocardiographic targets seen just beyond the pulmonary valve leaflets. Measurable microbubbles had to follow the constraints described in a previous study by Shiina et al.[3] Doppler velocities were read directly from the machine calibration marks (centimeters per second) recorded with the fast Fourier output. Instantaneous and peak velocities were determined at time-matched systolic points in cardiac cycles of identical R-R intervals. Significant but low level correlations were found between contrast echocardiography and Doppler instantaneous ($r = +0.45$) or peak ($r = +0.11$) systolic velocities. Our results suggest that while contrast echocardiographic microbubbles can be measured to yield a velocity, they do not behave like moving red blood cells that reflect ultrasound to produce a Doppler shift. Therefore, contrast echocardiography cannot be used reliably to measure flow velocities in the right heart.**

Recently, there has been interest in analyzing echocardiographic contrast targets (microbubbles) as qualitative indicators of blood flow patterns in the right heart, specifically for identifying tricuspid or pulmonary insufficiency, or both.[1,2] Attempts at quantitation suggest that the slopes of linearly moving contrast echocardiographic microbubbles imaged within the tricuspid and pulmonary valve orifices afford reasonably accurate estimates of instantaneous blood flow velocity at those sites.[3] These results imply that microbubbles behave physiologically like moving red cells within the bloodstream. The present study was designed to test this hypothesis and to assess the accuracy of contrast echocardiographic velocities by comparing them with simultaneously measured instantaneous and peak velocities recorded with a quantitative 2-dimensional range-gated echocardiographic Doppler flow meter (Electronics for Medicine/Honeywell). The Doppler flow meter measurements had previously been calibrated against an electromagnetic flow meter in open-chest dogs and against indicator dilution and oximetry in children during cardiac catheterization.[4,5]

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## Methods

The study population consisted of 10 postoperative patients, aged 6 months to 16 years, with lesions in the left side of the heart (coarctation of the aorta in 5, patent ductus arteriosus ligation in 3, and aortic stenosis in 2). All underwent clinically indicated echocardiographic contrast studies and all had a stable central hematocrit of 30 to 38% measured within 12 hours of the study.

Bedside Doppler studies were performed with the patient in the supine position using a prototype Electronics for Medicine/Honeywell range-gated pulsed Doppler unit. This unit contains a 3.5 MHz single element transducer, mechanically swept through a 60° arc to achieve a real-time 2-dimensional echocardiographic image that can be stopped along any image line. A variable-sized Doppler sample volume can then be positioned at any depth on that line, allowing appreciation of its location and angulation relative to flow (Fig. 1). The operational mode of the unit can then be switched from real-time to range-gated pulsed Doppler in less than 1/10 second. Two outputs are available in Doppler mode, the first an audio signal, and the second a fast Fourier transform spectral analysis sampled at 200 times/s. The Doppler output and simultaneous echocardiographic trace can be recorded on a strip chart or video tape, or both (Fig. 1). The fast Fourier output can be converted to velocity of flow in centimeters per second based on the formula: Velocity of flow = frequency shift × velocity of sound in the medium/2 × transmitted frequency × cos $\theta$, where cosine $\theta$ equals the angle between the Doppler beam and the direction of flow.

Ultrasonic studies began with 2-dimensional imaging of the right ventricular outflow tract, pulmonary valve, main pulmonary artery, and its bifurcation from a standard parasternal short-axis plane. The Doppler sample volume was then positioned along the direction of flow in the pulmonary valve orifice immediately distal to the plane of the closed pulmonary valve. It was adjusted so that no pulmonary valve echoes crossed through it (Fig. 1). Once the optimal 2-dimensional image and Doppler output were obtained and the sample volume was confirmed to be as parallel as possible to the apparent direction of flow (cos 0° = 1), the 2-dimensional image was recorded on a strip chart to verify Doppler position followed by recording of the fast Fourier outputs of the Doppler flow velocity curves on strip chart and videotape.

Immediately after the Doppler study, and with the patient still in the supine position, an M-mode echocardiogram of the pulmonary valve was derived from the 2-dimensional short-axis view along the same line as that used to position the preceding Doppler sample volume, passing through the pulmonary valve. While continuously recording this M-mode on a strip chart and videotape, 2 to 10 ml of normal saline solution was forcefully hand-injected through a previously positioned peripheral venous line.

A lead II electrocardiogram was recorded throughout the entire study for timing purposes. All recordings were made at a paper speed of 100 mm/s.

**Analysis of records:** Beats selected for measurement of echocardiographic contrast slopes and Doppler flow curves occurred at peak inspiration and were R-R matched from the preceding to the following cardiac cycle.

Instantaneous echocardiographic contrast flow velocities were determined by measuring the slopes of 2 to 6 contrast targets for each patient with a computerized clinical graphics analyzer (Numonics®) calibrated for distance (centimeters) and time (milliseconds) before each measurement. The time of each microbubble slope was measured relative to the pulmonary valve opening. Following the methods described by Shiina et al,[3] measurable microbubbles had the following constraints: They had to be straight, had to measure at least 1.5 cm in length, and had to occur within 120 ms after pulmonary valve opening, the most rapid phase of right ventricular ejection. With the onset of systolic flow as indicative of pulmonary valve opening, points in the corresponding Doppler flow velocity curve were time-matched to those of the previously measured microbubbles. Instantaneous Doppler velocities were read directly from the machine calibration marks (centimeters per second) recorded with the fast Fourier outputs (Fig. 1).

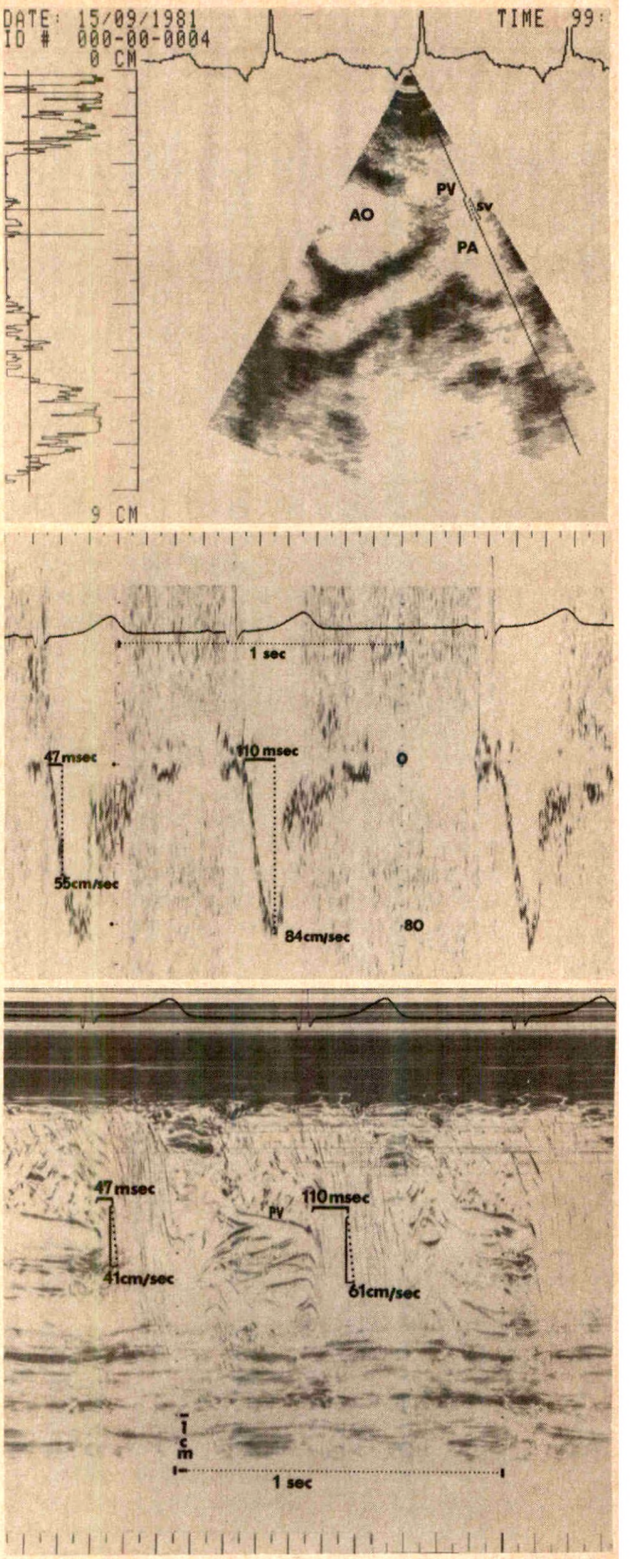



**FIGURE 1. Top,** parasternal short-axis view of the pulmonary valve, main pulmonary artery, and branches with Doppler sample volume positioned along the line of flow within the main pulmonary artery distal to the pulmonary valve. **Middle,** Doppler output derived from that sampling site. Instantaneous and peak velocities, read directly from calibration marks (cm/s), are indicated at 47 and 110 ms, respectively. **Bottom,** the saline contrast injection recorded at the pulmonary valve. The slopes of the linearly moving microbubbles, selected at time-matched points, are indicated in the figure. See text for details.

Peak Doppler velocity was read directly from the recorded calibration marks, and its time from the onset of systolic flow determined in milliseconds. For each patient, microbubbles occurring at the same systolic time were then selected from the corresponding M-mode trace and their slope was measured using the aforementioned graphics analyzer (Fig. 1).

**Repeatability of measurements:** To determine repeatability, each slope and Dopper velocity were measured in duplicate. To test interobserver variability, slopes and Doppler curves were measured by a second investigator who was unaware of previous results or patient identity.

**Statistical analysis:** Correlation coefficients were used to compare velocity results obtained by Doppler with those obtained by echocardiographic contrast. The paired $t$ test was used to analyze measurement repeatability and interobserver variability.

## Results

Contrast and Doppler studies were satisfactory in all 10 patients. Instantaneous velocities were measured from 2 to 6 contrast echocardiographic targets in each patient and matched to their corresponding systolic points in the Doppler flow curve, which resulted in 38 matched instantaneous velocities. In addition, peak Doppler velocities were compared with echocardiographic contrast slopes in all 10 patients, resulting in 10 individual peak velocity points.

**Correlation of Doppler with echocardiographic contrast velocities (Fig. 2):** Significant but low level correlations were found between time-matched echocardiographic contrast and Doppler instantaneous (r = +0.45) or peak (r = +0.11) systolic velocities.

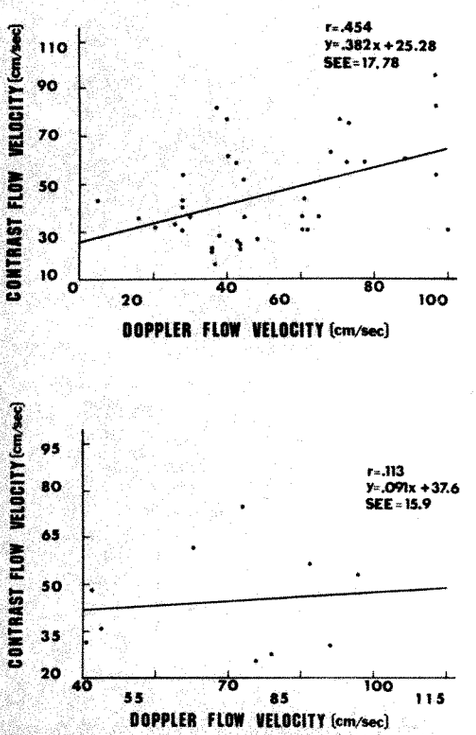



**FIGURE 2.** Regression lines comparing the instantaneous (**top**) and peak (**bottom**) velocities measured by echocardiographic contrast slopes and by the Doppler flow meter. Only low level correlations were found for each of the 2 regression lines.

**Interobserver variability and errors of repeatability:** The echocardiographic contrast slope and Doppler velocity measurements were highly repeatable. The standard error of the mean testing repeatability was <5% when comparing duplicate measurements on a given record. Furthermore, interobserver variability in measuring the slopes or Doppler velocities was also <5%.

## Discussion

Our results indicate that the slope of the trajectory of linear echocardiographic contrast targets correlates poorly with the flow velocity of red blood cells measured by a range-gated 2-dimensional echocardiographic Doppler flow meter.

Use of Doppler methods to measure flow velocity has been plagued with technical problems, mostly related to the inability to assess the intercept angle at which flow is being sampled and to difficulties in linearly measuring Doppler frequency shifts.[3,6–14] Doppler measurement of flow velocity is a function of the cosine of the intercept angle; consequently, flow determination is maximized when the Doppler beam is oriented exactly parallel (at 0° angle) to the direction of flow. Peak velocity is significantly reduced when the sound beam is deviated from 0°. Units combining Doppler with M-mode echocardiography allow estimation of the position of the sample volume; however, the critical intercept angle cannot be determined. The prototype system used in this study permits control and approximation of such an angle in 2 planes. The angle in the third plane (elevational) cannot be measured. However, minimal deviations from an intercept angle of 0° are of no practical importance, because the cosine of the small deviant angle is still quite close to unity.

Accuracy of the Doppler flow meter used in our study was verified in our animal and clinical laboratories.[4,5] Doppler measurements of blood flow velocity (and derived stroke volume and cardiac output) in the ascending aorta of open chest dogs compared favorably with simultaneous determinations made with an electromagnetic flow meter (r = +0.95, standard error of the estimate [SEE] = 0.035).[4] More recently, Doppler flow velocities measured in the ascending aorta and pulmonary artery of children during cardiac catheterization and used to calculate systemic and pulmonary blood flows and QP:QS correlated well with simultaneous determinations made with standard indicator dilution or oximetric techniques (r = 0.86, SEE = 0.83).[5] These 2 separate studies indicate that velocity measurements obtained with the 2-dimensional range-gated Doppler flow meter and used as the reference standard in this study are accurate estimates of flow velocity in both the experimental and the clinical setting.

We did not take advantage of the capability of our instrumentation to record echocardiographic contrast targets simultaneously with Doppler (that is, the potential for a QM or flow M-mode tracing), because in our experience the velocities detected by Doppler while contrast is injected are the velocities of microbubbles and not those of red cells. The reason is that microbubbles present an overwhelmingly stronger signal than do the red cells; consequently, simultaneous sampling

would not allow determination of whether microbubble velocities reflect those of red cells. As stated in the Methods section, the Doppler sample volume was placed directly within the pulmonary valve orifice just distal to the closed position of the leaflets and just far enough so that no pulmonary valve echoes crossed through it. The slopes were measured in systole after the valve had opened and at a position along the M-mode line which was posterior or distal to the closed position of the valve (Fig. 1). Therefore, the position at which the microbubble slopes were measured within the pulmonary valve orifice corresponds quite closely to the position of the Doppler sample volume, that is, both were <1 cm distal to the level of the closed pulmonary valve.

In this investigation, we elected to measure echocardiographic contrast and Doppler velocities exclusively in the main pulmonary artery just distal to the pulmonary valve to minimize errors due to irregular blood flow patterns elsewhere. In addition, following the recommendations of Shiina et al,[3] we only considered echocardiographic contrast targets measuring >1.5 cm in length to assure that the selected target was moving approximately parallel to the ultrasound beam and therefore represented close to maximal echocardiographic contrast velocity.[3] Furthermore, because theoretically the vector velocity of the microbubbles could be the result of a complex relation between blood flow and gravity, all patients were studied supine to avoid changes in gravity factor with different patient positions. Finally, all patients selected for inclusion in the study had a similar hematocrit level and had lesions in the left side of the heart with no clinical or Doppler evidence of turbulent pulmonary flow, or both. Because motion of microbubbles could be affected by the density of the medium, that is, the blood, which in turn may vary in conditions of turbulent versus laminar flow, imposing these added constraints was an attempt to minimize these potential sources of error. Despite these precautions and acceptable errors in repeatability and interobserver variability, only low level correlations were found between Doppler and echocardiographic contrast instantaneous and peak velocities.

We conclude that contrast echocardiographic targets (microbubbles) do not behave physiologically like the moving red blood cells that produce the Doppler shift. Although the slopes of their trajectories can be measured to yield a velocity, these do not match the velocity of red cells within the blood stream as measured with a range-gated 2-dimensional echocardiographic Doppler system. Therefore, contrast echocardiography cannot be used to reliably measure flow velocity in the right heart.

## References


1. **Meltzer RS, Serruys PW, Roelandt J.** Contrast echocardiography in valvular regurgitation. In: Rijsterborgh H, ed. Echocardiology. The Hague: Martinus Nijhoff Publishers, 1981:233–243.
2. **Bonzel T, Fassbender D, Bogunovic N, Trieb G. Gleichmann U.** Analysis of right heart blood flow from contrast patterns on the echocardiogram. In Ref 1:255–262.
3. **Shiina A, Kondo K, Nakasone Y, Tsuchiya M, Yaginuma T, Hosoda S.** Contrast echocardiographic evaluation of changes in flow velocity in the right side of the heart. Circulation 1981;63:1408–1416.
4. **Friedman MJ, Sahn DJ, Larson D, Flint A.** 2D echo-range gated Doppler measurements of cardiac output and stroke volume in open chest dogs (abstr). Circulation 1980;62:101.
5. **Hoenecke H, Goldberg SJ, Carnahan Y, Sahn DJ, Allen HD, Valdes-Cruz LM.** Controlled quantitative assessment of pulmonary and arotic flow by range gated pulsed Doppler in children with heart disease (abstr). Circulation 1981;64:167.
6. **Stegall HF, Rushmer RF, Baker DW.** A transcutaneous ultrasonic blood-velocity meter. J Appl Physiol 1966;21:707–711.
7. **Sivaciyan V,Ranganathan N.** Transcutaneous Doppler jugular venous flow velocity recording. Circulation 1978;57:930–939.
8. **Kalmanson D, Veyrat C, Deral C, Savier C-H, Berkman M, Chiche P.** Noninvasive techniques for diagnosing atrial septal defect and assessing shunt volume using directional Doppler ultrasound. Br Heart J 1972;34: 981–991.
9. **Kalmanson D, Veyrat C, Chiche P.** Atrial versus ventricular contribution in determining systolic venous return. Cardiovasc Res 1971;5:293–302.
10. **Griffith JM, Henry WL.** An ultrasound system for combined cardiac imaging and Doppler blood flow measurement in man. Circulation 1978;57:925–930.
11. **Magnin PA, Stewart JA, Myers S, von Ramm O, Kisslo JA.** Combined Doppler and phased array echocardiographic estimation of cardiac output. Circulation 1981;63:388–392.
12. **Steingart RM, Meller J, Barovick J, Patterson R, Herman MV, Teichholz L.** Pulsed Doppler echocardiography: measurement of beat to beat changes in stroke volume in dogs. Circulation 1980;62:542–548.
13. **Angelsen AJ, Brubakk AO.** Transcutaneous measurement of blood velocity in the human aorta. Cardiovasc Res 1976;10:368–379.
14. **Walker AR, Phillips DJ, Powers JE.** Evaluating Doppler devices using a moving string test target. J Clin Ultrasound 1982;10:25.
15. **McDonald DA.** Blood Flow in Arteries. Baltimore: Williams & Wilkins, 1960:40–45.

# Cardiac Localization of Transvascular Bioptome Using 2-Dimensional Echocardiography

JAMES W. FRENCH, MD, RICHARD L. POPP, MD, and PAUL T. PITLICK, MD

**Two-dimensional (2-D) echocardiography was added to standard fluoroscopic localization of transvascular endomyocardial biopsy in 7 children with heart muscle disease whose ages were 6 months to 18 years. One left ventricular and 11 right ventricular biopsies were carried out without complications using the fluoroscopic-echocardiographic technique. Two-dimensional echocardiographic monitoring has the advantages of reducing radiation exposure and providing anatomic information about intracardiac structures as well as bioptome localization. Lateral beam spread and reverberation artifacts represent potential problems with 2-D echocardiography, but they did not cause significant difficulties in this study.**

Transvascular endomyocardial biopsy was described by Sakakibara and Konno[1] in 1962. Although application of the procedure remains limited,[2] the technique is used in several medical centers to diagnose and monitor various forms of heart muscle disease.[3–12] A special bioptome is passed into a peripheral vessel and guided into a ventricular chamber using fluoroscopic control. Access to the right heart is usually obtained by percutaneous introduction of the bioptome into the right internal jugular vein.[3,4] Femoral approaches to both the right and left ventricle also have been described.[5–7] This report evaluates the addition of 2-D echocardiography to the biopsy procedure to facilitate positioning of the bioptome in the heart.

## Methods

Patients with a clinical diagnosis of cardiomyopathy were selected for biopsy to make a specific diagnosis of myocarditis, to confirm the clinical impression of heart muscle disease, or to monitor drug effects on the myocardium (Table I). The patient, parents, or both were fully informed and consent was obtained. Patients were prepared for the biopsy as previously reported for the jugular (right heart) or femoral (left heart) approach.[3–7] Either heavy sedation with a combination of meperidine and diazepam or light general anesthesia was employed, depending upon patient anxiety. The biopsy procedure was usually combined with standard right or left heart catheterization.

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Two-dimensional echocardiography using commercially available instruments and 2.25, 3.5, or 5 MHz transducers was used to position the bioptome. The 2.25 and 3.5 MHz transducers were wide angle (80°) phased array units (Hewlett-Packard). In 2 cases (Patients 5 and 7) a 5 MHz 30° oscillating head (Smith Kline Instruments) was employed. The higher frequency instrument improved the picture quality, but the oscillating motion created a significant problem during attempts to maintain a stable chest position. In all patients sector scanning was initiated from a subcostal or apical window and the transducer was orientated for an optimal 4-chamber or long-axis view which allowed imaging of the septal and, with transducer angulation, the inferior surface of the ventricular chamber. Each patient required some variation in transducer placement. Because the patient was positioned on the fluoroscopy table to optimize catheter introduction and was relatively fixed, we tested several transducer positions before introduction of the bioptome. In the left heart study, alternating between an apical long axis and a left ventricular

**TABLE I Clinical Synopsis of Patients**

| Patient | Age | Biopsy | Clinical Diagnosis |
|---|---|---|---|
| 1 | 13 yr | RV | Myopathy (C, restrictive; S) |
| 2 | 11 yr | RV | Histiocytosis |
| 3 | 16 yr | RV | VT, VF, rule out CM |
| 4 | 7 yr | RV (2)* | Kearns-Sayre syndrome |
| 5 | 6 mo | RV | Myocarditis |
| 6 | 18 yr | RV (4)* | Myocarditis |
| 7 | 9 mo | RV, LV | Myocarditis |

* Number of procedures. C = cardiac muscle; CM = cardiomyopathy; LV = left ventricular biopsy; RV = right ventricular biopsy; S = skeletal muscle; VF = ventricular fibrillation; VT = ventricular tachycardia.

short axis provided the best visualization of the bioptome position relative to the septal surface and the posteromedial papillary muscle. Although it was possible to image a large part of the bioptome shaft as it passed through the right atrium or the aorta, during the biopsy procedure the view which provided an optimal image of the bioptome head contacting the myocardium was utilized (Fig. 1). During a single biopsy procedure, 3 to 5 tissue samples were obtained for analysis.

Initially, the ultrasound transducer was positioned so that it was out of the fluoroscopic field. The echocardiographer wore a lead glove in addition to the usual protective vest and 2-D echocardiography was used simultaneously with fluoroscopsy. When used in this manner the lead glove and the fluoroscopy unit made it difficult to properly position the ultrasonic transducer and impossible to maintain a position for more than a few minutes. In the last 6 procedures, as we gained confidence in ultrasonic localization, we alternated fluoroscopic and echocardiographic imaging: fluoroscopic monitoring was used to place the bioptome across the tricuspid or aortic valve, and 2-D echocardiography was then used for ventricular positioning. Each patient was checked for pneumothorax by fluoroscopy and for pericardial effusion by echocardiography at the completion of the procedure.

## Results

Two-D echocardiography was used to monitor 1 left ventricular and 11 right ventricular biopsy procedures in 7 patients. Patient 6 had 4 serial biopsy procedures to monitor the effect of steroids and immunosuppression on his myocarditis. In Patient 4 there were diagnostic problems, and myocarditis was initially thought to be the cause of acquired complete heart block. The first biopsy was equivocal, while the second suggested noninflammatory cardiomyopathy. The remaining patients had single biopsy procedures, although Patient 7 had both left and right ventricular biopsies. All right ventricular biopsies were accomplished with a percutaneous internal jugular approach, while the left ventricular study was done through the femoral artery. In each case the bioptome and its relation to valve leaflets, chordae, papillary muscles, and the myocardium were readily visualized by echocardiography (Fig. 1 and 2). Frequently, initial positioning directed the bioptome into the ventricular free wall, or toward the atrioventricular valve apparatus (Fig. 2). In more than 50% of our cases some repositioning of the catheter was necessary before the tissue sample was obtained. This usually involved backing and rotating the catheter in the ventricle, and was easily accomplished using 2-D echocardiography (Fig. 2). In this series of patients the myocardial abnormality was considered homogeneous, and no particular attempt was made to direct the catheter to a "new" myocardial position for each tissue sample. No complications were identified using the combined technique. The biopsy procedure was not significantly prolonged as a result of the echocardiographic monitoring.

## Discussion

Since its introduction, transvascular endomyocardial biopsy has provided valuable data on several of the heart muscle disease groups. The most important at Stanford, in terms of patient numbers, have been staging of anthracycline-induced cardiomyopathy,[8] the histologic diagnosis of myocarditis,[9] and detection of rejection in patients who have undergone heart transplantation[3] or heart and lung transplantation.[10] The

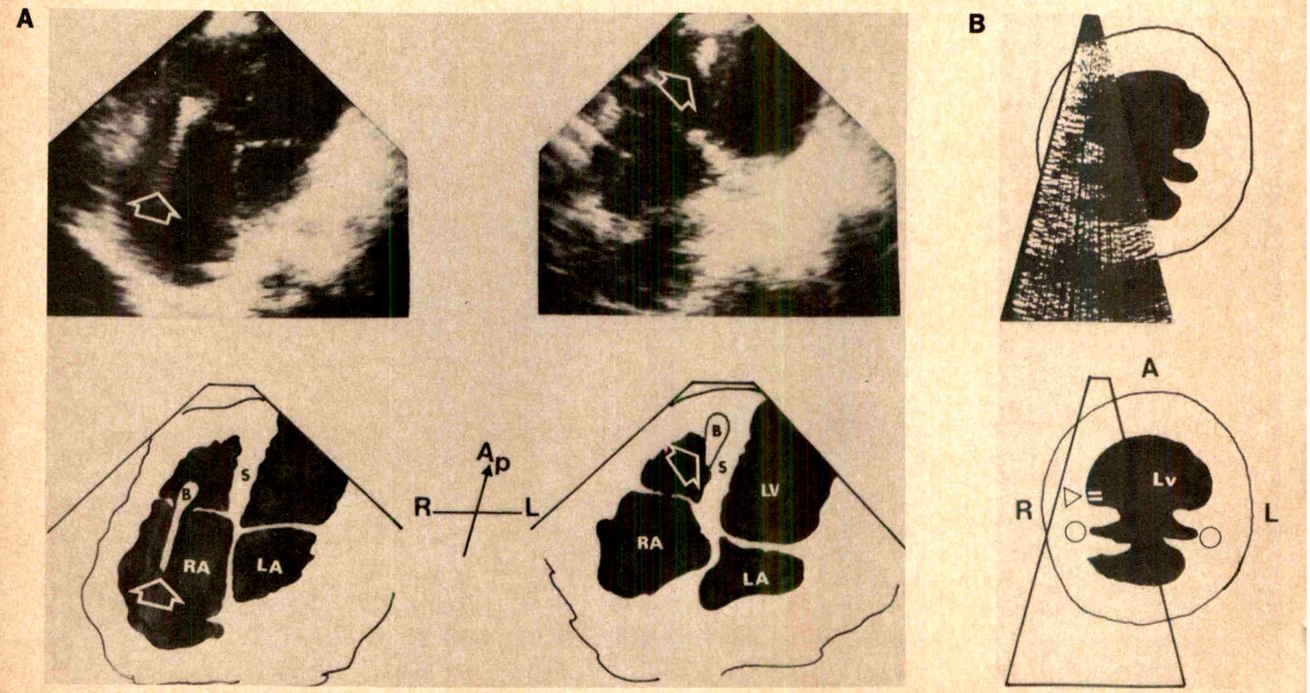



**FIGURE 1.** Proper bioptome position. **A: Left panel,** 4-chamber view, with **arrow** pointing at bioptome. Tip of bioptome (B) is in the tricuspid anulus. **Right panel,** tip of bioptome has been advanced to the right side of the ventricular septum (S) near the apex, the proper location to obtain a specimen. **B,** short-axis view of left ventricle (Lv), with bioptome (**triangle**) correctly positioned adjacent to ventricular septum and avoiding papillary muscle. **Open circles** identify papillary muscles. A = Anterior; $A_p$ = apex; L = left; LA = left atrium; R = right; RA = right atrium.

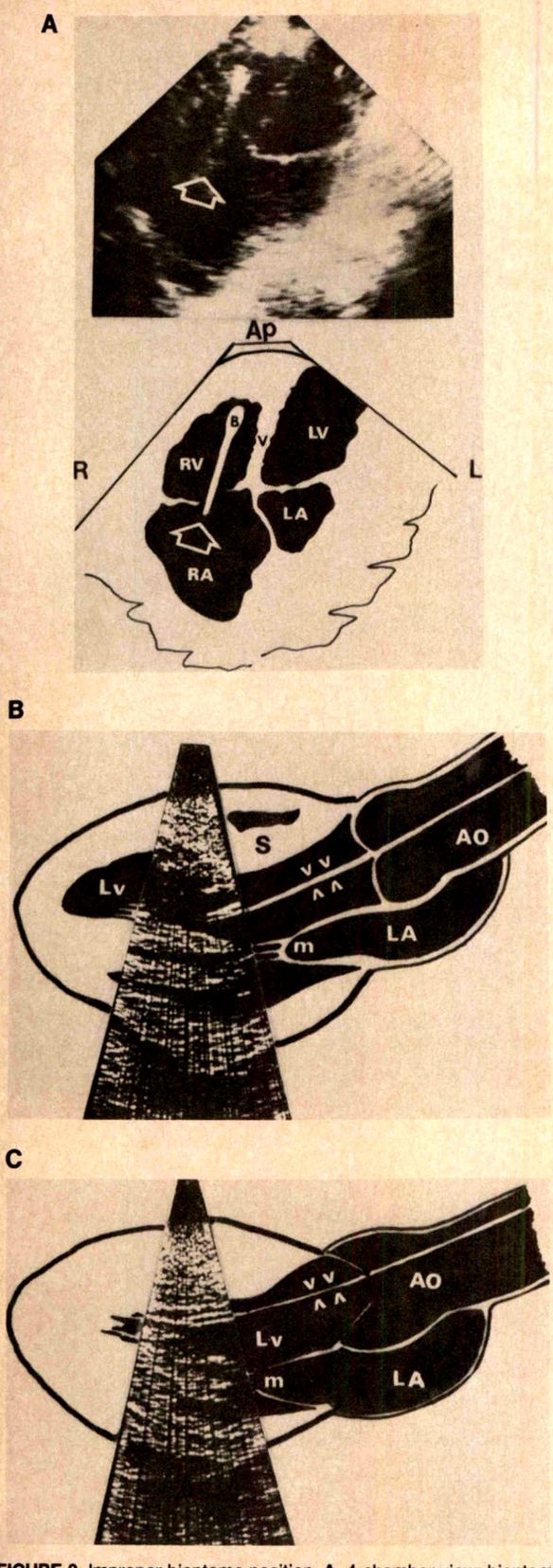



**FIGURE 2.** Improper bioptome position. **A**, 4-chamber view; bioptome tip is directed toward the free wall of the right ventricle (RV). **B**, long-axis view of the heart; bioptome (**arrows**) has been passed through the aortic valve and tip is directed toward the papillary muscles of the mitral valve (m). **C**, same view as in **B**; the catheter has been properly repositioned. AO = aorta; other abbreviations as in Figure 1.

technique is also useful in patients with the suspected diagnoses of infiltrative or storage abnormalities of the myocardium such as amyloidosis, sarcoidosis, or hemochromatosis.[11,12] Patients in the current study group had biopsies for a more precise histologic diagnosis when the differential diagnosis included cardiomyopathy or myocarditis, or both; to monitor immunosuppressive therapy for inflammatory myocardial disease; or to rule out myocardial infiltrative disease (histiocytosis) in a patient who had previously received doxorubicin.

The standard approach to right ventricular biopsy in our institution is to introduce the bioptome percutaneously into the right internal jugular vein and advance the biopsy catheter into the right ventricle under fluoroscopic control. The appearance of premature ventricular contractions on the electrocardiogram and "resistance" to catheter advancement identify contact with the ventricular wall. Although cardiac perforation, pneumothorax, embolism, arrhythmias, and nerve palsies have been reported,[4] meticulous attention to technique has resulted in a very low incidence of complications. The procedure is well tolerated and can be performed on adult outpatients, although fluoroscopy is required. With continuing improvement in echocardiographic instrumentation and the demonstration that other types of intracardiac catheters could be imaged with ultrasound,[13–15] the addition of 2-D echocardiography to the biopsy protocol offered the potential for reducing radiation exposure and for providing an anatomically detailed intracardiac image to position the biopsy catheter. The introduction of 2-D echocardiography was not expected to reduce the already-low incidence of biopsy-related complications in the adult with dilated (congestive) cardiomyopathy. However, in young children or in other patients whose ventricles are small or abnormally shaped (as in hypertrophic or obliterative cardiomyopathy, endocardial fibroelastosis, or myocardial storage disease), the ability to visualize ventricular boundaries and intracardiac structures such as atrioventricular valve apparatus assumes greater importance. The right ventricle is biopsied more often, but the capacity to identify left ventricular structures is equally valuable. Even though the thicker left ventricular wall makes perforation less likely, the integrity of the valve structures is more critical.

This patient series demonstrates some important differences between fluoroscopy and 2-D echocardiography as imaging techniques. Fluoroscopy presents positional information about the overall cardiac silhouette. With the use of fluoroscopy the catheter is positioned near the apex of the cardiac shadow in the frontal plane. No additional anatomic information is available for bioptome localization. It is assumed that this position plus the catheter rotation used to manipulate the bioptome orients the catheter tip into the apical portion of the ventricular septum.[4] In patients without congenital anatomic abnormalities and with normal or large ventricular chambers this has been a very satisfactory technique. Multiple imaging planes, although available, usually are not used. Anatomic variations, as in the infants (Patients 5 and 7) with relatively small hearts and the child (Patient 1) with restrictive cardiomyopathy and small ventricular

chambers, are better evaluated with the anatomic information available from the echocardiographic image. Multiple variations in image planes were used in all patients to identify the catheter and important anatomic landmarks. Although fluoroscopy times were not examined systematically we now use 2-D echocardiography almost exclusively for ventricular positioning, thus avoiding that radiation exposure. A disadvantage to the combined use of 2-D echocardiography and fluoroscopy is the necessity of an additional physician or technician to operate the echocardiographic equipment.

An inherent problem in biopsy procedures of this type is the question of representative sampling.[2] Most heart

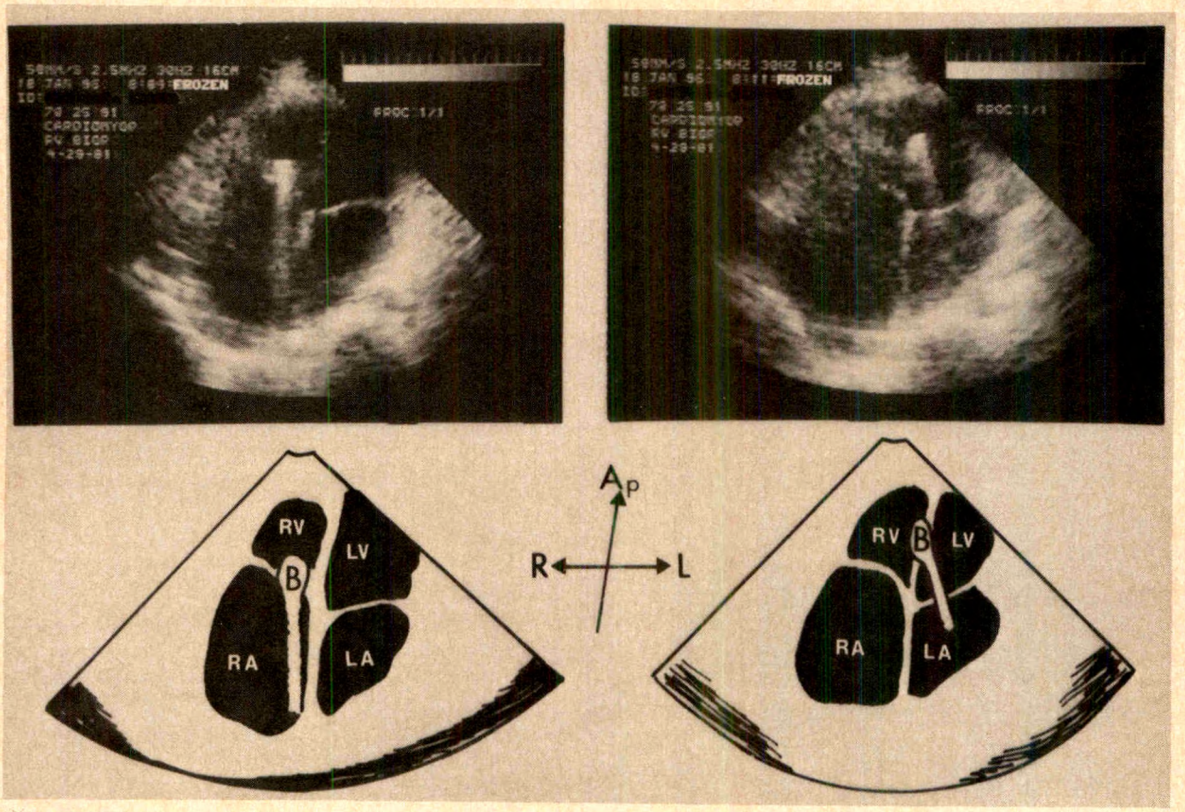



**FIGURE 3.** Reverberation artifacts. **Left panel,** 4-chamber view, bioptome positioned in the mid-right ventricle. There is a reverberation artifact which does not cross the atrial or ventricular septa. **Right panel,** 4-chamber view, same study, slight change in image plane and catheter position. Note that the artifact now makes the catheter appear to cross the mitral valve, enter the left ventricle, and cross the plane of the ventricular septum. Abbreviations as in Figures 1 and 2.

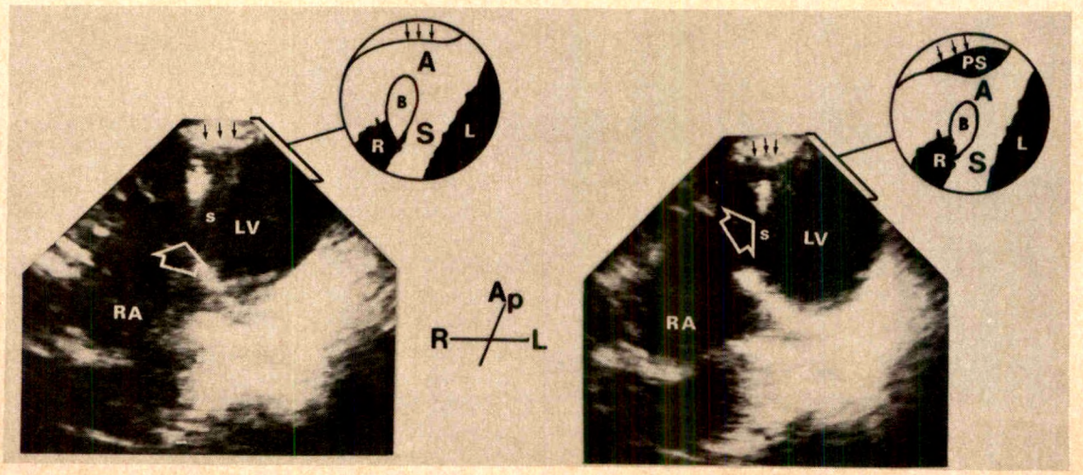



**FIGURE 4.** Monitoring the biopsy myomectomy. **Left panel,** 4-chamber view, with bioptome tip positioned to remove a specimen. **Right panel,** when the bioptome was withdrawn, the myocardium briefly separated from the pericardium (**small arrows**). Abbreviations as in Figure 1.

muscle disease has some degree of heterogeneity, and there is frequently concern whether the sampled site is an accurate reflection of the generalized myocardial disease process. This study demonstrates that 2-D echocardiography currently allows visual identification of the site before biopsy. The ease with which multiple echocardiographic imaging planes can be obtained should help assure multiple sampling sites and an accurate knowledge of the site of each sample. With the real possibility that ultrasonic tissue characterization of a designated area of myocardium may be available in the future,[16,17] 2-D echocardiography offers the potential for both gross identification and ultrasonic interrogation of the biopsy site before the tissue sample is taken. The enhanced ability to localize the bioptome with echocardiography may also allow applications in localized myocardial disease such as intramural tumors or myocardial disease in patients with cardiac malposition where fluoroscopic orientation is not adequate for biopsy localization.

Lateral beam spread and reverberation artifacts create potential limitations on the accuracy of catheter localization using 2-D echocardiography. Lateral beam spread was not a major problem in this study because we localized the catheter tip and tended to ignore other parts of the catheter; furthermore, variations of a few millimeters were not critical for structure identification during the biopsy procedures in our patients. However, when the ventricle or ventricles are very small, in infants for example, or where the value of the biopsy depends upon precise localization of the biopsy site, resolution requirements may exceed the capabilities of some echocardiographic instruments. Reverberation artifacts from the metal catheter were common (Fig. 3) but did not cause problems during this study. Because the tip of the catheter was closest to the transducer, artifact trailing posteriorly (away from the area of greatest interest) did not interfere with tip localization and usually did not obscure structures near the tip. At times the catheter seemed to cross the plane of the ventricular septum (Fig. 3), but this phenomenon could be identified as artifact by changing the echocardiographic imaging plane, moving the catheter slightly, or noting that the catheter tip remained within the proper ventricle.

Echocardiography also provides a dynamic picture of the biopsy procedure. For example, in Patient 1 the myocardium was fibrosed and initial attempts to retrieve the closed bioptome caused sufficient myocardial displacement that a significant pericardial "space" was created without separation of a biopsy sample (Fig. 4). The bioptome was opened, repositioned in the ventricular apex, and a satisfactory biopsy sample was obtained. The most sensitive indicator of "reasonable force," a term used to guide new practitioners, when separating the tissue sample from the myocardium is the experience of the bioptome operator. However, the capacity to observe the initial position of the bioptome and the degree of pericardial separation using 2-D echocardiography during the biopsy provide secondary information which is valuable when repositioning of the bioptome is necessary.

An interesting observation was the appearance of periodic waves of ultrasonic targets when the bioptome was moved or when a specimen was obtained. The phenomenon was not associated with any clinical adverse effects. The targets probably resulted from atmospheric gas adhering to the surface of the bioptome. The ultrasonic appearance is analogous to the previously described "ultrasonic contrast injections" using indocyanine green, saline solution, or the patient's blood.[18]

We conclude that the addition of 2-D echocardiography to the myocardial biopsy procedure allows enhanced visualization of the bioptome position, particularly with regard to intracardiac structures. This is most advantageous with small, unusually shaped, or abnormally positioned ventricles, or when a specific biopsy site is required. A combination of fluoroscopy and 2-D echocardiography used alternately provided the best visualization and allowed immediate monitoring for complications such as pneumothorax or pericardial effusion.

## Addendum

Since submission of this work, we performed right ventricular endomyocardial biopsies in 2 more children, aged 11 and 14 months, and whose weights were 7 and 8 kg, respectively. In both, echocardiographic localization of the bioptome was superior to fluoroscopy, and there were no complications.

## References


1. **Sakakibara S, Konno S.** Endomyocardial biopsy. Jpn Heart J 1962;3: 537–543.
2. **Ferrans VJ, Roberts WC.** Myocardial biopsy: a useful diagnostic procedure or only a research tool? Am J Cardiol 1978;41:965–967.
3. **Caves PK, Stinson EB, Billingham ME, Shumway NE.** Percutaneous transvenous endomyocardial biopsy in human heart recipients. Ann Thorac Surg 1973;16:325–336.
4. **Mason JW.** Techniques for right and left ventricular endomyocardial biopsy. Am J Cardiol 1978;41:887–892.
5. **Ali N, Ferrans VJ, Roberts WC, Massumi RA.** Clinical evaluation of transvenous catheter technique for endomyocardial biopsy. Chest 1973; 63:399–402.
6. **Brooksby IAB, Swanton RH, Jenkins BS, Webb-Peploe MM.** Long sheath technique for introduction of catheter tip manometer or enmyocardial bioptome into left or right heart. Br Heart J 1974;36:908–912.
7. **Lurie PR, Masahiro F, Neustein HB.** Transvascular endomyocardial biopsy in infants and small children: description of a new technique. Am J Cardiol 1978;42:453–456.
8. **Bristow MR, Thompson PD, Martin RP, Mason JW, Billingham ME, Harrison DC.** Early anthracycline cardiotoxicity. Am J Med 1978;65:823–832.
9. **Mason JW, Billingham ME, Ricci DR.** Treatment of acute inflammatory myocarditis assisted by endomyocardial biopsy. Am J Cardiol 1980;45: 1037–1044.
10. **Reitz BA, Wallwork JL, Hunt SA, Pennock JL, Billingham ME, Oyer PE, Stinson EB, Shumway NE.** Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. N Engl J Med 1982;306: 557–564.
11. **Mason JW, Billingham ME.** Myocardial biopsy. In: Yu PN, Goodwin JF, eds. Progress in Cardiology. Philadelphia: Lea & Febiger, 1980:9:113–141.
12. **Short EM, Winkle RA, Billingham ME.** Myocardial involvement in idiopathic hemochromatosis: morphologic and clinical improvement following venesection. Am J Med 1981;70:1275–1279.
13. **Drinkovic N.** Subcostal echocardiography to determine right ventricular pacing catheter position and control advancement of electrode catheters in intracardiac electrophysiologic studies. M-mode and two dimensional studies. Am J Cardiol 1981;47:1260–1265.
14. **Bapineedu G, Nanda N.** Real-time, two-dimensional echocardiographic features of pacemaker perforation. Circulation 1981;64:97–106.
15. **Allan LD, Leanage R, Wainwright R, Joseph MC, Tynan M.** Balloon atrial septostomy under two dimensional echocardiographic control. Br Heart J 1982;47:41–43.
16. **Green SE, Joynt L, Fitzgerald P, Rubenson D, Popp RL.** *In vivo* ultrasonic tissue characterization of human intracardiac masses (abstr). Circulation 1981;64:Suppl II:II–980.
17. **Logan-Sinclair R, Wong CM, Gibson DG.** Clinical application of amplitude processing of echocardiographic images. Br Heart J 1981;45:621–627.
18. **Gramiak R, Shah PM, Kramer DH.** Ultrasound cardiography: contrast studies in anatomy and function. Radiology 1969;92:939–948.

# Validation of the Angiographic Accuracy of Digital Left Ventriculography

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**Digital subtraction angiography enhances the contrast to background signal, enabling the performance of angiography with reduced doses of contrast medium. The objectives of the present study were (1) to validate the accuracy of digital left ventriculography for measurement of left ventricular volumes and segmental contraction; and (2) to compare the hemodynamic effects resulting from low- and high-dose intraventricular contrast injections. Twenty-eight patients underwent digital left ventriculography, performed by intraventricular injection of 7 ml of contrast medium diluted in saline solution, followed by conventional cineangiography of the left ventricle performed with 45 ml of undiluted contrast medium. Left ventricular volumes calculated from digital ventriculograms correlated well with volumes calculated from conventional ventriculograms: end-diastolic volume (r = 0.97, standard error of estimate [SEE] 23.4 ml; end-systolic volume (r = 0.97, SEE 15.4 ml); stroke volume (r = 0.95, SEE 14.7 ml); and ejection fraction (r = 0.97, SEE 3.8%). Segmental left ventricular contraction, measured as percent chordal shortening of hemiaxes, correlated moderately well (r = 0.81, SEE 11.5%). After injection of undiluted contrast medium, left ventricular systolic pressure decreased (133 ± 31 to 123.5 ± 27 mm Hg; p <0.01) and left ventricular end-diastolic pressure increased (12.0 ± 7 to 16.9 ± 10 mm Hg; p <0.001). Left ventricular systolic and end-diastolic pressures did not change significantly after injection of diluted contrast medium, and patients had no discomfort. Thus, digital subtraction angiography permits the performance of left ventriculography with markedly reduced doses of contrast medium, obviating the hemodynamic effects resulting from injection of conventional doses of contrast medium. This new approach to left ventriculography provides high resolution ventriculograms for accurate measurement of left ventricular volumes, stroke volume, and ejection fraction.**

The diagnostic potential of conventional left ventriculography is limited by the relatively large doses of contrast medium necessary to adequately opacify the left ventricular cavity. Conventional doses of contrast medium cause hemodynamic alterations[1,2] which have been attributed to the direct myocardial depressant effect of contrast medium,[3,4] to the effect of a sudden increase in left ventricular volume caused by power injection,[5] and to peripheral vasodilation and secondary reflex responses resulting from the hypertonicity of contrast medium.[6] In studies in animals, intraventricular injections of cortrast medium cause an acute increase in left ventricular volumes,[7,8] but the effect of contrast injections on ventricular volumes in patients is controversial. Finally, the nephrotoxicity resulting from high doses of contrast medium[9] precludes multiple contrast injections for ventriculographic assessment of the effect of therapeutic interventions on left ventricular performance.

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Digital subtraction angiography[10–12] markedly enhances the iodine contrast signal, permitting the performance of left ventriculography after intravenous injection of conventional doses of contrast medium. We have found that the contrast enhancement afforded by digital subtraction angiography permits the performance of left ventriculography with very low doses of contrast medium when injected directly into the left ventricle. This method obviates the hemodynamic alterations resulting from intraventricular injection of conventional doses of contrast material. The present study was designed to validate the accuracy of digital left ventriculography for measurement of left ventricular volumes and regional wall contraction in comparison with conventional left ventriculography, and to compare the hemodynamic effects resulting from low-dose and conventional-dose intraventricular contrast injections.

## Methods

**Patient protocol:** Digital and conventional left ventriculography was performed at the time of routine cardiac catheterization in 28 patients, 16 men and 12 women with a mean age of 56 years (range 19 to 74). Sixteen patients had coronary artery disease, 6 had valvular heart disease, 4 had congestive cardiomyopathy, and 2 had normal coronary arteriograms. Informed consent for digital ventriculography was obtained from each patient according to a protocol approved by the Institutional Review Board of the Columbia-Presbyterian Medical Center.

Each patient underwent digital left ventriculography performed with diluted (14%) contrast medium and conventional left ventriculography with undiluted contrast medium. Left ventricular pressures were recorded before and after each ventriculogram. Identical volumes (45 ml) and delivery rates (15 ml/s) were used for both diluted and undiluted contrast injections to permit direct comparison of hemodynamic effects.

**System specifications:** The x-ray system consisted of a Philips modular generator, an SRN 10/80 x-ray tube, and a trimodal (6, 10, 14 in) cesium iodide image intensifier mounted on a Poly diagnost A-™ arm and scanned with a Plumbicon video tube. A prototype Philips Digital Vascular Imaging system, which has a 512 × 512 pixel matrix, an 8 bit A/D converter, and 12 bit memory word depth logarithmically amplified and digitized the video signal. During a continuous 6 second exposure, 30 video frames/s were processed and stored on magnetic tape. For frame-by-frame analysis, the digitized images were simultaneously acquired on a 300 track disc recorder, which sampled 1 frame in 3. Subtracted digital ventriculograms were simultaneously displayed on the television monitor during contrast injection, permitting immediate assessment of the adequacy of the study.

**Digital left ventriculography:** Single-plane digital left ventriculograms were recorded in a 30° to 35° right anterior oblique projection during power injection of diluted contrast material through 7 French pigtail catheters positioned in the left ventricular cavity. Seven ml of sodium meglumine diatrizoate (Renografin® 76) was diluted in 43 ml of normal saline solution, mixed thoroughly in the injection syringe of the power injector, and injected at a rate of 15 ml/s for 3 seconds. The injection was not electrocardiographically synchronized with end-diastole. The concentration of diluted contrast medium used (14%) was found optimal for the adjusted enhancement levels of the digital video system used in this study. Lower concentrations (10%) provided inadequate opacification, and higher concentrations (20%) resulted in excessive opacification.

The kVp (55 to 60 range) and mA (100) were first adjusted on preliminary exposures of 80 ms. An initial digitized image, or mask frame, was recorded in the continuous mode over 320 ms during held inspiration. Immediately afterwards, the digital left ventriculogram was recorded in the same mode, and the contrast injection was delayed until 1 nonopacified cardiac cycle was recorded. During the contrast injection, fully subtracted and enhanced images were continuously displayed for 6 seconds at 30 frames/s.

The digitized subtracted images were then replayed from the disc frame by frame, and the frames showing end-diastole and end-systole were selected visually from the first fully opacified cardiac cycle. Cycles with premature contractions and postectopic cycles were excluded. Postprocessing was done in the serial mode with dual video screens to further enhance image quality. The end-systolic image from the opacified cardiac cycle was displayed on 1 video screen, and the frames of the nonopacified cardiac cycle, recorded just before contrast injection, were displayed on the second video screen. The frames from the nonopacified cardiac cycle were subtracted sequentially frame by frame from the end-systolic opacified image until the corresponding end-systolic image was located, which resulted in the least misregistration. This second order subtraction image was then stored in computer memory, and the enhancement level adjusted appropriately for recording the image on radiographic film. This procedure was repeated for selecting and enhancing the end-diastolic image. The end-diastolic and end-systolic frames were recorded on single emulsion Kodak MR-1 film (8 × 10 in) with a multiformat video camera system (Matrix Instruments). As a spatial reference, a 1 cm crosshatched radiopaque grid was positioned at the level of the left ventricle and recorded on the magnetic disc in serial mode. This digital grid image was also transferred to computer memory and recorded on 8 × 10 in film.

**Conventional left ventriculography:** Conventional contrast ventriculograms were recorded 10 minutes after the digital left ventriculograms in the identical right anterior oblique projection without altering the patient's position or the height of the image intensifier or the angiographic table. During held inspiration, 45 ml of undiluted sodium meglumine diatrizoate was power-injected through the 7 French pigtail catheter at a rate of 15 ml/s. The ventriculogram was recorded on 35 mm cineangiographic film at 32 frames/s using the 10-inch field size of the image intensifier. Following ventriculography, the radiopaque crosshatched 1 cm grid was recorded at the level of the left ventricle as a spatial reference. End-diastolic and end-systolic cineangiographic frames were selected by the same criteria used for digital ventriculography.

**Left ventricular analysis:** Left ventricular silhouettes in end-diastole and end-systole were traced manually from the digital and cineangiographic ventriculograms using a computer-assisted light pen. The long axis of the left ventricle was measured as the longest straight line from the apex to the midpoint of the aortic valve. End-diastolic and end-systolic volumes were calculated using the single-plane, area-length method of Sandler and Dodge.[13] Digital and conventional ventriculograms were analyzed separately by a blinded investigator, who was unaware of the results of each ventriculographic analysis.

Segmental left ventricular contraction patterns were analyzed quantitatively by the method of Herman et al.[14] The

long axis of the ventricular silhouettes was quadrisected, and percent shortening from end-diastole to end-systole was calculated for the following transverse hemiaxes: anterobasal, anterolateral, apical, diaphragmatic, and posterobasal. In addition, percent shortening of the long axis was calculated.

**Hemodynamic measurements:** Left ventricular pressures were measured through fluid-filled 7 French pigtail catheters inserted percutaneously into the femoral artery. Pressures were recorded on a switched-beam oscilloscopic recorder using Statham P23Db pressure transducers positioned to a zero level 5 cm below the sternal angle. Left ventricular systolic and end-diastolic pressures were recorded immediately before each digital and conventional left ventriculogram. Twenty to 30 seconds after each ventriculogram, pressure measurements were repeated after the catheter was flushed with heparinized saline solution. Left ventricular systolic pressure was calculated as the peak systolic pressure averaged over 10 seconds. The end-diastolic pressure was determined as the mean of the diastolic pressure coinciding with the R wave, averaged over 10 seconds.

**Statistical analysis:** Correlations between ventriculographic measurements were tested by linear regression.[15] Differences between hemodynamic variables measured before and after contrast injections were evaluated by Student's paired *t* test.[16]

## Results

**Digital left ventriculography:** Digital subtraction left ventriculograms, displayed in real time from magnetic tape at 30 frames/s, appeared qualitatively identical to cineangiographic left ventriculograms. Representative end-diastolic and end-systolic digitized images of the left ventricle, resulting after second-order mask subtraction, are shown in Figure 1, compared with end-diastolic and end-systolic frames of the conventional cineangiographic left ventriculogram recorded in the same patient. The cavity of the left ventricle is as well opacified on the digitized ventriculogram as on the conventional ventriculogram, and the margins of the left ventricle are seen equally well. Second-order mask subtraction enhanced image quality and contrast density considerably.

**Left ventricular volumes:** Left ventricular angiographic end-diastolic volumes ranged from 58 to 359 ml, and end-systolic volumes ranged from 22 to 305 ml. The mean end-diastolic volume calculated from digital left ventriculograms (160.6 ± 89 ml) did not differ significantly from the mean end-diastolic volume calculated by conventional left ventriculography (152.5 ± 90 ml).

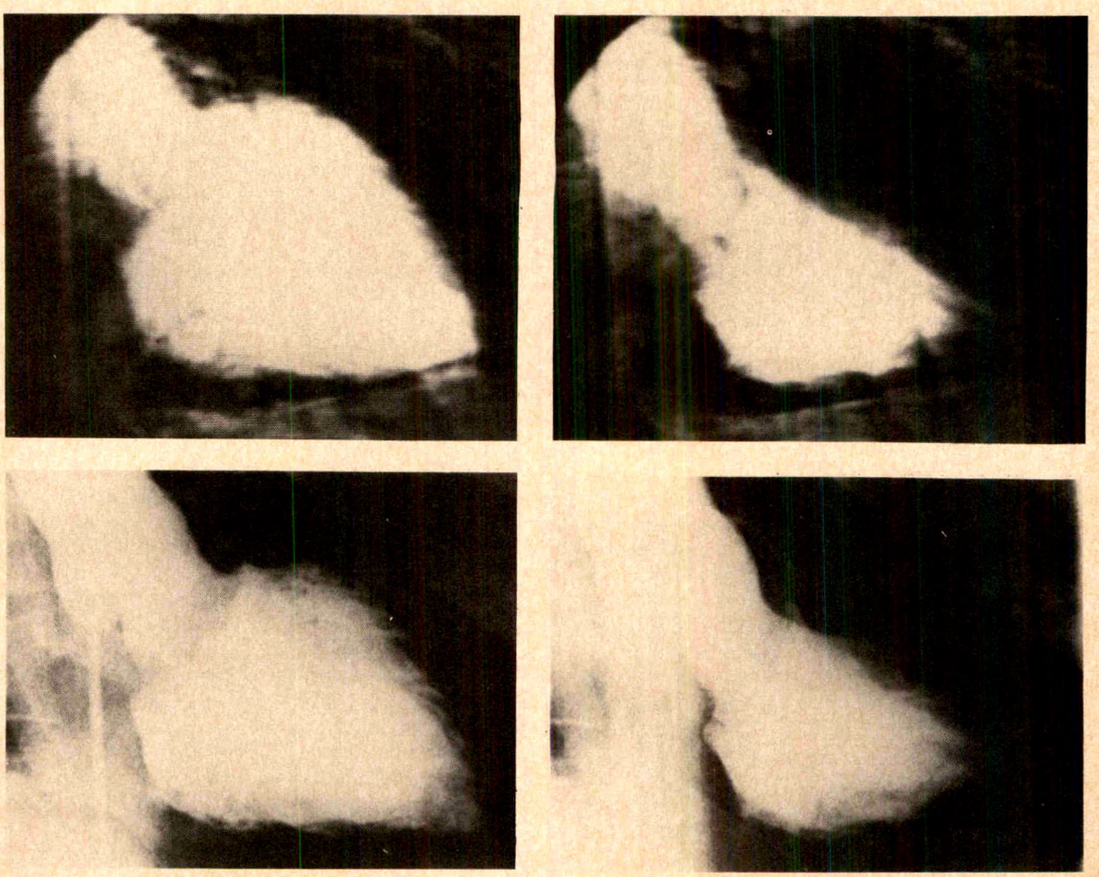


**FIGURE 1.** End-diastolic (**top left**) and end-systolic (**top right**) frames of a representative digital left ventriculogram recorded during intraventricular injection of diluted contrast medium. End-diastolic (**bottom left**) and end-systolic (**bottom right**) frames of the conventional cineangiogram of the left ventricle recorded in the same patient.

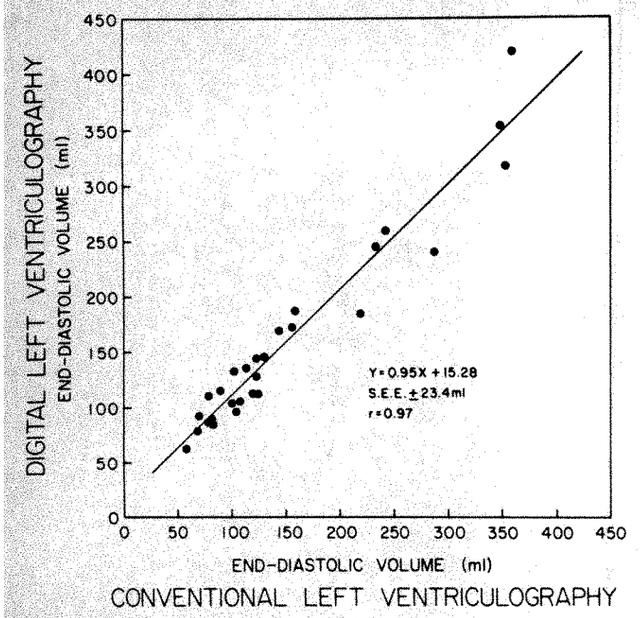



**FIGURE 2.** Correlation for left ventricular end-diastolic volumes calculated from digital and conventional left ventriculograms.

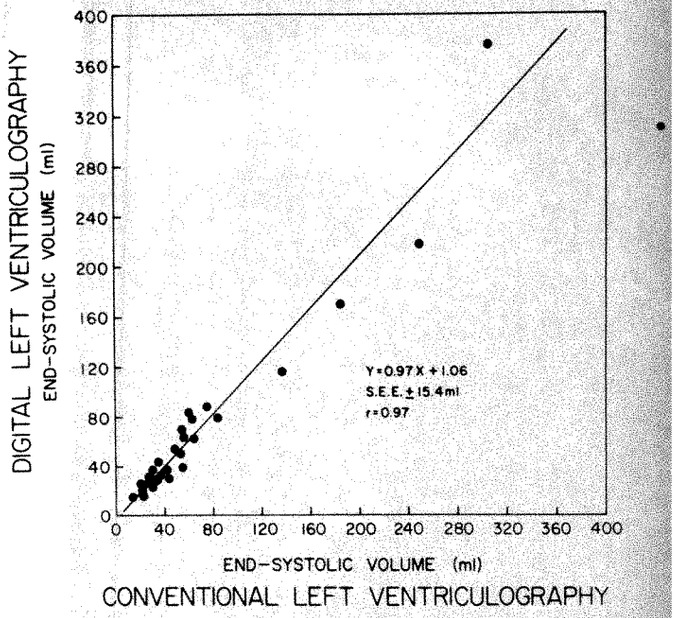



**FIGURE 3.** Correlation for end-systolic volumes calculated from digital and conventional left ventriculograms.

Similarly, mean end-systolic volumes (71.3 ± 75 versus 68.1 ± 70 ml), mean left ventricular stroke volumes (91.1 ± 48 versus 84.5 ± 45 ml), and mean left ventricular ejection fraction (61 ± 18 versus 60 ± 16%) calculated from digital and conventional left ventriculograms did not differ significantly.

Regression analysis of end-diastolic and end-systolic volumes calculated from digital (D) and conventional (c) left ventriculograms is presented in Figures 2 and 3. The regression equation relating end-diastolic volumes was $EDV_D = 0.95\ EDV_c + 15.3$ ml (r = 0.97, SEE 23.4 ml), indicating a close linear correlation. For end-systolic volumes, the regression equation was $ESV_D = 0.97\ ESV_c + 1.06$ (r = 0.97, SEE 15.4 ml).

Regression analysis of left ventricular stroke volume and ejection fraction is presented in Figures 4 and 5. The regression equation relating stroke volumes calculated from digital and conventional left ventriculograms was $SV_D = 1.03\ SV_c + 3.8$ ml (r = 0.95, SEE 14.7 ml). The regression equation relating left ventricular ejection fraction was $EF_D = 1.09\ EF_c - 4.5\%$ (r = 0.97, SEE = 3.8%).

The reproducibility of ventricular volume measurements was determined for conventional and digital ventriculograms by repeating ventriculographic analyses for a subset of 14 patients. The following correlation coefficients resulted from repeated analysis of conventional ventriculograms: EDV 0.98, ESV 0.99, SV 0.97, and EF 0.97. For repeated analysis of digital ventriculograms, the following correlation coefficients resulted: EDV 0.98, ESV 0.95, SV 0.97, and EF 0.99.

**Regional left ventricular wall motion:** The percent chordal shortening values for 140 hemiaxes and the 28 measurements of long-axis shortening calculated

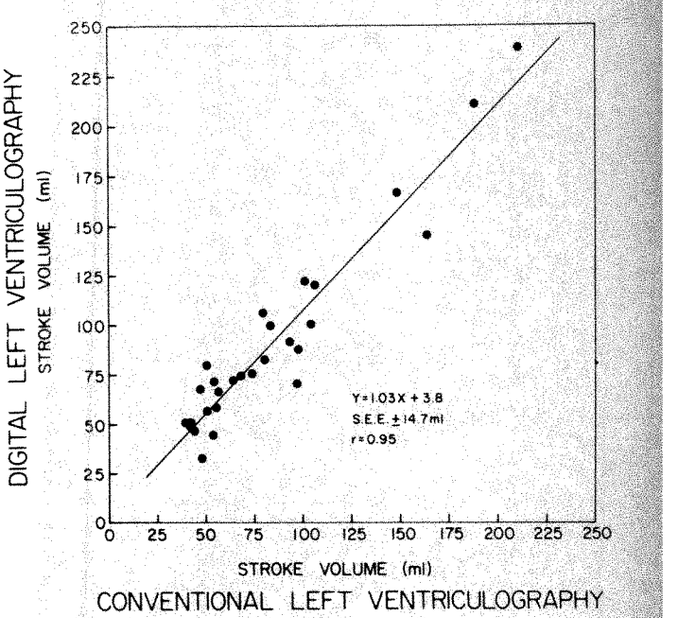



**FIGURE 4.** Correlation for stroke volumes calculated from digital and conventional left ventriculograms.

from digital left ventriculograms and conventional ventriculograms are compared in Figure 6. The correlation coefficient (r = 0.81) and SEE (±11.5%) indicate a moderate correlation. Correlation coefficients for individual hemiaxes were as follows: anterobasal (r = 0.72), anterolateral (r = 0.77), apical (r = 0.86), diaphragmatic (r = 0.76), posterobasal (r = 0.64), and long-axis shortening (r = 0.76).

**Hemodynamic changes:** After injection of undiluted contrast medium for conventional ventriculography, mean systolic left ventricular pressure decreased from 133.0 ± 31 to 123.5 ± 27 mm Hg ($p < 0.01$) and mean left ventricular end-diastolic pressure increased from 12.0 ± 7 to 16.9 ± 10 mm Hg ($p < 0.001$). After injection of diluted contrast medium for digital ventriculography, mean systolic left ventricular pressure (133.6 ± 28 versus 131.2 ± 28 mm Hg) and left ventricular end-diastolic pressure (13.0 ± 8 versus 13.3 ± 8 mm Hg) were not significantly changed. Heart rate and peak left ventricular dP/dt were not changed significantly after either conventional or digital left ventriculography.

Fifteen of the patients experienced a warm flushed sensation after injection of undiluted contrast medium. Only 1 of the patients had any discomfort after injection of diluted contrast medium. Isolated ventricular premature contractions occurred in 4 patients during injection of undiluted contrast medium and in 3 patients during injection of diluted contrast medium. Two patients with congestive cardiomyopathy tolerated low-dose diluted contrast injections well but developed pulmonary edema after full-dose injections of undiluted contrast medium.

## Discussion

Digital subtraction angiography enhances contrast density by a factor >8,[11] enabling the performance of angiography with markedly reduced doses of contrast medium. The present study demonstrates that digital subtraction angiography permits the performance of contrast left ventriculography with very low doses of contrast medium. This new approach to left ventriculography provides high resolution ventriculograms for accurate measurement of left ventricular volumes, stroke volume, and ejection fraction.

Low-dose contrast ventriculography has several advantages. First, as shown in the present study, low-dose intraventricular contrast injections do not cause the hemodynamic disturbances which result from injection of conventional doses of contrast material. Second, low-dose contrast injections should obviate the risk of nephrotoxicity associated with larger doses. Third, patients do not experience any discomfort during low-dose injections. Fourth, since the data are in digital form, digitized images can be readily analyzed by computer, facilitating videodensitometric quantification of ventricular function. This approach may enable measurement of left ventricular ejection fraction independent of geometric assumptions.[17]

On the basis of these considerations, digital left ventriculography with diluted contrast medium is suitable for serial ventriculography for assessment of the effect of therapeutic interventions on left ventricular function. The low doses of contrast medium made possible by digital left ventriculography are clinically advantageous in patients with severe congestive heart failure, impaired liver function, diabetes, or renal insufficiency, who tolerate multiple contrast injections poorly.[18,19] Digital left ventriculography will be useful in catheterization laboratories without biplane angiography facilities, since multiple digital angiograms can be performed in different projections with low total doses of contrast medium and minimal patient discomfort.

Other investigators have recently described digital left ventriculography performed with 5 to 10 ml of undiluted contrast medium injected into the left ventricle over 1 or 2 seconds.[20,21] In our experience, rapid injection of small doses of undiluted contrast medium results in incomplete opacification of the left ventricular cavity due to inadequate mixing. We found that dilution of the contrast medium with saline solution permitted injection of larger volumes over a longer period and resulted in full opacification of the ventricle for several cardiac cycles. The quality of the resulting left ventriculograms was excellent, and measurements of end-diastolic volume, end-systolic volume, stroke volume, and ejection fraction correlated highly with values measured by conventional contrast left ventriculography.

A disadvantage of the prototype digital video system used in the present study, however, is the limited recording capacity of the magnetic disc. Although digital frames were acquired and displayed in a cineangiographic format at 30 frames/s on magnetic tape, the disc recorder used for selecting end-systolic and end-diastolic frames was capable of recording only 1 frame in 3. Hence, the effective frame rate was 10/s. Frame rates of this magnitude are marginally adequate for measuring left ventricular volumes[22] but are inadequate for accurately measuring segmental left ventricular contraction. This limitation is the most probable explanation for the moderate correlation observed between segmental left ventricular contraction assessed by digital ventriculography and conventional ventriculog-

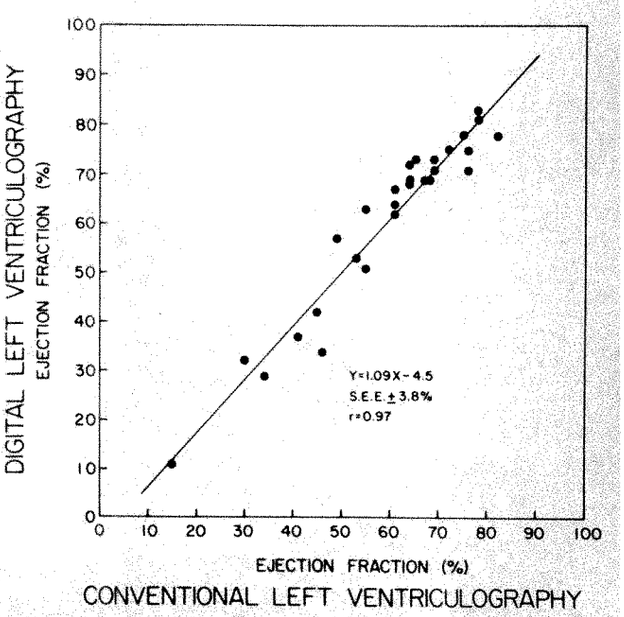



**FIGURE 5.** Correlation for ejection fractions calculated from digital and conventional left ventriculograms.

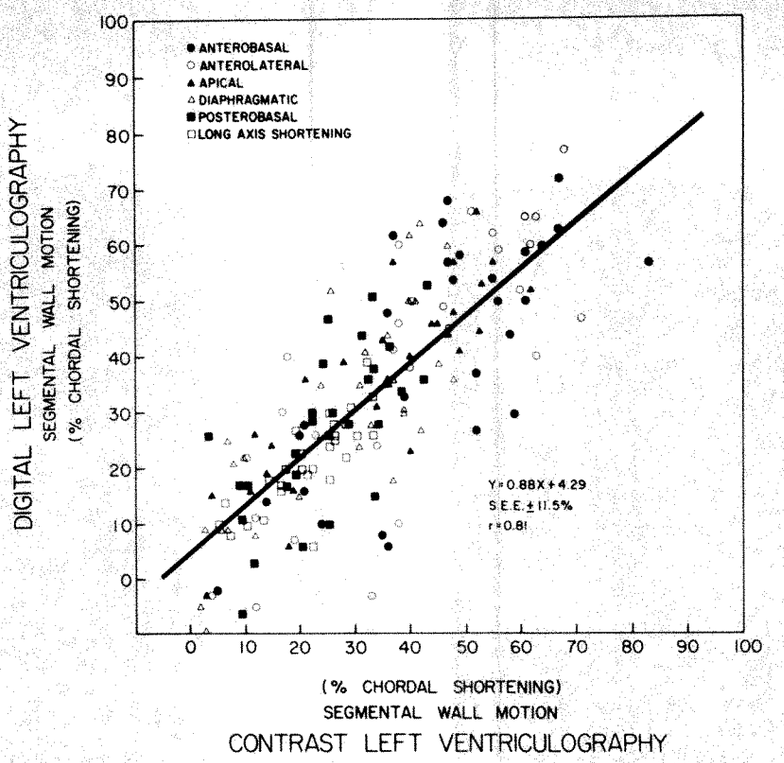



**FIGURE 6.** Percent chordal shortening for 5 left ventricular hemiaxes and the long axis of the left ventricle, measured from digital and conventional left ventriculograms.

raphy. Real-time video discs are available which are capable of acquiring 30 frames/s. Use of these discs will improve the accuracy of quantification of segmental left ventricular contraction by digital ventriculography.

One advantage of the digital video processor used in the present study is that it produces fully processed, time-subtracted images immediately available for viewing and for recording on radiographic film. The capability for second-order subtraction of individual frames from the nonopacified cardiac cycle recorded just before contrast injection was found to enhance contrast density and image quality considerably. Furthermore, geometric distortion at the borders of the fluoroscopic field is eliminated with the present system by the curvature of the output fiberoptics of the image intensifier. This digital subtraction system will have other useful applications in cardiovascular angiography, particularly for aortography with small doses of contrast medium injected selectively.

The effect of intraventricular contrast injections on the accuracy of angiographic measurements of left ventricular volumes is controversial. Studies in animal models have shown that end-diastolic and end-systolic volumes are increased immediately after intraventricular contrast injections.[4,7] In patients undergoing contrast left ventriculography, Carleton[7] reported a significant increase in end-diastolic volume by the third cycle after contrast injection. Hammermeister and Warbasse,[23] however, found no significant change in left ventricular volumes measured sequentially after contrast injection. To measure left ventricular volumes in patients without injection of contrast medium, Vine et al[24] introduced a method for calculating left ventricular volumes radiographically from metallic epicardial markers implanted during coronary artery surgery. Using this approach, they found that ventricular volumes were not affected by injection of contrast medium through the sixth beat.

The high correlations observed in the present study for ventricular volumes measured during the high- and low-dose contrast injections support the conclusion of Vine et al.[24] There was no evidence in the present study that injection of conventional doses of contrast medium significantly altered left ventricular volumes. Furthermore, the changes in left ventricular pressure caused by injection of standard doses of contrast medium were measured 20 to 30 seconds after completion of ventriculography, and thus would be unlikely to influence volume measurements.

## References

1. **Brown R, Rahimtoola SH, Davis GD.** The effect of angiocardiographic contrast medium on circulatory dynamics in man. Circulation 1965;31: 234–240.
2. **Friesinger GC, Schaffer J, Criley JM.** Hemodynamic consequences of the injection of radiopaque material. Circulation 1965;31:730–740.
3. **Gensini GG, Di Giorgi S.** Myocardial toxicity of contrast agents used in angiography. Radiology 1964;82:24–33.
4. **Gootman N, Rudolph AM, Buckley NM.** Effects of angiographic contrast media on cardiac function. Am J Cardiol 1970;25:59–65.
5. **Sanmarco ME, Fronek K, Philips CM, Davila JC.** Continuous measurements of left ventricular volume in the dog. II. Comparison of washout and radiographic techniques with the external dimension method. Am J Cardiol

1966;18:584–593.
6. **Kloster FE, Bristow JD, Porter GA, Judkins MP, Griswold HE.** Comparative hemodynamic effects of equimolar injections of angiographic contrast materials. Invest Radiol 1967;2:353–359.
7. **Carleton RA.** Change in left ventricular volume during angiocardiography. Am J Cardiol 1971;27:460–463.
8. **Mullins CB, Leshin SJ, Mierzwiak DS, Alsobrook HD, Mitchell JH.** Changes in left ventricular function produced by the injection of contrast media. Am Heart J 1972;83:373–381.
9. **Port FK, Wagoner RD, Fulton RE.** Acute renal failure after angiography. AJR 1974;121:544–550.
10. **Kruger RA, Mistretta CA, Houk TL, Riederer SJ, Shaw CG, Goodsitt MM, Crummy AB, Zwiebel W, Lancaster JC, Rowe GG, Flemming D.** Computerized fluoroscopy in real time for noninvasive visualization of the cardiovascular system. Radiology 1979;130:49–57.
11. **Kruger RA, Mistretta CA, Houk TL, Kubal W, Riederer SJ, Ergun DL, Shaw CG, Lancaster JC, Rowe GG.** Computerized fluoroscopy techniques for intravenous study of cardiac chamber dynamics. Invest Radiol 1979;4: 279–287.
12. **Crummy AB, Strother CM, Sackett JF, Ergun DL, Shaw CG, Kruger RA, Mistretta CA, Turnipseed WD, Lieberman RP, Myerowitz PD, Ruzicka FF.** Computerized fluoroscopy: digital subtraction for intravenous angiocardiography and arteriography. AJR 1980;135:1131–1140.
13. **Sandler H, Dodge HT.** The use of single-plane angiocardiograms for the calculation of left ventricular volume in man. Am Heart J 1968;75:325–332.
14. **Herman MV, Heinle RA, Klein MD, Gorlin R.** Localized disorders in myocardial contraction. Asynergy and its role in congestive heart failure. N Engl J Med 1967;277:222–232.
15. **Draper NR, Smith H.** Applied Regression Analysis. New York: John Wiley and Sons, 1966:89–92.
16. **Dixon WJ, Massey FJ Jr.** Introduction to Statistical Analysis. 3rd ed. New York: McGraw-Hill, 1969:114–119.
17. **Gerber K, Bhargava V, Slutsky R, Mattrey R, Ashburn W, Higgins C.** Quantitation of regional and global left ventricular function by digital intravenous ventriculography with functional image analysis (abstr). Circulation 1981;64:Suppl IV:IV-219.
18. **Weinrauch LA, Healy RW, Leland OS Jr, Goldstein HH, Kassissieh SD, Libertino JA, Takacs FJ, D'Elia JA.** Coronary angiography and acute renal failure in diabetic azotemic mephropathy. Ann Intern Med 1977;86:56–59.
19. **Swartz RD, Rubin JE, Leeming BW, Silva P.** Renal failure following major angiography. Am J Med 1978;65:31–37.
20. **Sasayama S, Nonogi H, Kawai C, Fujita M, Eiho S, Kuwahara M.** Automated method for left ventricular volume measurement by cineventriculography with minimal doses of contrast medium. Am J Cardiol 1981;48: 746–753.
21. **Tobis JM, Nalcioglu O, Seibert JA, Roeck WW, Iseri LT, Elkayam U, Johnston WD, Henry WL.** Use of digital angiography in assessment of ventricular ejection fraction and pacing induced wall motion abnormalities (abstr). Circulation 1981;64:Suppl IV:IV–250.
22. **Freeman E, Ziskin MC, Bove AA, Gimenz JL, Lynch PR.** Cineradiographic frame rate selection for left ventricular volumetry. Radiology 1970; 96: 587–591.
23. **Hammermeister KE, Warbasse JR.** Immediate hemodynamic effects of cardiac angiography in man. Am J Cardiol 1973;307–314.
24. **Vine DL, Hegg TD, Dodge HT, Stewart DK, Frimer M.** Immediate effect of contrast medium injection on left ventricular volumes and ejection fraction. Circulation 1977;56:379–384.

# In Vivo Ultrasonic Tissue Characterization of Human Intracardiac Masses

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**Interactions between an ultrasonic signal and cardiac tissue have been used to characterize the histologic state of myocardium in vitro. To assess the utility of in vivo ultrasonic tissue characterization, stochastic analysis was applied to the digitized echocardiographic signals from 15 patients with 2-dimensional echocardiograms suggesting intracardiac masses. Ten subjects with echocardiograms suggesting mural thrombi underwent subsequent surgery or necropsy, which confirmed thrombi in 6 and revealed no thrombi (designated artifact) in 4. Five other patients had intracardiac tumors. The amplitudes within the digitized ultrasonic signals were displayed as histograms, which were described by a parameter k that represented the degree to which each histogram departed from a totally random probability density function. In 5 of 6 thrombi, k = 0, but in all 4 artifacts, k >0. The sixth thrombus had k = 0.5 due to the specular effect of the interface between the thrombus' 2 lobes. All 5 tumors had k >0. Ultrasonic tissue characterization using a stochastic analysis of backscatter can be performed in vivo and helps differentiate thrombus from artifact and tumor in the heart.**

The role of echocardiography in cardiac diagnosis continues to evolve as the technology and our understanding of the properties of ultrasound increase. Current clinical use of echocardiography relies mostly on images or patterns of motion formed by signals reflected off tissue surfaces. Although gray-scale ultrasonography provides visual "texture" to the tissue encompassed by such surfaces, the signal from the intervening tissue is usually not analyzed quantitatively. However, the interactions between internal tissue components and an ultrasonic signal can be analyzed to characterize the histologic state of normal and diseased organs,[1] as studies of the breast,[2,3] liver,[4,5] and eye[6] have demonstrated. In vitro studies of cardiac muscle have been performed,[7–11] but in vivo characterization of human cardiac tissue in a clinical setting is only beginning.[12] We undertook the present study to assess the ability of in vivo ultrasonic tissue characterization to differentiate intracardiac masses of varying histologic types and to eliminate common sources of error in their diagnosis.

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## Methods

We attempted ultrasonic tissue characterization in 22 patients with clinical, 2-dimensional echocardiographic evidence of intracardiac thrombi. We excluded 12 subjects because of the lack of subsequent surgery or necropsy in 8 and inability to obtain sufficient data for tissue characterization in 4. The remaining subjects, who had technically adequate characterization studies and underwent cardiotomy or necropsy within days of tissue characterization, were included in the study. The decision to operate was made on clinical grounds, independent of echocardiographic findings. The subjects in whom no thrombus was found on anatomic examination were believed to have spurious echoes (technical artifact) causing suspicious echocardiographic images. Seven subjects had had myocardial infarction with ventricular aneurysm, 2 had congestive cardiomyopathy, and 1 had mitral stenosis with a suspected left atrial thrombus. We also performed in vivo ultrasonic tissue characterization in 5 additional consecutive patients with echocardiographic evidence of left atrial tumor. Four of these subjects later underwent surgery; the fifth refused operation. One patient with an atrial tumor confirmed at surgery had coexistent mitral stenosis. Preoperatively, the atrial mass could not be distinguished from thrombus by clinical or echocardiographic means.

Two-dimensional echocardiograms were obtained from commercially available sector scanners (V-3000, Varian Associates, Palo Alto, California; 77020A, Hewlett-Packard, Andover, Massachusetts) with focused, 2.25 MHz transducers coupled to a high-speed data acquisition system (Fig. 1). The region of the suspected thrombus or tumor was imaged in the

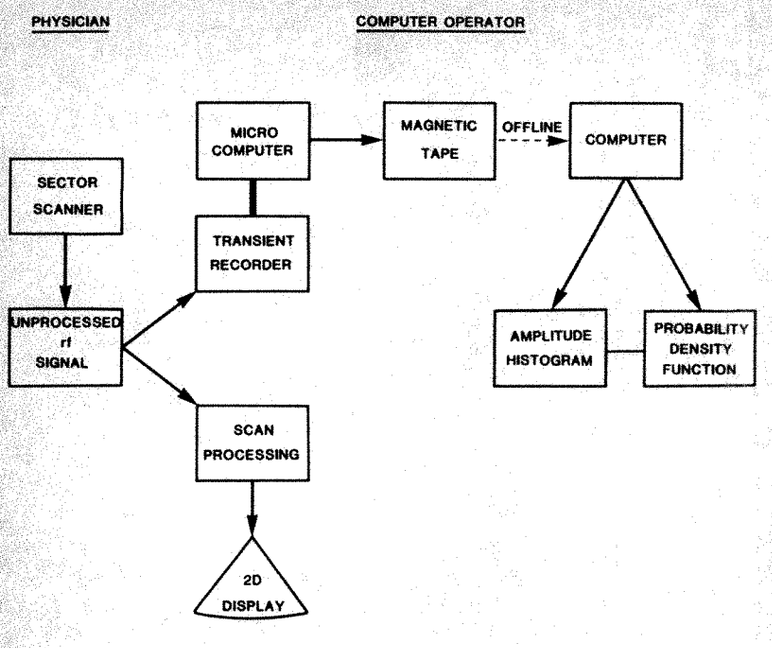



**FIGURE 1.** Diagram of data acquisition and analysis. The physician obtains the subject's echocardiogram, and the computer operator controls data sampling. The unprocessed signal is stored on tape and transferred to computer, where amplitude histograms and probability density functions are derived off-line. 2D = 2-dimensional; rf = radiofrequency.

apical 4-chamber or parasternal long- or short-axis projections,[13] and the M-mode cursor was directed through the suspected mass (Fig. 2). The unprocessed radiofrequency (rf) signal from the cursor-selected scan line was sampled at 20 MHz and digitized with a Biomation 8100 Transient Recorder under minicomputer control (Z-2, Cromemco, Mountain View, California). The signal was sampled for 40 pulses, with each sample requiring less than 1.2 ms and containing 500 to 1,000 data points. The data were transferred to a large, slow-speed buffer, where they were stored until processed off-line by a computer (2100-A, Hewlett Packard, Palo Alto, California). The unprocessed rf signal was displayed as amplitude versus tissue depth, as in Figure 2. The operator selected the depth corresponding to the anatomic region of interest, and the computer derived a histogram representing the distribution of component amplitudes of the digitized signal from that region. Each amplitude distribution was described by a parameter k, corresponding to the degree to which the histogram departed from the probability density function expected from a collection of small, random, independent scatterers. Thus, a random array of scatterers reflects a signal with an amplitude histogram described by $k = 0$, whereas an array of scatterers with nonrandom or correlated amplitudes is characterized by $k > 0$.[14] (see Appendix.) We attempted to differentiate thrombus from tumor and artifact on the basis of the amplitude histograms of their backscattered signals. We modeled thrombus as a random array of small, statistically independent scatterers. Tumor and artifact were modeled as random, independent, small scatterers mixed with nonrandom, correlated scatterers.

## Results

Direct visual examination of the heart at operation confirmed the presence of intracardiac thrombi in 6 of the 10 subjects with suspected thrombi and revealed no thrombus in the other 4. Thrombi were located in apical left ventricular aneurysms in 3 patients, in apical regions of myopathic hearts in 2, and in a posterobasal aneurysm in 1. Three of the 4 spurious images were located in the region of apical aneurysms. The fourth spurious image, in a patient with stenosis of the mitral valve, was located in the left atrium. The 4 subjects with echocardiographic evidence of left atrial tumor who underwent surgery were found to have myxomas.

Figures 2 through 4 show data obtained by in vivo tissue characterization of 3 suspected intracardiac masses. Figure 2 is a composite of data from a patient with a left ventricular thrombus. The cursor passes through the thrombus indicating the scan line that contains the unprocessed rf signal that is sampled. The portion of the signal reflected from the region of interest is digitized and displayed as a histogram of the component amplitudes of the backscattered signal. The amplitude histogram of thrombus fits a probability density function with $k = 0$, implying a randomly spaced, independent collection of scatterers. In contrast, Figure 3 depicts data obtained from a subject with a similar-appearing intracavitary image on 2-dimensional study, but backscatter amplitude analysis revealed $k > 0$, suggesting that there is a nonrandom, nonindependent component to the scatterer architecture. The subject had no thrombus at surgery, and the image was classified as artifact. Figure 4 shows data obtained from a subject with a left atrial myxoma. Tissue character-

**TABLE I Summary of Data***

| Thrombus | | Myxoma | | Artifact | |
|---|---|---|---|---|---|
| Subject | k | Subject | k | Subject | k |
| 1 | 0 | 1 | 2.5 | 1 | 1.0 |
| 2 | 0 | 2 | 1.5 | 2 | 1.5 |
| 3 | 0 | 3 | 1.5 | 3 | 2.5 |
| 4 | 0 | 4 | 2.0 | 4 | 1.5 |
| 5 | 0.5 | 5 | 1.5 | ... | ... |
| 6 | 0 | ... | ... | ... | ... |

* K is a variable representing the ratio of nonrandom to random features in the probability density function. See Appendix.

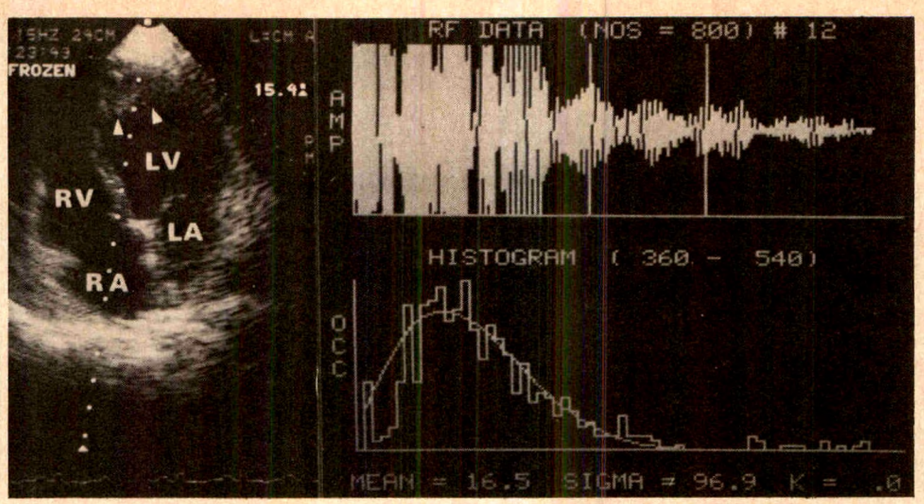



**FIGURE 2.** Composite of data obtained from a patient with an apical left ventricular thrombus confirmed at necropsy. The **left panel** shows a 2-dimensional echocardiographic image in the apical 4-chamber projection. The M-mode cursor passes through the thrombus (**arrows**), identifying the scan line from which the ultrasonic signal is sampled. The **upper right panel** is the 12th of 40 unprocessed signal samples and consists of 800 data points. Signal amplitude is represented on the **ordinate** and tissue depth on the **abscissa**. The operator-determined region of interest is enclosed by 2 **vertical lines**. The **lower right panel** depicts a histogram representing the number of occurrences (**ordinate**) of the digitized component amplitudes (**abscissa**) of the signal from the region of interest. A theoretical probability density function, derived from the mean amplitude and variance of the signal, is superimposed on the histogram. The histogram is described by k = 0, suggesting a random, independent collection of small scatterers. AMP = amplitude; LA = left atrium; LV = left ventricle; OCC = number of occurrences of digitized component amplitude; RA = right atrium; rf = radiofrequency; RV = right ventricle.

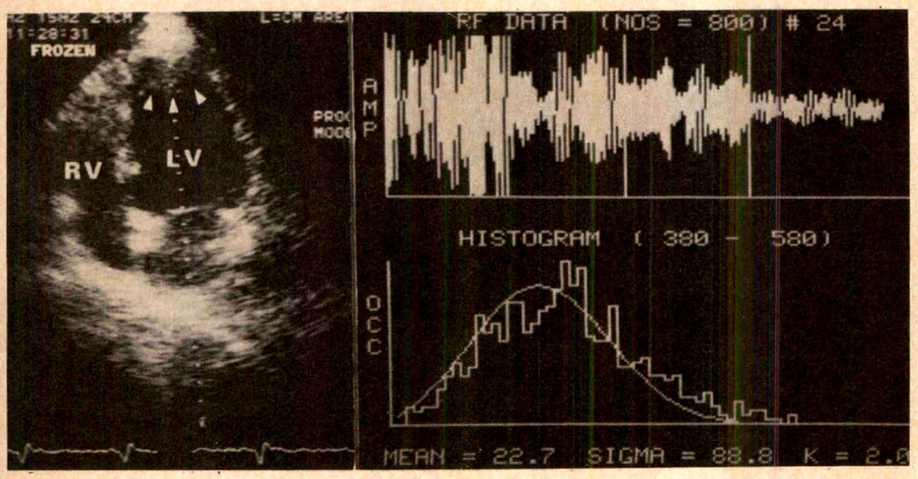



**FIGURE 3.** Composite of data from a subject with an apical image similar to that seen in Figure 2. The **left panel** shows the 2-dimensional display, with the suspected mass identified by **arrows.** The **upper right panel** depicts the unprocessed radiofrequency signal. The **lower right panel** represents the histogram and probability density function derived from the component amplitudes of the signal. The probability density function suggests a correlated component within the signal (k = 2.0). This subject had no thrombus at surgery and the apical echoes represented artifact. Abbreviations as in Figure 2.

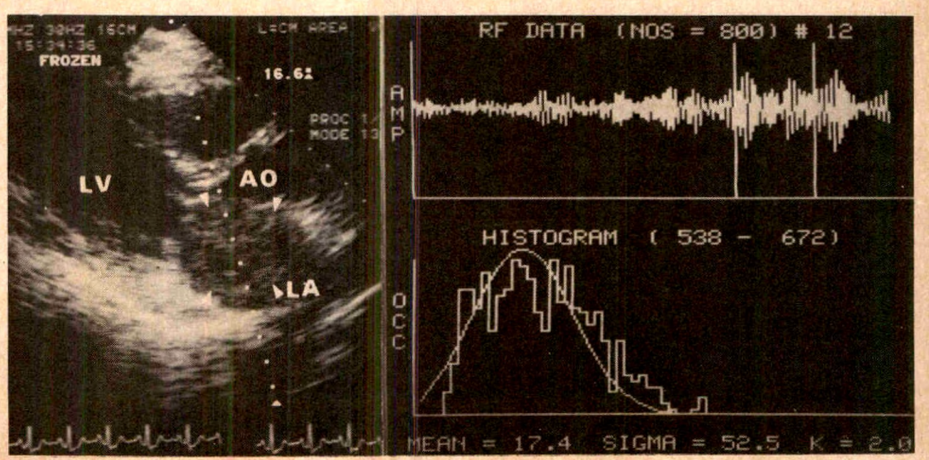



**FIGURE 4.** Composite of data from a subject with a left atrial myxoma. The **left panel** shows a parasternal long-axis 2-dimensional echocardiographic image. The M-mode cursor passes through the mass (**arrows**) in the left atrium. The **upper and lower right panels** depict data from the unprocessed and digitized radiofrequency signal, as in Figure 2. The probability density function (k = 0) suggests a correlated component within the signal. AO = aortic root; other abbreviations as in Figure 2.

ization suggests a nonindependent scattering arrangement with $k > 0$.

Data for the entire study group are summarized in Table I. Five of the 6 patients with thrombi had probability density functions with $k = 0$. One patient who had $k = 0.5$ had a small, bilobed thrombus, and the interface between lobes resulted in a backscattered signal with nonrandom characteristics. All subjects with artifact or myxoma had amplitude probability density functions with $k > 0$. Although k is a continuous variable, it is rounded to increments of 0.5 in Table I.

## Discussion

Initial applications of cardiac ultrasound were limited to descriptive identification of normal and pathologic cardiac structures and their motion. Subsequently, quantitative echocardiographic applications, such as determination of chamber size and wall thickness, were developed. Most standard ultrasonic techniques use specular reflections from interfaces having different acoustic impedance, with little emphasis on the tissue enclosed by such interfaces. However, the interaction between an ultrasonic beam and tissue is dependent on the tissue's physical properties and can result in a characteristic ultrasonic "signature" that varies with the histopathologic state of the tissue.

Although attempts at characterizing tissue histology on the basis of an ultrasonic examination date back at least to 1952,[2] quantitative ultrasonic tissue characterization still remains primarily a research tool. Ultrasonographers and engineers continue to explore the ways in which tissue components alter an ultrasonic signal. There is no consensus as to the optimal way to identify and quantitate the interactions between tissue and ultrasound. The interactions most extensively investigated include attenuation of the signal as it passes through tissue[15] and backscattering of the signal as it is reflected from multiple tissue components or scatterers.[16–18] As an ultrasonic wave propagates through a medium, its energy may be attenuated or absorbed by the medium. Different biologic tissues attenuate sound to distinct and different degrees,[15] which may vary with the health of the tissue. For example, in vitro animal experiments demonstrated that early ischemic myocardial injury decreased ultrasonic attenuation whereas attenuation was increased late after injury.[7,8] The early decrease in attenuation may result from tissue edema, but the late increase appears to result from increased collagen content of the infarcted myocardium.[10] However, application of such attenuation measurements to a living human subject is limited. To assess attenuation, the ultrasonic signal must be measured after it has passed through the organ. Current echocardiographic technology has not developed to the point where this can be done easily in the human subject. The study of reflected or backscattered ultrasound is more amenable to current clinical ultrasonic instruments which are engineered to receive a reflected signal returning from the organ studied. In vitro studies of human liver tissue show that, as in the case of attenuation, the quantity and distribution of collagen, fat, and protein in an organ influence the energy of sound reflected back to the transducer.[17] Other in vitro studies showed that myocardial infarction[9] and adriamycin-induced myocardial damage[11] increase the amount of ultrasonic backscatter. This increase in backscatter presumably represents the effect of increased collagen deposition in the involved areas. The ability to identify normal and abnormal noncardiac tissue structure has been demonstrated in vivo. Wells et al[4] noted increased echocardiographic amplitude reflected from a cirrhotic liver as opposed to a normal liver.[4] Sommer et al,[5] using a stochastic approach similar to ours, also noted increased amplitude of echoes reflected from the cirrhotic liver. Furthermore, the amplitude distribution of the cirrhotic liver was broader than normal, reflecting heterogeneity of hepatic structure in cirrhosis. In the same report, the investigators differentiated the spleen involved with advanced lymphoma and the liver with malignant infiltration from the normal spleen and liver. As in cirrhosis, the amplitude and variance of the signal from diseased organs were consistently greater than normal. Despite these exciting preliminary results, ultrasonic tissue characterization has found little clinical use to date, primarily because of difficulties in acquiring data and in applying appropriate mathematical models to in vivo clinical situations.

We undertook the present study to assess the feasibility of applying ultrasonic tissue characterization to human subjects in vivo to assist in the differentiation of intracardiac masses. Two of the most commonly encountered intracardiac masses are mural thrombi and atrial myxomas. Intracardiac thrombi may complicate myocardial infarction,[19,20] congestive cardiomyopathy,[21] and mitral valve disease.[22] The availability of 2-dimensional echocardiography may lead to improved antemortem diagnosis of intracardiac thrombi,[23–25] but pitfalls remain in attempting to make the correct diagnosis.[24,25] Normal or diseased intracavitary structures such as papillary muscles, intramural, or intracavitary calcifications or myocardial scar may be confused with thrombi.[24,25] Specular reflectors may be located in the region of interest or erroneously displayed in the image field because of beam geometry effects.[26] Spurious echoes, possibly representing reverberation from the transducer or from chest wall structures, appear in the near field of many imaging systems. These images may appear visually similar to thrombus. Although the classic, large, layered mural thrombus is easily distinguished from other structures and artifact,[25] subtle abnormalities are more difficult to assess, especially in patients who cannot be imaged from multiple transducer positions.

Atrial myxomas usually have distinct echocardiographic features,[27–29] yet their clinical presentation may be similar to that of intracardiac thrombi, with systemic emboli being manifestations of either.[30] Furthermore, neoplasm may be echocardiographically indistinguishable from thrombus,[31] especially when the tumor is associated with another cardiac disease, as in our patient with coexistent mitral stenosis. Similarly, a pedunculated thrombus may be indistinguishable from myxoma on standard echocardiography.[32]

To provide an objective means of differentiating intracardiac thrombi from commonly encountered artifacts and tumors, we applied a stochastic approach to the analysis of the echocardiographic signals representing the images in question.[14] A received ultrasonic signal is the sum of the echoes from scatterers contained within a given sample volume. Some tissues may be modeled as a great number of individual scatterers of small cross-sectional area relative to the ultrasonic wavelength. These small scatterers represent random variables, and the amplitude of the signal reflected from each scatterer is statistically independent of the signals reflected from all other scatterers. Therefore, the distribution of amplitudes within the received signal will approximate the probability density function expected from an array of random, independent scatterers.[14] The components of thrombus, an interlacing network of fibrin, platelets, erythrocytes, and leukocytes,[33] are small and arranged homogeneously relative to our scanner's ultrasonic wavelength. Thus, thrombus fits the model of many small scatterers randomly spaced in the sample volume, and the component amplitudes of an ultrasonic signal reflected from thrombus should be distributed in the appropriate probability density function. Conversely, myxomas are composed of cells, strands of collagen and elastin, foci of calcium, islands of extramedullary hematopoieses, and cystic spaces,[30] resulting in multiple acoustic interfaces that are large relative to the ultrasonic wavelength. The signals returned from various parts of these large reflectors are correlated to a degree and therefore do not fit a totally random, independent probability density function.[14] Similarly, near field and beam geometry artifacts do not represent small, independent scatterers distributed throughout the sample volume. They result from specular, inhomogeneous reflectors and therefore do not manifest a totally random probability density function.

By using stochastic analysis of the amplitudes of the backscattered signals, we noninvasively differentiated thrombus from artifact and myxoma. In 5 of our 6 patients with anatomically proven thrombi, the histograms of backscattered amplitudes approximated random probability density functions, whereas all artifact and myxoma studies demonstrated nonindependent components in their functions. Only 1 patient with thrombus departed from the expected random probability density function. This patient had a bilobed thrombus, and because the individual lobes were too small for accurate analysis, we included the entire bilobed structure in the sample volume. The interface between the lobes created a relatively large, specular reflector, resulting in $k = 0.5$. Although the result is not what would be predicted for typical thrombus, this finding is consistent with the modeled effect of an acoustic interface of large cross-section and illustrates the importance of sampling from the internal structure, and not the surface, of the image being analyzed.

The distinction between mural thrombus and artifact or myxoma is clinically important, because the management and prognosis of each are different. However, the major benefit of this study is the demonstration that echocardiographic tissue characterization can be performed reliably in vivo. This approach may allow differentiation of normal and pathologic cardiac structures and assist in identification of ischemic, infarcted, or myopathic myocardium.

Problems remain in refining the techniques of ultrasonic tissue characterization. The parameter k accurately separates random from nonrandom amplitude distributions. However, k does not differentiate the various types of nonrandom processes. Thus, we could not differentiate, on the basis of k alone, artifact from myxoma. We expect thrombus with discrete calcification to be a problem, but have not seen this problem so far. Further refinement of our approach is necessary to improve its ability to differentiate various nonrandom processes. Factors that alter the acoustic signal during in vivo imaging include the effects of intervening tissue on the incident and reflected signal, variations in the angle of incidence of the interrogating beam, and cardiac motion.[8,9,12,16,34] By obtaining large quantities of data over a very brief time interval and analyzing them as a function of probability, the stochastic approach minimizes, but does not eliminate, these problems.[12,14,16] The effects of intervening tissue may result in inaccuracy in more subtle efforts at tissue characterization. The resolution of current instruments dictates a minimal target tissue thickness of 1 cm for statistically adequate data collection. For this reason, we currently are unable to perform characterization on smaller structures, such as cardiac valves and small masses. An example of the limitation imposed by sample size is our patient with a bilobed thrombus. We now limit our clinical studies to structures large enough to allow sampling within, but not including, tissue surfaces to minimize the specular effects of these surfaces.

We think it is important to digitize the rf signal before it undergoes electronic processing. Video image processing is used in commercial 2-dimensional echocardiography to produce a pleasing visual image. However, the image modifications distort the information obtained by the interaction of the tissue with sound. The degree of change varies among patients and instruments. By analyzing the signal before it is processed, we may be more able to evaluate the interaction of tissue with sound independent of manipulations by the ultrasonic apparatus.[16]

Our approach to in vivo cardiac tissue characterization uses analysis of the amplitude domain of a reflected ultrasonic signal. Analysis of the frequency domain also conveys information about tissue structure. Biologic tissue consists of regularly arranged structural units. If these repetitive units, such as the portal triads of normal liver, are on the order of the ultrasonic wavelength, their spacing can be measured by analyzing periodic peaks in the signal's frequency spectrum.[5,14] The development of edema, cellular infiltration, or fibrosis may produce changes in tissue spacing and in frequency spectral peaks. Studies in lung,[18] breast,[3] liver, spleen,[5] and eye[6] have demonstrated the use of frequency domain analysis in tissue characterization. Analysis in the frequency domain could be expected to have a similar role in cardiac tissue characterization. However, the structural unit of the heart, the myocardial fiber, is very small

relative to the 0.7 to 1.4 mm wavelength of commercial echocardiographic instruments.[35] Transducers that emit higher frequency signals with wavelengths on the order of myocardial fiber size do not penetrate deeply into the adult chest.[36] Therefore, we have not used frequency analysis in our in vivo studies.

Our study population represents a selected group of patients with a specific clinical problem. Although such selection limits the general applicability of our findings, the selection process is beneficial, because it allows anatomic confirmation of the nature of the echocardiographic signal in question. Our single subject who did not undergo surgery or necropsy had an echocardiographic examination that was classic for myxoma, with attachment of the mass by a stalk to the interatrial septum.

In conclusion, we have shown that echocardiographic tissue characterization, applying a stochastic analysis of the component amplitudes of backscattered ultrasound, can be performed in vivo. The technique provides an exciting new approach to the diagnosis of selected intracardiac masses.

**Acknowledgment:** We thank Gretchen Houd and Margaret Corazza for assistance in the preparation of this manuscript.

## Appendix

The histogram is based on the distribution of amplitudes within the reflected signal and is described as fitting a Raleigh or non-Raleigh probability density function. An array of independent scatterers would be expected to reflect a signal with a mean amplitude ($\bar{a}$) and variance ($\sigma^2$) in the relation $\bar{a}^2 = 2\sigma^2$ (Raleigh). However, if a nonindependent component is included in the array of scatterers, then $\bar{a}^2 = \sigma^2 (2 + k^2)$.[14] Therefore, if $k = 0$, the histogram would be distributed in a fashion resembling a Raleigh probability density function. If $k > 0$, the histogram would resemble a non-Raleigh probability density function. The parameter k is defined as $S/\sigma$. In the modeling of abnormal tissue, S is a constant biasing phasor which represents the effect of larger elastic variations or specular reflectors that lead to a lack of independent scattering. This effect is often superimposed on the homogeneous normal tissue pattern and provides the basis for our differentiation of various kinds of tissue.

## References


1. **Reid JM.** Challenges and opportunities in ultrasound. In: Linzer M, ed. Ultrasonic Tissue Characterization. US Dept of Commerce, Nat Bur Stand, Spec Publ 453. Washington DC: US Government Printing Office, 1976: 11–17.
2. **Wild JJ, Reid JM.** Further pilot echographic studies on the histologic structure of tumors of the living intact human breast. Am J Pathol 1952; 28:839–861.
3. **Fry EK, Sanghvi NT, Fry FJ, Gallager HS.** Frequency dependent attenuation of malignant breast tumors studied by the fast Fourier transform technique. In: Linzer M, ed. Ultrasonic Tissue Characterization. II. US Dept of Commerce, Nat Bur Stand, Spec Publ 525. Washington DC: US Government Printing Office, 1979:85–91.
4. **Wells PNT, Mountford RA, Halliwell M, Atkinson P.** Quantitative A-scan analysis of normal and cirrhotic liver. In Ref 1:61–70.
5. **Sommer FG, Joynt LF, Carroll BA, Macovski A.** Ultrasonic characterization of abdominal tissues via digital analysis of backscattered waveforms. Radiology 1981;141:811–817.
6. **Lizzi FL, Elbaum ME.** Clinical spectrum analysis techniques for tissue characterization. In Ref 3:111–119.
7. **Mimbs JW, Yuhas DE, Miller JG, Weiss AN, Sobel BE.** Detection of myocardial infarction in vitro based on altered attenuation of ultrasound. Circ Res 1977;41:192–198.
8. **Mimbs JW, O'Donnell M, Miller JG, Sobel BE.** Changes in ultrasonic attenuation indicative of early myocardial ischemic injury. Am J Physiol 1979;236:H340–H344.
9. **Gramiak R, Waag RC, Schenk EA, Lee PPK, Thomson K, MacIntosh P.** Ultrasonic detection of myocardial infarction by amplitude analysis. Radiology 1979;130:713–720.
10. **O'Donnell M, Mimbs JW, Miller JG.** The relationship between collagen and ultrasonic attenuation in myocardial tissue. J Acoust Soc Am 1979; 65: 512–517.
11. **Cohen RD, Mimbs JW, O'Donnell M, Miller JG, Sobel BE.** Ultrasonic detection of the altered acoustic properties of myocardium characteristic of adriamycin induced cardiomyopathy (abstr). Am J Cardiol 1981;47:471.
12. **Joynt L, Boyle D, Rakowski H, Popp R, Beaver W.** Identification of tissue parameters by digital processing of real-time ultrasonic clinical cardiac data. In Ref 3:267–273.
13. **Henry WL, DeMaria A, Gramiak R, King DL, Kisslo JA, Popp RL, Sahn DJ, Schiller NB, Tajik A, Teichholz LE, Weyman AE.** Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-Dimensional Echocardiography. Circulation 1980;62:212–217.
14. **Joynt LF.** A stochastic approach to ultrasonic tissue characterization. Technical report G557-4, Integrated Circuits Laboratory, Stanford Electronics Laboratories, Stanford University, Stanford, California, 1979.
15. **Dunn F.** Ultrasonic attenuation, absorption, and velocity in tissues and organs. In Ref 1:21–28.
16. **Reid JM.** The scattering of ultrasound by tissues. In Ref 1:29–47.
17. **Freese M, Lyons EA.** Dependence of ultrasound backscatter from human liver tissue on frequency and protein/lipid composition. In Ref 3:157–163.
18. **Rhyne TL.** An ultrasonic tissue signature for the lung surface. In Ref 3: 135–141.
19. **Yater WM, Welsh PP, Stapleton JF, Clark ML.** Comparison of clinical and pathologic aspects of coronary artery disease in men of various age groups: a study of 950 autopsied cases from the Armed Forces Institute of Pathology. Ann Intern Med 1951;34:352–392.
20. **Asinger RW, Mikell FL, Elsperger J, Hodges M.** Incidence of left-ventricular thrombosis after acute transmural myocardial infarction. Serial evaluation by two-dimensional echocardiography. N Engl J Med 1981;305:297–302.
21. **Brigden W.** Uncommon myocardial diseases. The non-coronary cardiomyopathies. Lancet 1957;2:1179–1184.
22. **Weiss S, Davis D.** Rheumatic heart disease. III. Embolic manifestations. Am Heart J 1933;9:45–52.
23. **DeMaria AN, Neumann A, Bommer W, Weinert L, Grehl T, Amsterdam EA, Mason DT.** Left ventricular thrombi identified by cross-sectional echocardiography. Ann Intern Med 1979;90:14–18.
24. **Meltzer RS, Guthaner D, Rakowski H, Popp RL, Martin RP.** Diagnosis of left ventricular thrombi by two-dimensional echocardiography. Br Heart J 1979;42:261–265.
25. **Asinger RW, Mikell FL, Sharma B, Hodges M.** Observations on detecting left ventricular thrombus with two-dimensional echocardiography: emphasis on avoidance of false positive diagnoses. Am J Cardiol 1981;47:145–156.
26. **Roelandt J, van Dorp WG, Bom N, Laird JD, Hugenholtz PG.** Resolution problems in echocardiography; a source of interpretation errors. Am J Cardiol 1976;37:256–262.
27. **Effert S, Domanig E.** Diagnostik intraaurikularer Tumoren und grosser Thromben mit dem Ultraschallechoverfahren. Dtsch Med Wochenschr 1959;86:6–10.
28. **Wolfe SB, Popp RL, Feigenbaum H.** Diagnosis of atrial tumors by ultrasound. Circulation 1969;39:615–622.
29. **Lappe DL, Bulkley BH, Weiss JL.** Two-dimensional echocardiographic diagnosis of left atrial myxoma. Chest 1978;74:55–58.
30. **McAllister HA Jr, Fenoglio JJ Jr.** Tumors of the cardiovascular system. In: Atlas of Tumor Pathology, 2d series, fasc 15. Washington DC: Armed Forces Institute of Pathology, 1978:5–20.
31. **Edwards WD.** Aneurysms and mural thrombi of the left ventricle. Mayo Clin Proc 1981;56:129–131.
32. **Levisman JA, MacAlpin RN, Abbasi AS, Ellis N, Eber LM.** Echocardiographic diagnosis of a mobile, pedunculated tumor in the left ventricular cavity. Am J Cardiol 1975;36:957–959.
33. **Sandritter W, Thomas C.** Color Atlas and Textbook of Histopathology. Chicago: Yearbook Medical, 1979:73.
34. **Klepper JR, Brandenburger GH, Busse LJ, Miller JG.** Phase cancellation, reflection, and refraction effects in quantitative ultrasonic attenuation tomography. 1977 Ultrasonics Symposium Proceedings. IEEE Cat #77CH1264-1SU, 1977:182–188.
35. **Copenhaver WM, Kelly DE, Wood RL.** Bailey's Textbook of Histology. 17th ed. Baltimore: Williams & Wilkins, 1978:269.
36. **Wells PNT.** Biomedical Ultrasonics. London: Academic Press, 1977: 162.

# Dialog of the Hearts –by Shakespeare:

**JULIET**

"Wilt thou be gone? It is not yet near day.
It was the nightingale, and not the lark,
That pierced the fearful hollow of thine ear.
Nightly she sings on yond pomegranate tree.
Believe me, love, it was the nightingale.

**ROMEO**

It was the lark, the herald of the morn;
No nightingale. Look, love, what envious streaks
Do lace the severing clouds in yonder East.
Night's candles are burnt out, and jocund day
Stands tiptoe on the misty mountain tops.
I must be gone and live, or stay and die.

**JULIET**

Yond light is not daylight; I know it, I.
It is some meteor that the sun exhales
To be to thee this night a torchbearer
And light thee on thy way to Mantua.
Therefore stay yet; thou need'st not to be gone."

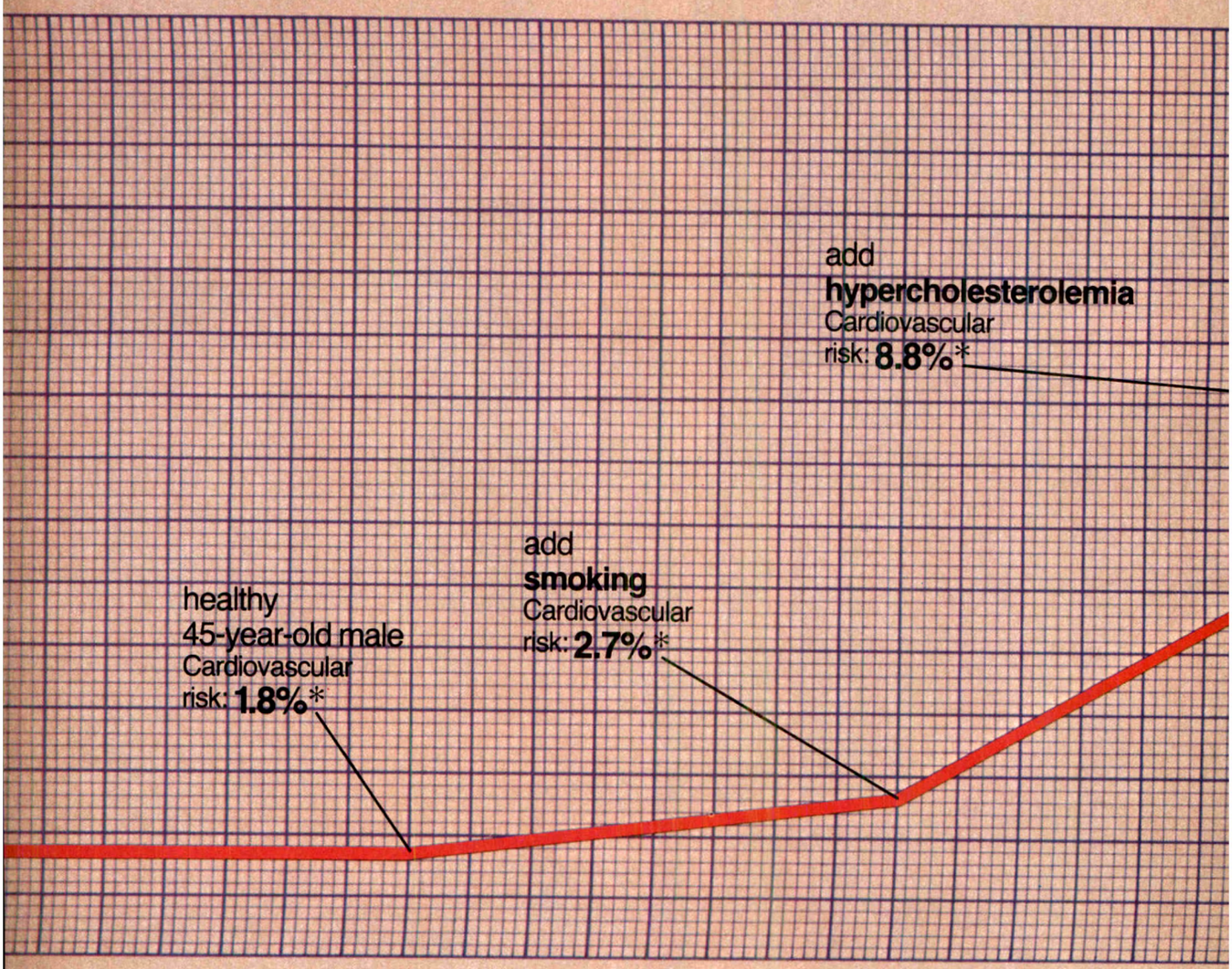
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# In hypertensive patients

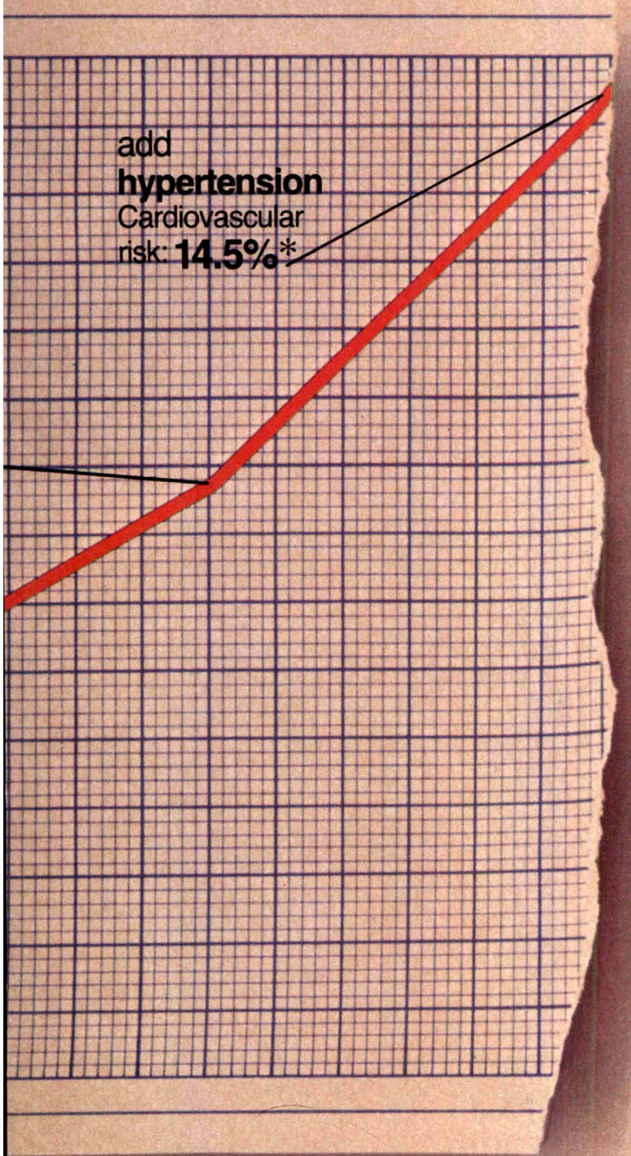



Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

# Consider the Risks




▪ When selecting antihypertensive therapy, clinical consideration should be given to the effects of the specific drug on coronary risk factors. Blood pressure control should be achieved without adversely affecting blood lipids.

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**INDICATIONS:** MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.
**WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.**
If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.
Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.
More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.
***Usage in Pregnancy:*** Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.
***Usage in Children:*** No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.
**ADVERSE REACTIONS:** The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.
The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)
Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular: edema, dyspnea, syncope, tachycardia.
Central Nervous System: nervousness, vertigo, depression, paresthesia.
Dermatologic: rash, pruritus, alopecia, lichen planus.
Genitourinary: urinary frequency, incontinence, impotence, priapism.
EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.
Other: diaphoresis.
Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.
In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.
**DOSAGE AND ADMINISTRATION:** The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:
***Initial Dose:*** 1 mg two or three times a day. (See Warnings.)
***Maintenance Dose:*** Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.
***Use With Other Drugs:*** When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.
**HOW SUPPLIED:** MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).
*More detailed information available on request.*

**References:** 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet*: 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.

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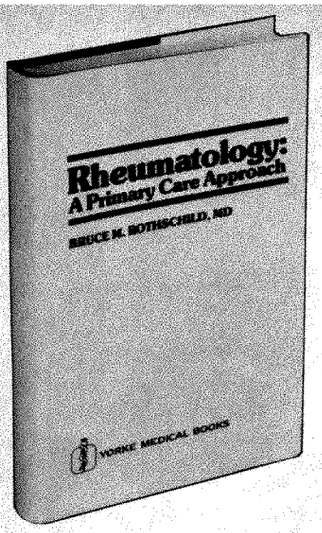
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Written by:

**Bruce M. Rothschild, MD**

Director, Division of Rheumatology, University Health Sciences, The Chicago Medical School Chief, Section of Rheumatology, V. A. Medical Center North Chicago, Illinois

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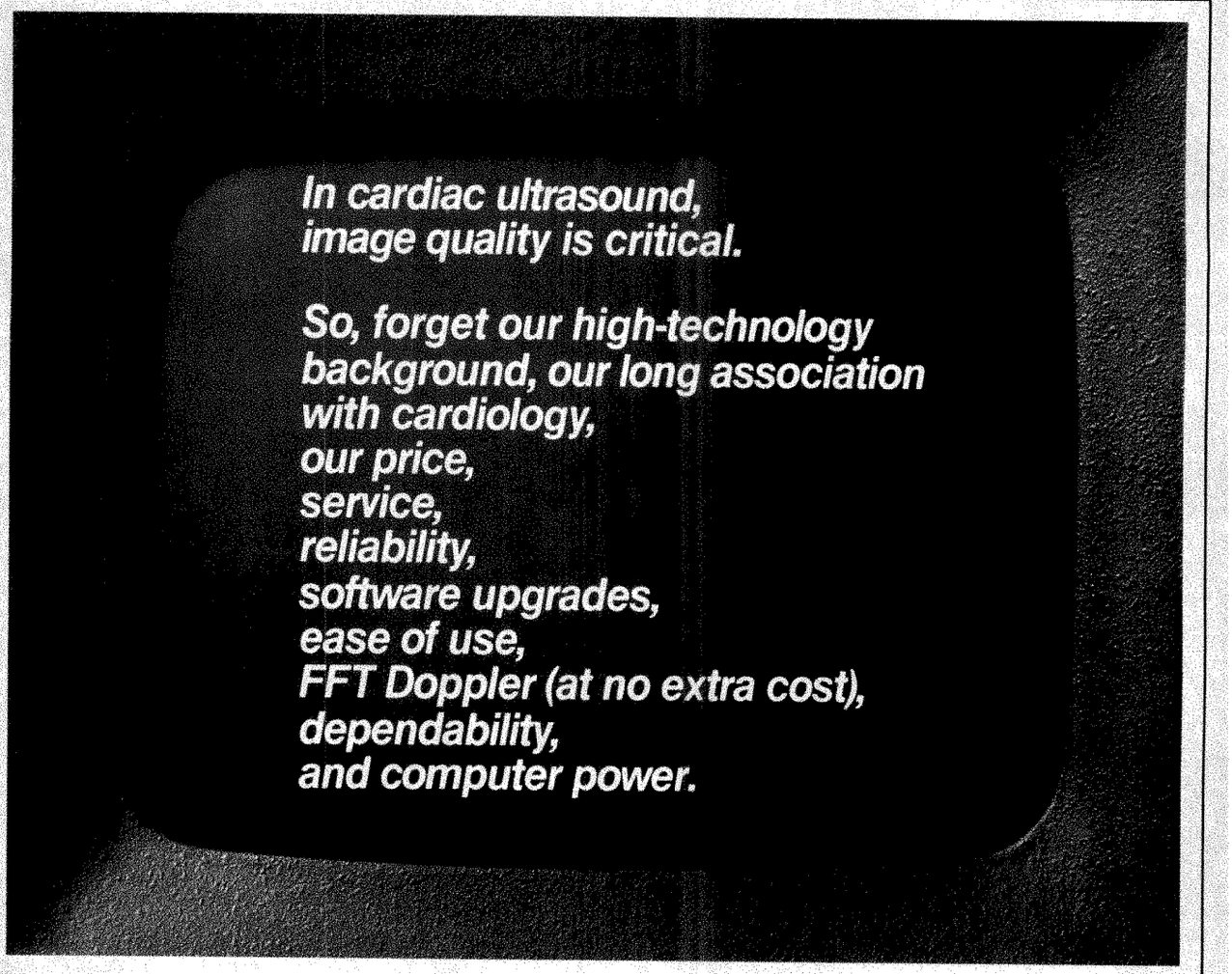
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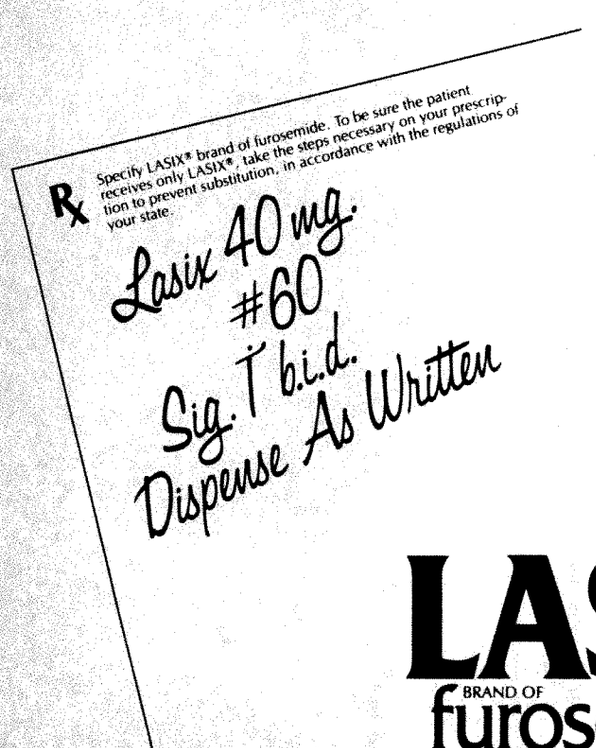
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**INDICATIONS:** Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

**CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.**

**WARNINGS:** Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, $CO_2$, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

**PRECAUTIONS:** As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

**PREGNANCY:** Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**ADVERSE REACTIONS:** Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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## Who are the editors?

**Lawrence H. Cohn, MD,** is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

**Vincenzo Gallucci, MD,** is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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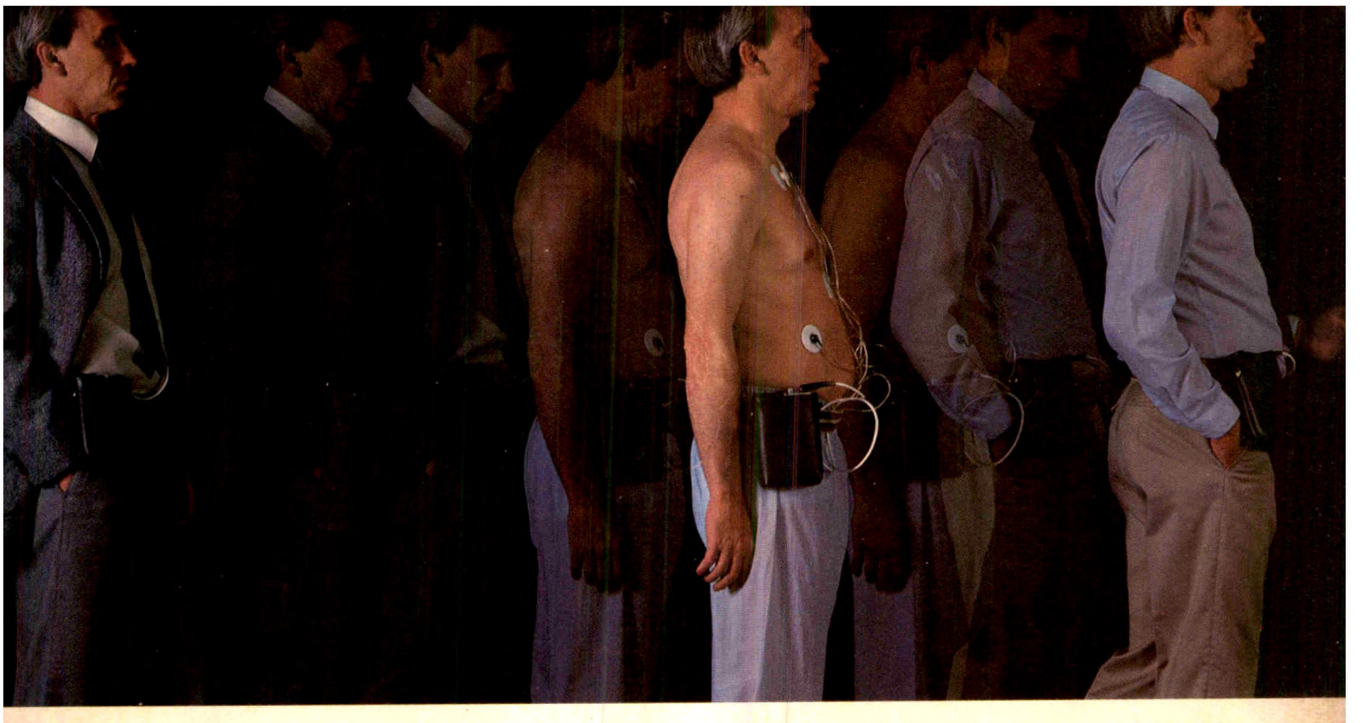
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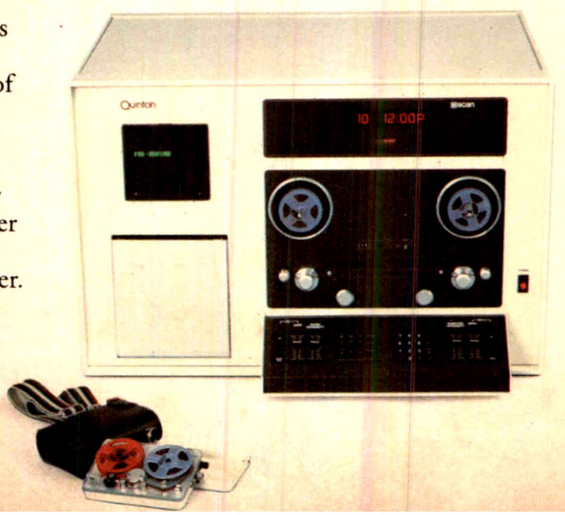
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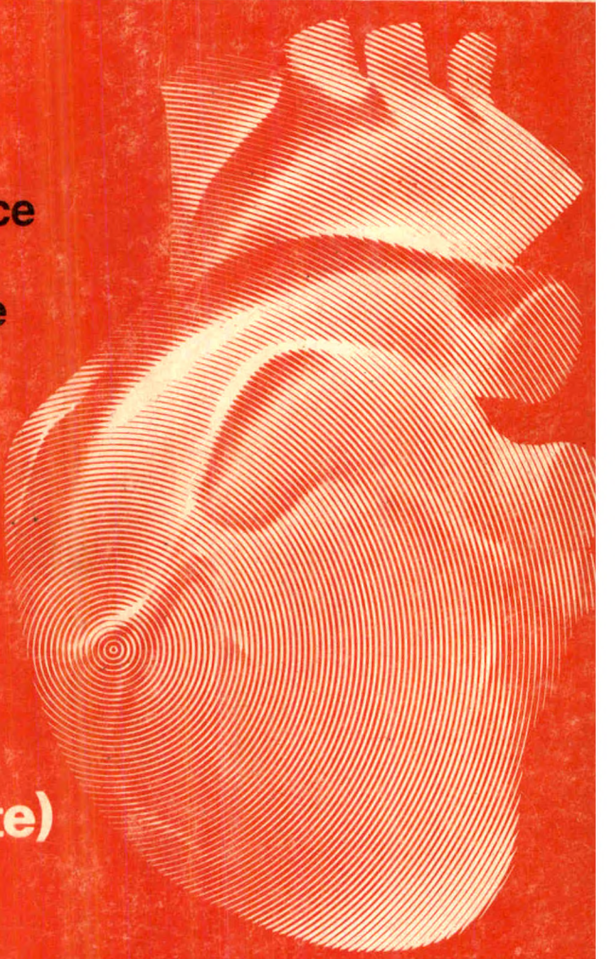
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DRUG INTERACTIONS OF QUINIDINE:

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| With anticholinergic drugs | Additive vagolytic effect. |
| With cholinergic drugs | Antagonism of cholinergic effects. |
| With carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics | Alkalinization of urine resulting in decreas excretion of quinidine. |
| With coumarin anticoagulants | Reduction of clotting factor concentration |
| With tubocurare, succinylcholine and decamethonium | Potentiation of neuromuscular blockade. |
| With phenothiazines and reserpine | Additive cardiac depressive effects. |
| With hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin) | Decreased plasma half-life of quinidine. |
| With digoxin | Increased plasma concentrations of digo (see WARNINGS). |

PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases whe the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: T drug should be used with caution due to excretion of the quinidine in breast milk. ADVERS REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headaches, and/ disturbed vision) may appear in sensitive patients after a single dose of the drug. GASTROINTE TINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Widening of QR complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (including ventricu tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypotension. HEM TOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranul cytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, delirium, a syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydrias blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, nig blindness, scotomata), optic neuritis. DERMATOLOGIC: Rash, cutaneous flushing with intem pruritus, urticaria. HYPERSENSITIVITY REACTIONS: Angioedema, acute asthmatic episo vascular collapse, respiratory arrest, hepatic toxicity. See package insert for Full Prescri information.

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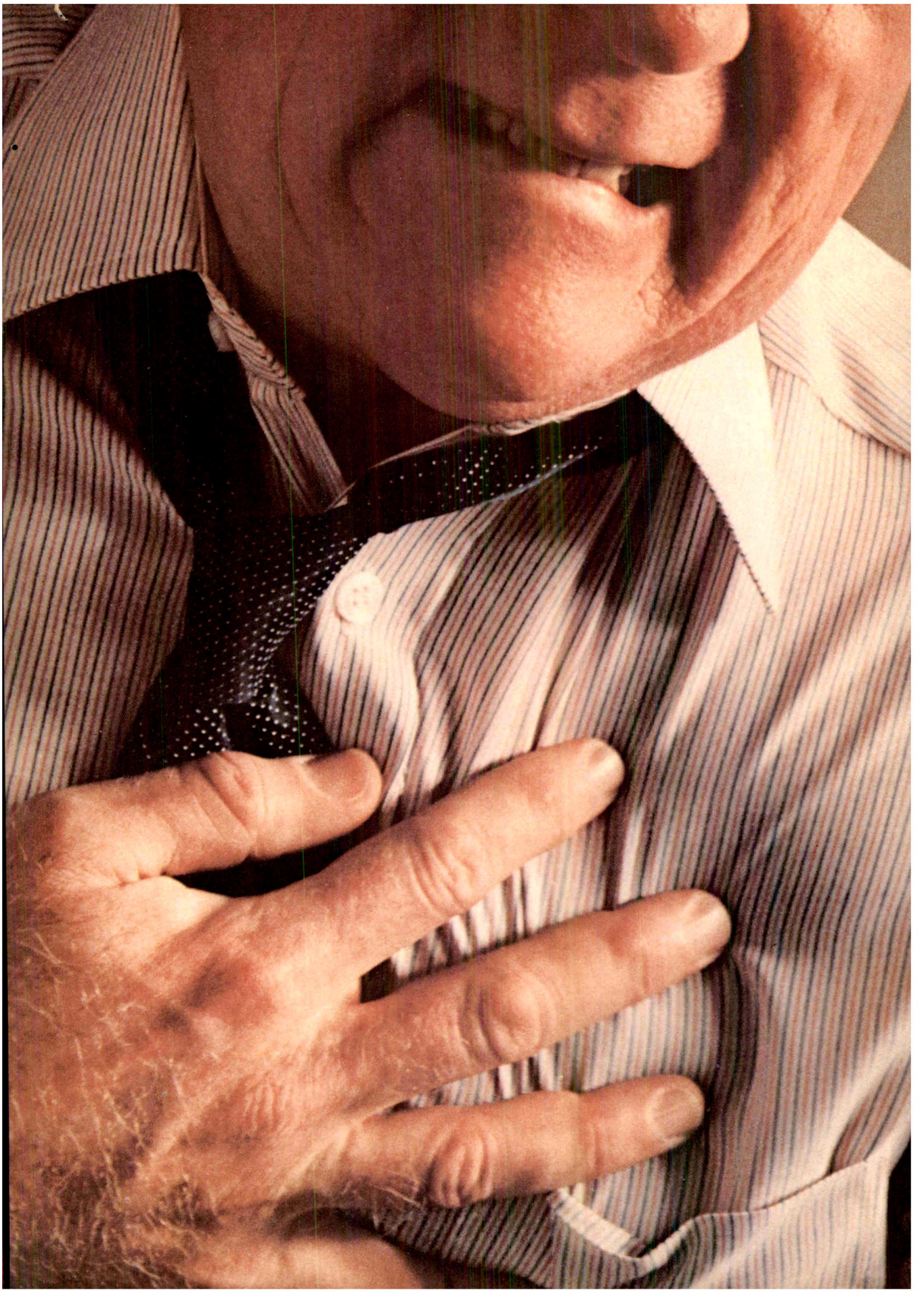
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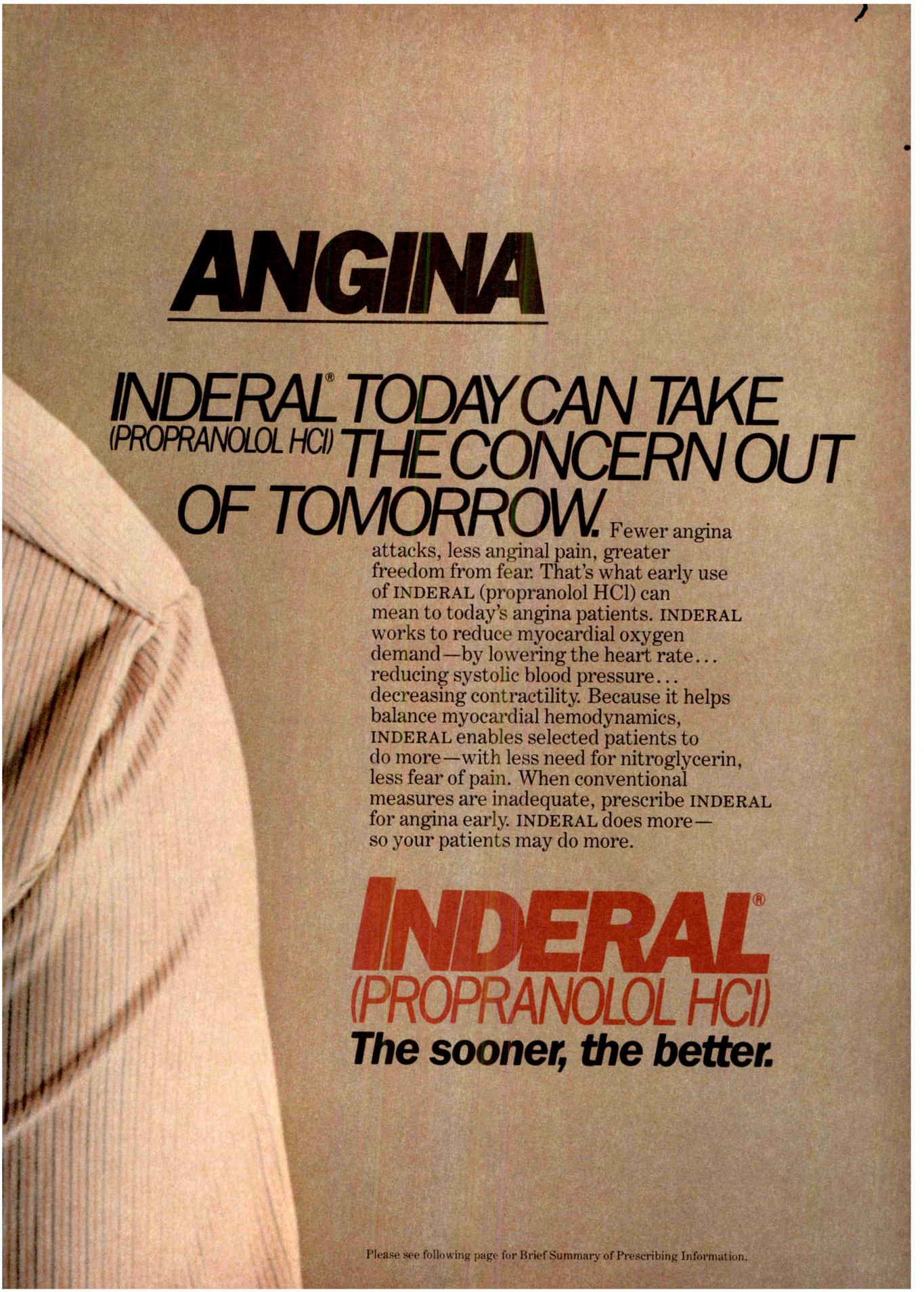

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### CONTRAINDICATIONS

1) bronchial asthma, 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless it is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

### WARNINGS

CARDIAC FAILURE: In congestive heart failure, inhibition with beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients already receiving digitalis, propranolol may reduce the positive inotropic action of digitalis and may have an additive depressant effect on AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac failure has developed during propranolol therapy. At the first sign of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and observed closely. a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery. In case of emergency surgery, the effects of propranolol can be reversed by administration of beta-receptor agonists such as isoproterenol or levarterenol, but such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), administer with caution, since propranolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY: Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

### PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

### ADVERSE REACTIONS

*Cardiovascular*: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System*: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal*: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic*: pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory*: bronchospasm. *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous*: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings*: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

### HOW SUPPLIED

TABLETS

--Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains 10 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-91). Also in unit dose package of 100 (NDC 0046-0421-99).

--Each hexagonal-shaped, blue, scored tablet is embossed with an "I" and imprinted with "INDERAL 20," contains 20 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0422-81) and 1,000 (NDC 0046-0422-91). Also in unit dose package of 100 (NDC 0046-0422-99).

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--Each hexagonal-shaped, yellow, scored tablet is embossed with an "I" and imprinted with "INDERAL 80," contains 80 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0428-81) and 1,000 (NDC 0046-0428-91). Also in unit dose package of 100 (NDC 0046-0428-99).

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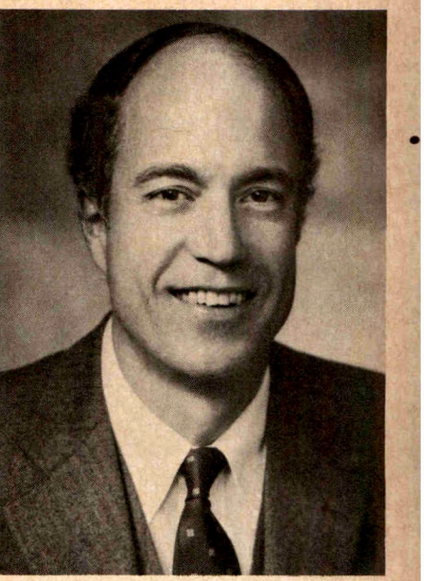
INJECTABLE

--Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

Store at room temperature (approximately 25° C).

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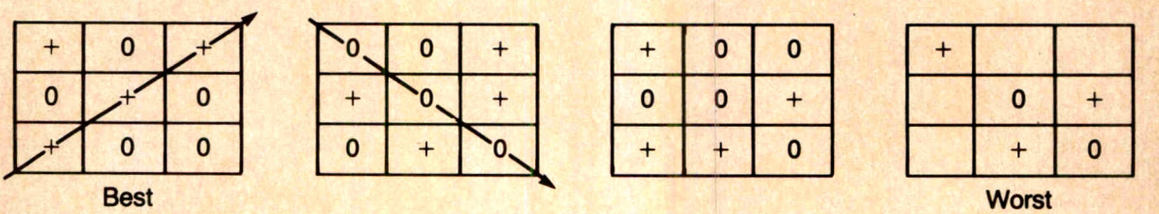
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# Getting the Manuscript Accepted: Think Like a Lawyer and Cover the Flanks

A manuscript might be viewed as a legal brief in which an author presents logical arguments supporting the contention that he has created and proven a new concept. Reviewers, in a way, are like defense lawyers who attempt to find a flaw in the author's contention. Finding such flaws often casts doubt on other claims of the author or claimant. Indeed, the finding by reviewers or the Editor of *omissions of mention* can be a major stumbling block preventing the acceptance of a manuscript.

A manuscript's quality may be compared to the game of tic-tac-toe, in which 2 players, in turn, fill in 9 compartments, 1 at a time, with X's and O's. The *best paper* fills in all the blocks—covers all the bases—and in addition lines up 3 X's in a row (see the figure below), signifying focus and clarity. A row of zeros indicates that the manuscript provides an essentially negative observation. A manuscript also can have all the blocks filled in but no symbols lined up in a row, indicating a lack of clarity and focus. The *worst paper* fails to fill in 1 or more compartments with either symbol (omissions of mention) and none line up in a row, an indication that the author has failed to mention all the points necessary to prove his case and to focus the points properly.




William C. Roberts

William C. Roberts, MD
Editor-in-Chief

# In Hypertension*...When You Need to Conserve $K^+$

# Every Step of the Way




Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a $K^+$ supplement or $K^+$-sparing agent), and a maintenance phase (a diuretic alone or in combination with a $K^+$ supplement or $K^+$-sparing agent).

Serum $K^+$ and BUN should be checked periodically (see Warnings).

**Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.**

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

**Contraindications:** Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

**Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum $K^+$ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict $K^+$ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

**Precautions:** Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

**Adverse Reactions:** Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

**Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.**

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Carolina, P.R. 00630




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# one-tablet-a-day dosage and... cardioselectivity*

ONE TABLET A DAY

# TENORMIN®

## (atenolol)

Tablets 50 mg

*Cardioselectivity denotes a relative preference for $\beta_1$ receptors, located chiefly in cardiac tissue. This preference is not absolute.

*See last page of this advertisement for brief summary of prescribing information.*

STUART PHARMACEUTICALS



## TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension.

**INDICATIONS AND USAGE:** TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

**CONTRAINDICATIONS:** TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

**WARNINGS: Cardiac Failure:** Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

**In Patients Without a History of Cardiac Failure:** Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

**Ischemic Heart Disease:** Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

**Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta,-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.**

**Anesthesia and Major Surgery:** As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

**Diabetes and Hypoglycemia:** TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

**Thyrotoxicosis:** Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

**PRECAUTIONS: Impaired Renal Function:** The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

**Drug Interactions:** Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

**Animal Toxicology:** Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

**USAGE IN PREGNANCY:** Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

**U.S. STUDIES (% ATENOLOL-% PLACEBO):**

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

**TOTALS U.S. AND FOREIGN STUDIES:**

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

**POTENTIAL ADVERSE EFFECTS:** In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

**Hematologic:** Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

**Allergic:** Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

**Central Nervous System:** Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

**Gastrointestinal:** Mesenteric arterial thrombosis, ischemic colitis.

**Other:** Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

**Miscellaneous:** The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

**OVERDOSAGE:** To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

**Bradycardia:** Atropine or another anticholinergic drug.

**Heart Block (Second or Third Degree):** Isoproterenol or transvenous cardiac pacemaker.

**Congestive Heart Failure:** Conventional therapy.

**Hypotension (Depending on Associated Factors):** Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

**Bronchospasm:** Aminophylline, isoproterenol, or atropine.

**Hypoglycemia:** Intravenous glucose.

**DOSAGE AND ADMINISTRATION:** The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment:

| Creatinine Clearance (ml/min/1.73 m²) | Atenolol Elimination Half-life (hrs) | Maximum Dosage |
|---|---|---|
| 15-35 | 16-27 | 50 mg daily |
| <15 | >27 | 50 mg every other day |

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

**HOW SUPPLIED:** Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.


ONE TABLET A DAY

TENORMIN® (atenolol)

The only beta blocker with both

□ one-tablet-a-day dosage and...

□ cardioselectivity

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The American Journal of CARDIOLOGY®

JANUARY 15, 1983 • VOLUME 51 • NUMBER 2

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# FOR ANGINA PROPHYLAXIS*

## ANNOUNCING

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2.5, 6.5, 9.0 mg CAPSULES

# NITROSTAT® SR

# (nitroglycerin capsules)

■ complementary therapeutic effect: nitrates and beta-adrenergic blocking agents reduce myocardial oxygen demand by different mechanisms.

**Mechanism I:** Nitrates reduce myocardial oxygen requirement by acting on systemic circulation. Their vasodilator action decreases venous return and systemic arterial resistance, thus improving the balance between the need and supply of oxygen. Reduction in the myocardial oxygen requirement appears to be the major action of nitrates in relieving typical angina. However, selective dilatation of large coronary vessels by nitrates may be the primary mechanism by which they benefit patients with angina due to coronary spasm.[1]

**Mechanism II:** In contrast, beta-blockers block the beta receptor sites in the heart itself. They work by reducing the heart rate and the force of contraction, thereby lowering oxygen demand. In addition to cardiac output and heart rate, blood pressure is also decreased.

Beta-blockers may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction.

■ diminished side effects: some of the negative aspects of the effects of each drug are reduced. For example, concomitant nitrates oppose the increased ventricular size, filling pressure, and end-diastolic pressure caused by beta-adrenergic antagonists.[1]

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■ all day and all night prophylactic action with just two or three daily doses*

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REFERENCE: 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS and Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833.

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# The American Journal of CARDIOLOGY®

VOLUME 51

NUMBER 2

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### CONGENITAL HEART DISEASE

**237 Fetal Echocardiography. A Tool for Evaluation of In Utero Cardiac Arrhythmias and Monitoring of In Utero Therapy: Analysis of 71 Patients**

CHARLES S. KLEINMAN, RICHARD L. DONNERSTEIN, C. CARL JAFFE, GREGGORY R. DeVORE, ELLEN M. WEINSTEIN, DIANA C. LYNCH, NORMAN S. TALNER, RICHARD L. BERKOWITZ, and JOHN C. HOBBINS

Fetal echocardiographic studies were performed on 71 patients who had been referred for evaluation of cardiac rhythm disturbances at 24 to 40 weeks' gestation. After 2-dimensional echocardiographic study of cardiac structure, M-mode echocardiograms were analyzed for measurement of cardiac rate, atrioventricular contraction sequence, atrioventricular valve motion, and duration of postectopic pauses. Arrhythmias were diagnosed in 59 cases. In 34 patients with isolated ectopic beats, the arrhythmia resolved during later pregnancy (26) or within the first 5 days of life (8). Fourteen patients with mild sinus bradycardia (6) or frequent sinus pauses (8) had resolution of the arrhythmia during pregnancy. Sustained arrhythmias were noted in 11 patients. Fatalities occurred when there was associated fetal congestive heart failure (hydrops fetalis) or structural heart disease, or both. M-mode echocardiography diagnosed supraventricular tachycardia in 3 fetuses. The echocardiogram was used thereafter for monitoring of transplacental digoxin therapy.

**244 Assessment of Ventricular Size and Function in Congenitally Corrected Transposition of the Great Arteries**

THOMAS P. GRAHAM, Jr., MARK D. PARRISH, ROBERT J. BOUCEK, Jr., ROBERT C. BOERTH, JAMES A. BREITWESER, SANDRA THOMPSON, ROSE M. ROBERTSON, JOHN R. MORGAN, and GOTTLIEB C. FRIESINGER

Quantitative angiography was performed in 19 patients with congenitally corrected transposition of the great arteries to assess right and left ventricular size and function. Both systemic (anatomically right) end-diastolic volume and pulmonary (anatomically left) end-diastolic volumes were within normal limits in a majority of the patients. Pulmonary ventricular ejection fraction was also normal in most patients. Systemic ventricular ejection fraction was normal in a majority of patients aged $<10$ years, but 2 of 5 patients aged $>17$ years had low systemic ejection fractions, and an additional patient had a value at the lower limit of normal. After childhood, systemic ventricular dysfunction is not uncommon and may reflect the inability of the anatomic right ventricle to function as the systemic pumping chamber over a normal lifetime in a majority of patients with congenitally corrected transposition of the great arteries.

**252 Quantitation of Aortic and Mitral Regurgitation in the Pediatric Population: Evaluation by Radionuclide Angiocardiography**

ROGER A. HURWITZ, SALVADOR TREVES, MICHAEL FREED, DONALD A. GIROD, and RANDALL L. CALDWELL

Aortic or mitral regurgitation, or both, were estimated by determining the ratio of left to right ventricular stroke volume, obtained during equilibrium ventriculography. The radionuclide measurement was compared with the results of cineangiography, with good correlation between both studies in 47 of 48 patients. Radionuclide stroke volume ratio was used to classify severity: The group with equivocal regurgitation differed from the group with mild regurgitation ($p < 0.02$); patients with mild regurgitation differed from those with moderate regurgitation ($p < 0.001$); and those with moderate regurgitation differed from those with severe regurgitation ($p < 0.01$). The results of this study demonstrate that a stroke volume ratio $>2.0$ is compatible with moderately severe regurgitation and that a ratio $>3.0$ suggests the presence of severe regurgitation.

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256 **Supraventricular Aortic Stenosis. A 20-Year Clinical Perspective and Experience With Patch Aortoplasty**

GREG FLAKER, DOUGLAS TESKE, JAMES KILMAN, DON HOSIER, and CHARLES WOOLEY

Supraventricular aortic stenosis has a wide range of clinical and morphologic expression, which influences the results of corrective surgery. Sixteen patients with supraventricular aortic stenosis underwent patch aortoplasty. At surgery, portions of the aortic valve cusps were frequently attached to supraventricular tissue. This "cusp tuck" resulted in distinctive angiographic features pre- and postoperatively. Of the 8 patients who underwent postoperative cardiac catheterization, all had a reduction in gradient between the left ventricle and the ascending aorta. Several patients had persistent gradients at the aortic valve level, which represented persistent attachment of aortic valve tissue to residual supraventricular tissue. Consequently, these morphologic features need to be recognized in order to plan an effective surgical approach.

261 **Radionuclide Stroke Count Ratios for Assessment of Right and Left Ventricular Volume Overload in Children**

MARK D. PARRISH, THOMAS P. GRAHAM, Jr., MARK L. BORN, JEROME P. JONES, ROBERT J. BOUCEK, Jr., MICHAEL ARTMAN, and C. LEON PARTAIN

A cineangiographic validation of the radionuclide determination of stroke count ratios in children for assessment of right and left ventricular volume overload is reported. Radionuclide stroke count ratios were determined in 60 children (aged 0.5 to 19 years, mean 11). Based on the diagnoses, these patients were divided into 3 groups: (1) normal (stroke count ratio 1.04 $\pm$ 0.17), (2) left ventricular volume overload (stroke count ratio 2.43 $\pm$ 0.86), and (3) right ventricular volume overload (stroke count ratio 0.44 $\pm$ 0.17). The radionuclide stroke count ratio clearly differentiated these groups ($p < .05$). In 22 of our 60 patients, radionuclide stroke count ratios were compared with cineangiographic stroke volume ratios, disclosing a correlation coefficient of 0.88. It is concluded that radionuclide ventriculography is an excellent tool for the qualitative and quantitative assessment of valvular regurgitation in children.

265 **Pulmonary Vascular Disease in Secundum Atrial Septal Defect in Childhood**

SHEILA G. HAWORTH

Pulmonary vascular structure was analysed in biopsy or autopsy tissue from the lungs of 10 patients with a secundum atrial septal defect (ASD) whom pulmonary hypertension had developed. Four patients were aged $\leq$6 months, 5 were aged 2 to 9 years, and 1 was 21 years old. Four infants presented in cardiac failure, all had a marked increase in pulmonary arterial smooth muscle, and only 1 infant survived surgery. Of the 5 older children, 3 had severe pulmonary vascular disease, similar to that seen in adults with hypertensive ASD, and only 2 underwent successful surgery. In 1 child and in the 1 adult, the severity of the pulmonary vascular disease precluded surgery. The ASD was closed in 8 patients, but only 3 children survived.

273 **Clinical Follow-Up Study of Paroxysmal Supraventricular Tachyarrhythmias After Operative Repair of a Secundum Type Septal Defect in Adults**

ROBERT O. BRANDENBURG, Jr., DAVID R. HOLMES, Jr., ROBERT O. BRANDENBURG, and DWIGHT C. McGOON

Paroxysmal supraventricular tachyarrhythmias are relatively common and may be the presenting symptom in adult patients with isolated atrial septal defects. The clinical course of these arrhythmias after surgical repair is unknown. Of 188 patients aged $\geq$44 years with isolated atrial septal defects, 27 (14%) had paroxysmal atrial tachyarrhythmias before operation: 16 with paroxysmal atrial fibrillation, 2 with paroxysmal atrial flutter, and 9 with paroxysmal supraventricular tachycardia. After operative repair, a mean follow-up of 12 years (range 1.5 to 25) was available. The outcome was dependent on the specific type of arrhythmia. Of the 18 patients with paroxysmal atrial flutter or fibrillation, 15 had sustained atrial fibrillation at follow-up, whereas of the 9 patients with preoperative paroxysmal supraventricular tachycardia, 5 had no further episodes at follow-up and 4 had a pronounced decrease in the frequency of paroxysmal arrhythmia.


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**Indications:** Premature atrial and ventricular contractions, aproxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, paroxysmal ventricular tachycardia when not associated with complete heartblock, maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.

**Contraindications:** Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

**Warning:** In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting in extremely rapid ventricular rate.

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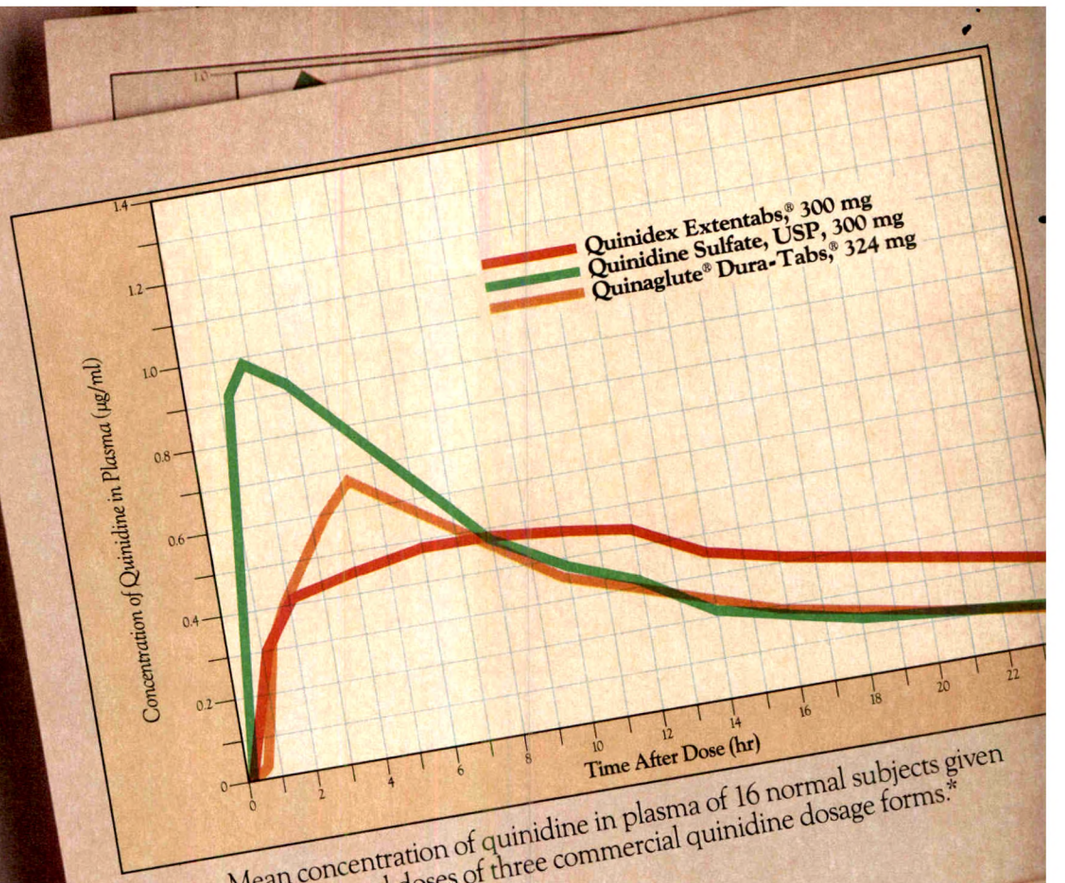
NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G.I. symptoms can also be minimized by giving the drug with food.

**Adverse Reactions:** Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

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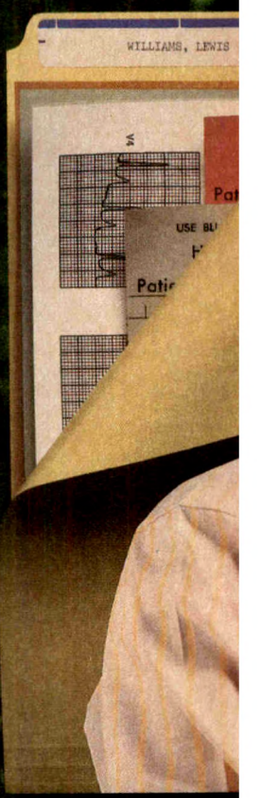
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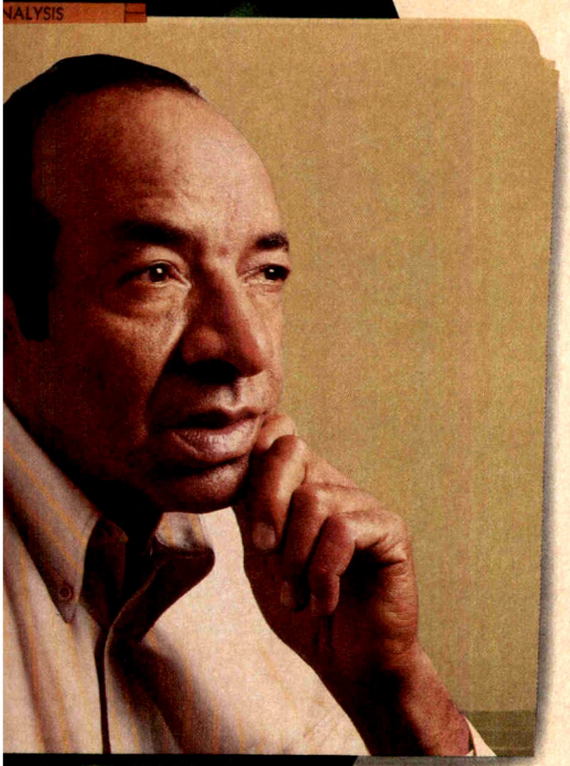

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*Sen S *et al*: *Hypertension 3*(Suppl 1):81-86, May-Jun 1981. By permission of the American Heart Association, Inc.

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## as well as the cause of his excessive anxiety

When the hypertensive patient also has anxiety which may cause him to resist, or even ignore, his medical regimen, discreet probing often provides sufficient information about possible underlying causes to help you deal with the situation. At times, however, neither counseling nor reassurance seems to work. The patient remains tense, apprehensive and—perhaps most damaging of all—noncompliant.

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The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.
**Contraindicated:** Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.
**Warnings:** Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.
***Usage in Pregnancy:*** **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
**Precautions:** If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.
**Side Effects:** Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.
**Dosage:** Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
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# CONTENTS


**277 Epicardial and Endocardial Activation in Patients With Endocardial Cushion Defect**

ROBERT M. CAMPBELL, MACDONALD DICK II, PAUL HEES, and DOUGLAS M. BEHRENDT

Examination of epicardial and left ventricular endocardial activation in 5 patients with endocardial cushion defect during surgical repair revealed an abnormal pattern of activation. Epicardial activation began at the diaphragmatic left ventricle surface and spread anterolaterally along the left ventricle, merged with right ventricle wave fronts, and then ended along the right ventricle anterior atrioventricular groove and outflow tract. Left ventricle endocardial activation also occurred earliest at the diaphramatic left ventricle segment with subsequent activation recorded laterally and anteriorly. This study demonstrates correlation between the pattern of left ventricle epicardial and endocardial activation, which is in accord with the known posteroinferior displacement of the specialized atrioventricular conduction system in patients with endocardial cushion defect.

**282 Atypical Fallot's Tetralogy With Doubly Committed Subarterial Ventricular Septal Defect. Diagnostic Value of 2-Dimensional Echocardiography**

HORACIO CAPELLI and JANE SOMERVILLE

Five patients with Fallot's tetralogy and doubly committed subarterial ventricular septal defect were correctly identified by 2-dimensional echocardiography before cardiac surgery. The short-axis view at the cardiac base from parasternal position best demonstrated the position of the defect in relation to the aortic, pulmonary, and tricuspid valves. By contrast, biplane angiography suggested the erroneous diagnosis of double outlet right ventricle with pulmonary valve stenosis in 3. This report emphasizes the importance of the preoperative diagnosis of this variant form which requires an outflow patch enlargement across the pulmonary ring although it frequently appears as a case of mild Fallot's tetralogy.

**286 Supraventricular Tachycardia in Infants: Use of the "Diving Reflex"**

VELIO SPERANDEO, DANIELE PIERI, PASQUALE PALAZZOLO, MARIO DONZELLI, and GIUSEPPE SPATARO

The effectiveness of the "diving reflex" in treating paroxysmal supraventricular tachycardia in 10 infants aged <6 months is demonstrated. The authors encountered no complications (rhythm disturbances), even when the maneuver was performed in patients who were receiving digitalis. The water temperature should be 5°C and the total time of facial immersion 6 to 7 seconds. We felt that the diving reflex must be considered as the first therapeutic approach in infants aged <6 months with paroxysmal supraventricular tachycardia.

**288 Impact of 2-Dimensional Echocardiography on the Management of Distressed Newborns in Whom Cardiac Disease Is Suspected**

MARY J. RICE, JAMES B. SEWARD, DONALD J. HAGLER, DOUGLAS D. MAIR, ROBERT H. FELDT, FRANCISCO J. PUGA, GORDON K. DANIELSON, WILLIAM D. EDWARDS, and ABDUL J. TAJIK

Forty consecutive sick newborns presenting with probable congenital heart disease were reviewed to determine the impact of 2-dimensional echocardiography in their management. Two-dimensional echocardiography correctly identified the major cardiac malformation in all cases. Only 40% of patients with congenital heart disease required cardiac catheterization in the neonatal period, and 43% of these procedures were primarily therapeutic (that is, balloon atrial septostomy). Forty-four percent of the patients treated surgically went directly to operation without preoperative catheterization. Two-dimensional echocardiography permits accurate noninvasive anatomic diagnosis of congenital heart disease in the newborn. Two-dimensional echocardiography thus expedites clinical management and reduces the need for cardiac catheterization.

**293 Rest and Exercise Ventricular Function in Adults With Congenital Ventricular Septal Defects**

GEORGE JABLONSKY, J. DAVID HILTON, PETER P. LIU, JOHN E. MORCH, MAURICE N. DRUCK, BEN-ZION BAR-SHLOMO, and PETER R. McLAUGHLIN, *With the technical assistance of* KATHY M. WINTER

Rest and exercise right and left ventricular function were compared in 19 normal control subjects and 34 patients with ventricular septal defect using gated radionuclide angiography. The patients were classified into 3 groups: (1) those with shunts closed at an early age; (2) patients with Eisenmenger complex; and (3) those with


**Continued on Page A20**

persistent small uncorrected shunts. All study patients failed to have an increase in ejection fraction in both ventricles on exercise as compared with the control subjects. It is concluded that (1) surgical correction failed to normalize ventricular function in patients with ventricular septal defect, (2) patients with Eisenmenger complex and abnormal resting left and right ventricular function, and (3) even patients with small shunts had an abnormal response to exercise, raising the possibility that chronic ventricular volume overload, even to a small degree, may be detrimental to ventricular function.

**299 Prognosis of Symptomatic Coarctation of the Aorta in Infancy**

PETER S. HESSLEIN, HOWARD P. GUTGESELL, and DAN G. McNAMARA

Medical and surgical advances have improved the outlook for infants with symptomatic coarctation of the aorta. In order to help predict the clinical course of individual patients and aid in individualizing their treatment, a 10-year experience with this condition was reviewed. Of 97 infants with symptomatic coarctation, 10 had isolated defects. In these patients, medical treatment was successful and surgical intervention could be postponed to allow for growth. The 87 other patients with associated cardiac defects were generally sicker at presentation and required earlier operation. Eleven of these died before surgical correction, 10 died at the time of repair, and 13 died later. The overall survival rate after 8 years was 62%, with most deaths occurring in the first 6 months of life. Late surgical results are flawed by a 32% rate of residual coarctation. Late postoperative hypertension is uncommon, and usually attributable to a residual coarctation.

**304 Instructions to Authors**

**VALVULAR HEART DISEASE**

**305 Equilibrium Radionuclide Gated Angiography in Patients With Tricuspid Regurgitation**

BRUCE HANDLER, DAN G. PAVEL, RAYMOND PIETRAS, STEVEN SWIRYN, ERNEST BYROM, WILFRED LAM, and KENNETH M. ROSEN

Equilibrium gated radionuclide angiography was performed in 2 control groups (15 patients with no organic heart disease and 24 patients with organic heart disease but without right- or left-sided valvular regurgitation) and in 9 patients with clinical tricuspid regurgitation. The regurgitant index was significantly lower in the tricuspid regurgitation group than in either control group. A hepatic expansion fraction using time-activity variation over the liver was significantly higher in the tricuspid insufficiency group than in either control group. Fourier analysis was used to generate amplitude and phase images. All patients in the tricuspid insufficiency group had $>100$ pixels over an area corresponding to the liver on the amplitude image. These pixels were of phase comparable to that of the right atrium and approximately 180° out of phase with the right ventricle. In contrast, no patient in the 2 control groups had any pixels in an area corresponding to the liver. In conclusion, patients with tricuspid regurgitation were characterized on equilibrium gated angiography by an abnormally low regurgitant index, reflecting increased right ventricular stroke volume, increased hepatic expansion fraction, and increased amplitude of count variation over the liver in phase with the right atrium.

**311 The Apex Impulse in Mitral Stenosis: Graphic Explanation of the Palpable Movements at the Cardiac Apex**

JON FLOYD, PARK W. WILLIS IV, and ERNEST CRAIGE

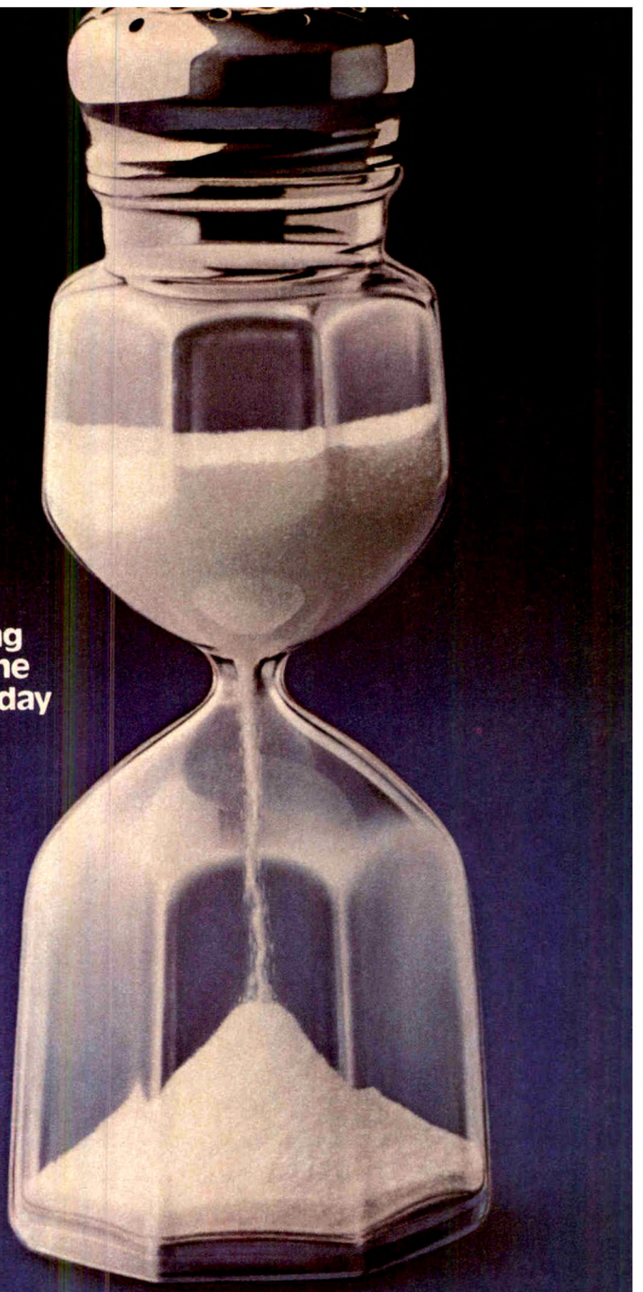
To analyze the complex palpable movements at the cardiac apex in mitral stenosis, the noninvasive graphic records of 39 patients were studied retrospectively. Each patient had predominant mitral stenosis confirmed by cardiac catheterization. The simultaneously recorded apex- and phonocardiograms showed that a notch on the upstroke of the apex impulse, coincident with the first heart sound, occurred in 18 cases (47%). The notch ratio or vertical distance from the onset of the apical impulse to the notch was calculated as a percentage of the total upstroke. Statistical analysis showed a significant relation ($r = 0.61$, $p < 0.01$) between the notch ratio and the mean mitral diastolic gradient. This graphic measurement of the extent of delay of the first heart sound with respect to the onset of the apical thrust can provide a rough measure of the severity of valvular obstruction.

Continued on Page A22

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# CONTENTS


**315 Coronary Vascular Reserve in Left Ventricular Hypertrophy Secondary to Chronic Aortic Regurgitation**

AUGUSTO D. PICHARD, HARRY SMITH, JAMES HOLT, JOSE MELLER, and RICHARD GORLIN

Coronary vascular reserve in 11 patients with left ventricular hypertrophy secondary to chronic aortic regurgitation was analyzed by looking at the hyperemic reaction induced in the coronary flow by the selective coronary injection of contrast agent. Compared with a control group, patients with hypertrophy had increased coronary flow at rest and decreased coronary reserve. This decrease is proportional to the increase in left ventricular mass; left ventricular wall thickness and not left ventricular volume is the critical component of left ventricular mass related to the decreased coronary reserve.

**321 Regurgitation of Prosthetic Heart Valves: Dependence on Heart Rate and Cardiac Output**

KEVIN C. DELLSPERGER, DAVID W. WIETING, DEBRA A. BAEHR, ROBERT J. BARD, JEAN-PIERRE BRUGGER, and EARL C. HARRISION

Prosthetic heart valves exhibit closure and leakage backflow; however, no well-controlled study to evaluate the influence of factors such as cardiac output and heart rate on backflow have been reported to date. Four clinically used prosthetic aortic valves (size 27 mm)—St. Jude Medical, Björk-Shiley Spherical Disc, Björk-Shiley Convexo Concave, and Start-Edwards model 1260—were studied in the aortic chamber of a pulse duplication system at heart rates of 50, 80, 110, and 140 beats/min, cardiac outputs of 2, 4, 6, and 8 liters/min, and mean aortic pressure of 100 mm Hg. Percent regurgitation varied directly with heart rate and inversely with cardiac output. Regurgitation associated with prosthetic heart valves may present a problem clinically, particularly under conditions of low cardiac output and tachycardia.

**MISCELLANEOUS TOPICS**

**329 Noninvasive Detection of Active Pericardial Bleeding Using Cardiac Blood Pool Scintigraphy**

TIMOTHY M. BATEMAN, RASHID MASSUMI, RICHARD J. GRAY, AURELIO CHAUX, MICHELE A. DeROBERTIS, DAVID E. BROWN, JACK M. MATLOFF, and DANIEL S. BERMAN

The diagnosis of active pericardial bleeding has traditionally depended upon an invasive documentation by needle aspiration, angiography, or direct inspection. Nuclear techniques that allow the localization of labeled erythrocytes may have considerable utility in the detection of active pericardial hemorrhage. In vitro technetium-99m labeled red blood cell scintigraphy performed in 2 patients before and again just after the development of hemopericardium revealed unique images in which acute pericardial bleeding was manifested by an additional blood pool adjacent to and surrounding the cardiac chambers. With appropriate attention to technical factors, such distinctive images should be highly specific for active bleeding into the pericardium.

**332 Assessment of the Cardiac Effects of Hemodialysis With Systolic Time Intervals and Echocardiography**

ABRAHAM BORNSTEIN, WILLIAM H. GAASCH, and JOHN HARRINGTON

Using externally recorded systolic time intervals and echocardiography, the acute effects of hemodialysis on left ventricular function were studied in 10 patients. The major hemodynamic change associated with dialysis was a decrease in stroke volume due to a decrease in preload. Dialysis was also associated with an increase in left ventricular contractility.

**336 Normal Left Atrial Function Determined by 2-Dimensional Echocardiography**

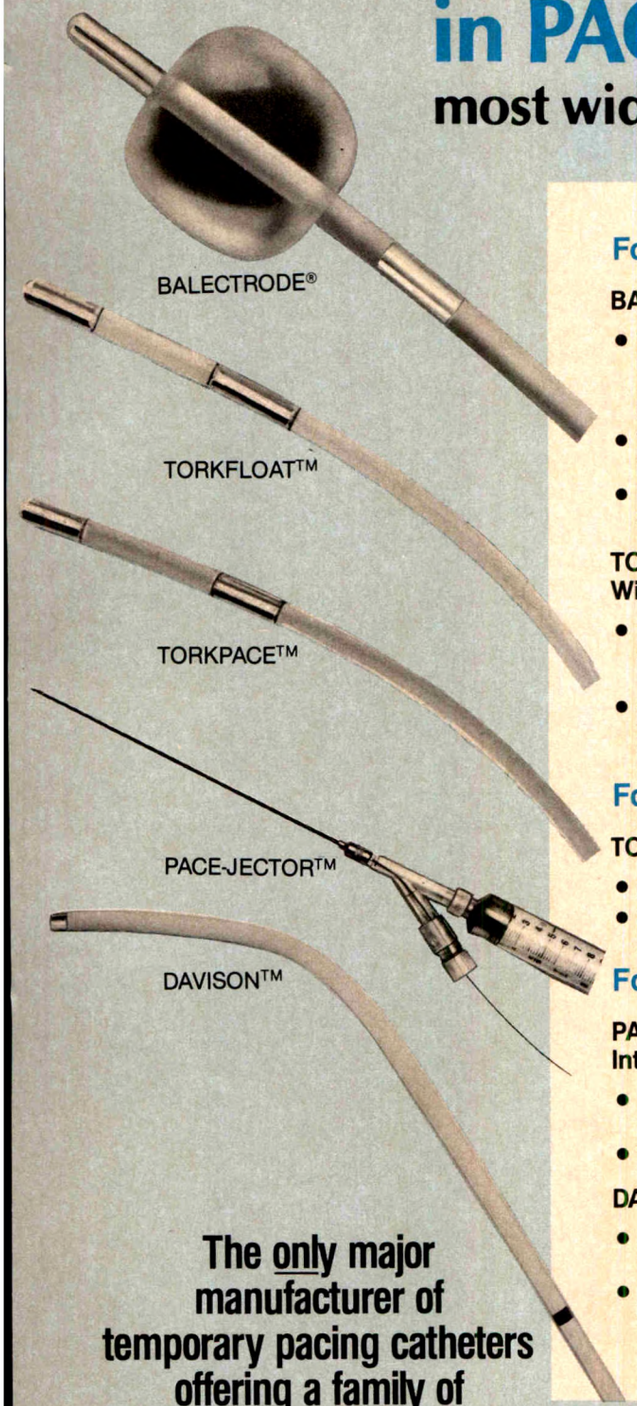
JACK GUTMAN, YIN SHI WANG, DENNIS WAHR, and NELSON B. SCHILLER

To obtain normal values for left atrial function noninvasively, the volumes of the left atrium and ventricle were calculated in each of 52 volunteer subjects by means of 2-dimensional echocardiography. A light pen digitizing and computation system, controlled by a microprocessor, was used to outline the left atrium and ventricle in orthogonal apical views. Then, to calculate end-systolic and end-diastolic atrial and ventricular volumes, a modified Simpson's rule formula was used. The mean (± standard deviation) end-systolic left atrial volume was 37 ± 11.7 ml or 21 ± 6.6 ml/m$^2$. The change in left atrial volume from end-systole to end-diastole was 24 ± 7.6 ml or 13.5 ± 4.3 ml/m$^2$, which represented 37 ± 12.9% of left ventricular stroke volume. The mean fractional emptying of the left atrium was 65 ± 8.9% and the conduit volume was 41 ± 14.0 ml or 23 ± 7.9 ml/m$^2$. These values are similar to those reported in studies which calculated left atrial function from contrast angiography.


Continued on Page A24

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# CONTENTS


**341 Myocardial Function in Rocky Mountain Spotted Fever: Echocardiographic Assessment**

JOSÉ MARIN-GARCIA and FRED F. BARRETT

Rocky Mountain spotted fever is a serious infectious disease that continues to occur with increasing incidence in various areas of the United States. A high case-fatality ratio (7 to 11%) persists despite availability of adequate chemotherapeutic agents. Cardiac involvement may play an important role in the final outcome in some cases. Nine children with Rocky Mountain spotted fever underwent echocardiographic examination on admission to a children's hospital. Increased left ventricular dimension was found in 2 and abnormal left ventricle function indexes in 7. One patient died and diffuse myocarditis was seen at autopsy. Abnormal echocardiographic findings remained in 3 patients at follow-up (mean 10 months). Awareness of the cardiac involvement in Rocky Mountain spotted fever is important and close follow-up warranted.

**344 Mechanisms for Decreased Exercise Capacity After Bed Rest in Normal Middle-Aged Men**

JOSEPH HUNG, DANIELLE GOLDWATER, VICTOR A. CONVERTINO, JAMES H. McKILLOP, MICHAEL L. GORIS, and ROBERT F. DeBUSK

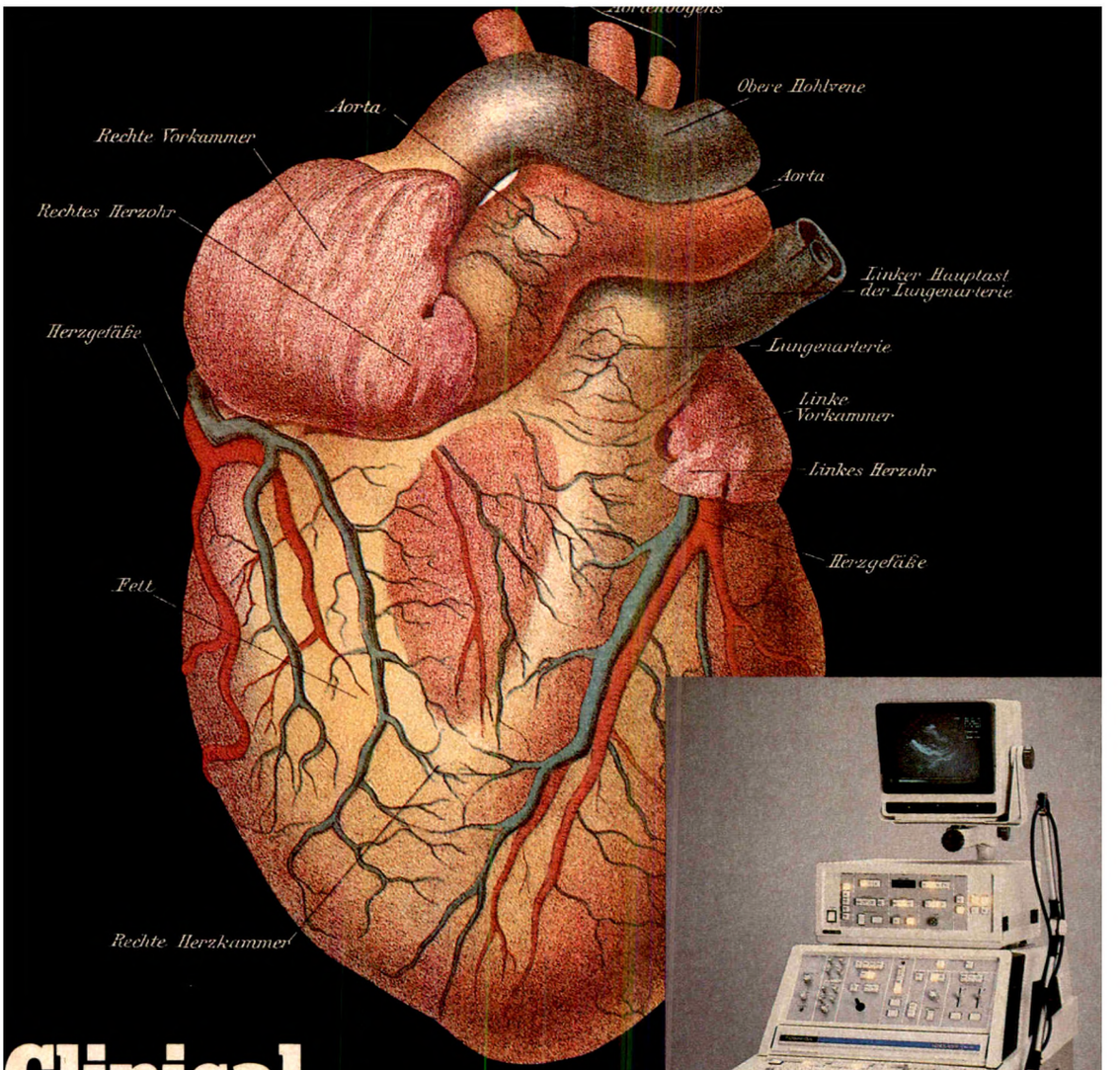
Echocardiographic and radionuclide studies in 12 healthy middle-aged men after 10 days of bed rest disclosed decreased left ventricular end-diastolic volume but increased exercise heart rate and left ventricular ejection fraction, so that peak oxygen uptake during supine effort did not decrease significantly after bed rest. These mechanisms were insufficient to compensate for the reduced cardiac volume in the upright position, and peak oxygen uptake during upright effort decreased significantly after bed rest. These results indicate that the major cause of reduced effort tolerance after prolonged bed rest in normal middle-aged men was orthostatistically induced cardiac underfilling, not physical deconditioning or left ventricular dysfunction.

**349 Cardiac Performance in Thyrotoxicosis: Analysis of 10 Untreated Patients**

ABDULMASSIH S. ISKANDRIAN, LESLIE ROSE, A-HAMID HAKKI, BERNARD L. SEGAL, and SALLY A. KANE

The purpose of this study was to define the cardiac performance at rest and during exercise in 10 patients with untreated thyrotoxicosis. Resting left ventricular function was normal in all patients, but the exercise ejection fraction response was abnormal in 3 of 10 patients. Thus, abnormal left ventricular reserve function during exercise can be detected in 30 percent of patients with untreated thyrotoxicosis.


**Index to Advertisers on page A36**




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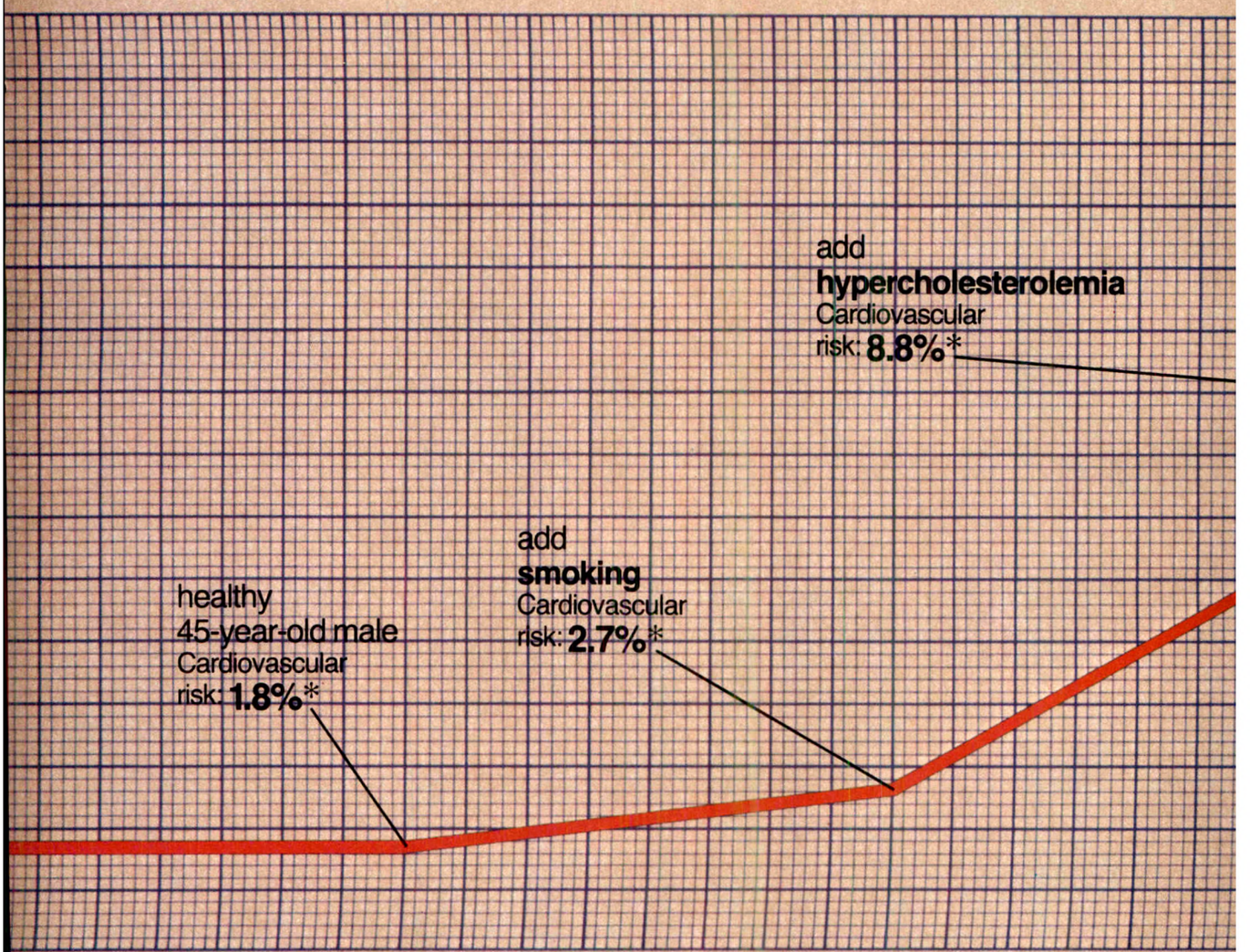
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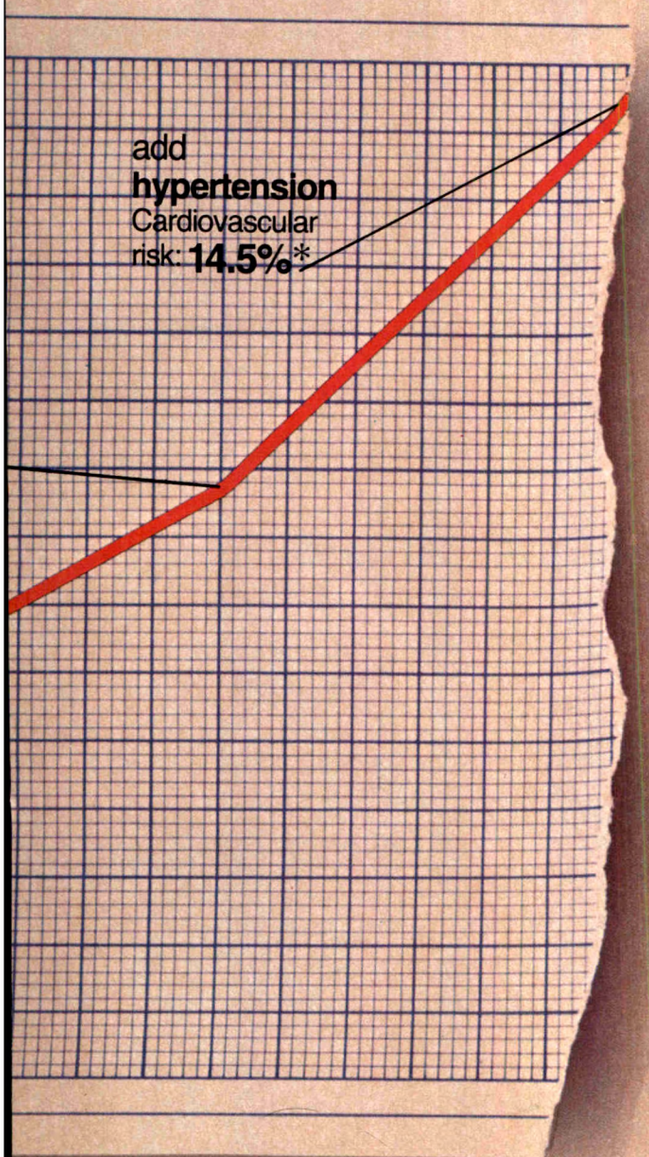



Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

# Consider the Risks




- When selecting antihypertensive therapy, clinical consideration should be given to the effects of the specific drug on coronary risk factors. Blood pressure control should be achieved without adversely affecting blood lipids.

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†Minipress is not indicated for the treatment of hyperlipidemia.

*Please see Minipress brief summary on following page.*

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**BRIEF SUMMARY**

**MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use***

**INDICATIONS:** MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

**WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.**

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

***Usage in Pregnancy:*** Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

***Usage in Children:*** No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

**ADVERSE REACTIONS:** The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

**DOSAGE AND ADMINISTRATION:** The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

***Initial Dose:*** 1 mg two or three times a day. (See Warnings.)

***Maintenance Dose:*** Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

***Use With Other Drugs:*** When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

**HOW SUPPLIED:** MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

*More detailed information available on request.*


**References:** 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet*: 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.


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VOLUME 51

NUMBER 2

CONGENITAL HEART DISEASE

# Fetal Echocardiography

## A Tool for Evaluation of In Utero Cardiac Arrhythmias and Monitoring of In Utero Therapy: Analysis of 71 Patients

CHARLES S. KLEINMAN, MD, RICHARD L. DONNERSTEIN, MD, C. CARL JAFFE, MD, GREGGORY R. DeVORE, MD, ELLEN M. WEINSTEIN, MD, DIANA C. LYNCH, RN, NORMAN S. TALNER, MD, RICHARD L. BERKOWITZ, MD, and JOHN C. HOBBINS, MD

**Fetal echocardiographic studies were performed in 71 patients referred for evaluation of cardiac rhythm disturbances at 24 to 40 weeks' gestation. After 2-dimensional echocardiographic study of cardiac structure was performed, M-mode echocardiograms were analyzed for measurement of cardiac rate, atrioventricular contraction sequence, atrioventricular valve motion, and duration of postectopic pauses. Arrhythmias were diagnosed in 59 patients. In 34 patients with isolated ectopic beats, the arrhythmia resolved during later pregnancy in 26 or within the first 5 days of life in 8. Six patients had mild sinus bradycardia and 8 had frequent sinus pauses; all 14 had resolution of the arrhythmia during pregnancy. Sustained arrhythmias occurred in 11 patients. Deaths occurred when there was associated fetal congestive heart failure (hydrops fetalis), structural heart disease, or both. M-mode echocardiography diagnosed supraventricular tachycardia in 3 fetuses. The echocardiogram was used thereafter for monitoring transplacental digoxin therapy.**

Over the past few years, echocardiographic imaging techniques have been applied by several groups interested in the detection of structural heart disease in utero.[1–5] There have also been isolated reports of cardiac rhythm disturbances detected by these techniques. We previously reported experience in detecting congenital cardiac malformations in a prospective study of patients deemed at higher than normal risk for such abnormalities, and we also reported an initial experience with the diagnosis of in utero cardiac arrhythmias.[1,6–14] This report expands our discussion of the use of ultrasound for the diagnosis of fetal cardiac rhythm disturbances and the use of M-mode and real-time fetal echocardiography for monitoring in utero antiarrhythmic therapy as illustrated by our experience with 71 patients.

From the Departments of Pediatrics, Obstetrics and Gynecology, and Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut. This study was supported in part by grants from the March of Dimes Birth Defects Foundation, White Plains, New York, and The Thrasher Research Fund, Salt Lake City, Utah. Manuscript received May 10, 1982; revised manuscript received July 6, 1982, accepted July 9, 1982.

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### Methods

Seventy-one patients at 21 to 40 weeks of gestation were referred by their obstetricians for evaluation of abnormal fetal cardiac rates or rhythms, or both. These included fetuses with regular heart rates >180 beats/min or <100 beats/min or those with irregular rhythms. Rhythmic variations of a regular rate, representing sinus arrhythmias, or transient accelerations or decelerations during labor of an otherwise regular rhythm, are considered normal. The normal fetal heart rate varies from 120 to 160 beats/min.[15,16]

Fetal echocardiography was performed after fetal position within the uterus, and the relation of the fetal heart to the maternal abdominal wall was determined using either an ATL

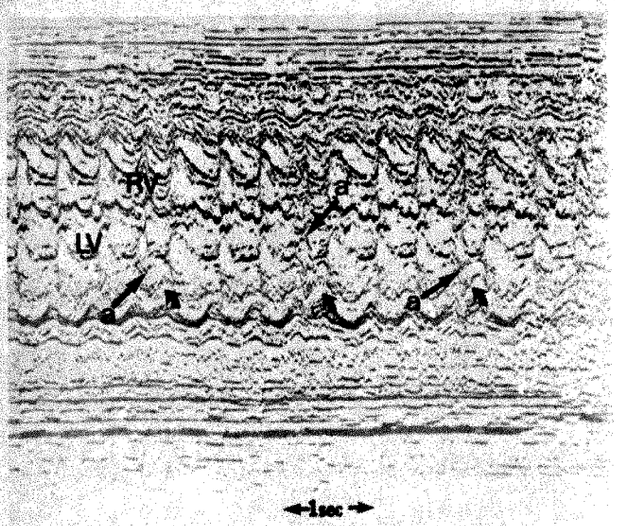



**FIGURE 1.** Supraventricular premature contractions demonstrated on an M-mode echocardiogram performed at the mid-ventricular level in a mid-trimester fetus. Three premature contractions are demonstrated. The mitral valve is seen within the left ventricular (LV) cavity. Presystolic atrial activity is reflected by the presence of A waves (**straight arrows**) of the mitral valve. These precede the premature ventricular responses which are represented by premature movement of the left ventricular posterior wall (**curved arrows**). RV = right ventricle.

Mark III, a Picker 80 CI, or a Diasonics CardioVue 100 2-dimensional cardiac sector-scanner with a 3.5 or 5.0 mHz transducer. After 2-dimensional echocardiographic analysis of fetal cardiac structure was performed and the rate and regularity of the cardiac rhythm were grossly evaluated in real-time, a simultaneous or sequential M-mode study, or both, were performed by stopping the motion of the mechanically swept transducer in the desired location. The 2-dimensional scan is indispensible for providing structural information regarding the heart and for defining the axis in which the M-mode study is performed. Two-dimensionally directed M-mode echocardiography, due to its rapid sampling rate and ability to obtain a hard copy of the tracing, demonstrating cardiac motion as a function of time, is well suited for evaluation of cardiac rhythm disturbances.[17] By allowing evaluation of atrioventricular contraction sequence, septal motion pattern, postectopic pauses, and atrioventricular valve motion, the site of origin of a premature contraction may be suggested. Premature supraventricular beats are usually preceded by demonstrable A waves before premature valve closure (Fig. 1), whereas in ventricular premature contractions the premature beats frequently precede atrial depolarization, therefore aborting mitral A waves during that cardiac cycle (Fig. 2). The postectopic pause may be suggestive (but not diagnostic) of the site of the origin of premature contractions (Fig. 3). In complete heart block, the atrioventricular dissociation may be demonstrated by examining atrioventricular valve motion which shows A waves which "march through" mitral valve closure points without a fixed relation between these events (Fig. 4).[1,13,14] The relation between atrial wall motion, atrioventricular valve motion, and ventricular wall response rate can be used to diagnose varying degrees of second-degree atrioventricular block (Fig. 5).

**TABLE I Fetal Arrhythmias in 58 Patients**

| Arrhythmia | Patients (n) |
|---|---|
| **Self-Limited** | |
| Supraventricular ectopic beats | 32 |
| Ventricular ectopic beats | 2 |
| Sinus bradycardia | 6 |
| Sinus pauses | 8 |
| Subtotal | 48 |
| **Sustained** | |
| Atrial flutter | 2 |
| Supraventricular tachycardia | 2 |
| Complex arrhythmia | 1 |
| Complete heart block | 2 |
| Supraventricular ectopic beats | 2 |
| Sinus bradycardia | 1 |
| Subtotal | 10 |

## Results

Satisfactory M-mode and real-time studies were obtained in all of the patients examined. A satisfactory M-mode study allowed accurate evaluation of fetal heart rate and the regularity of the cardiac rhythm. Fetal M-mode echocardiograms were compared to

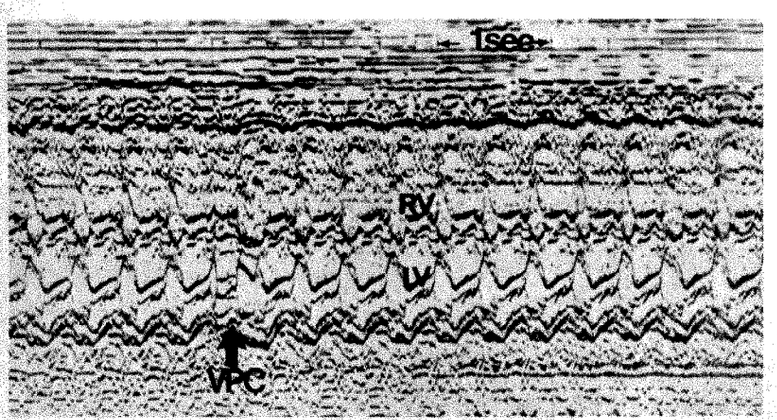



**FIGURE 2.** Ventricular premature contractions (VPC) seen on an M-mode echocardiogram performed at the mid-ventricular level in a mid-trimester fetus. The premature contraction is reflected by the presence of an early undulation of the left ventricular posterior wall (**bold arrow**). The mitral valve is seen within the left ventricular cavity. With this ventricular premature contraction, the premature beat preceded atrial depolarization, aborting mitral A-wave activity during that cardiac cycle. The postectopic pause is compensatory. LV = left ventricle; RV = right ventricle.

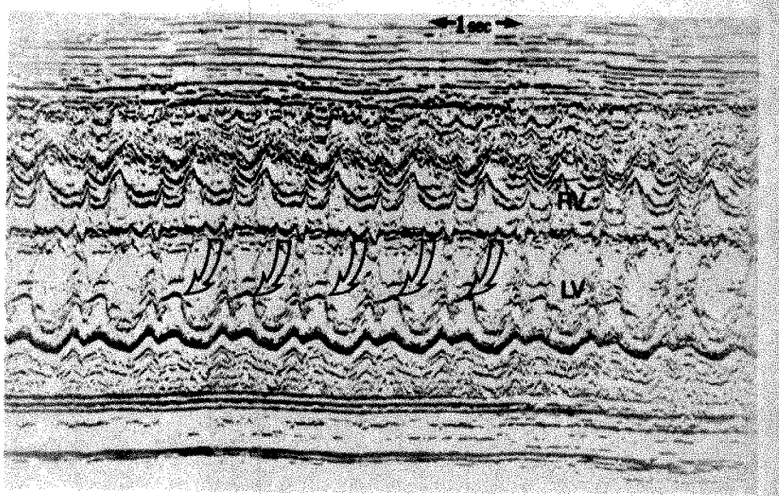



**FIGURE 3.** M-mode echocardiographic scan at the mid-ventricular level in the same patient depicted in Figure 1. At this time, the patient who had shown evidence of isolated supraventricular ectopy has developed atrial bigeminy. The atrial premature beats (**curved arrows**) appear coupled to the preceding normal beat. LV = left ventricle; RV = right ventricle.

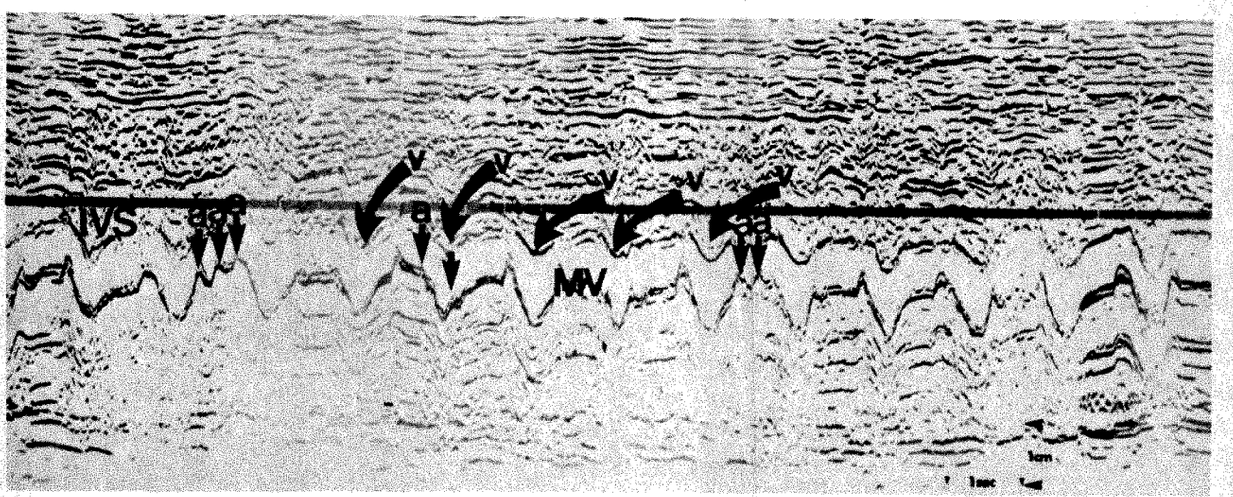



**FIGURE 4.** M-mode echocardiographic scan at the level of the left ventricle at 28 weeks' gestation. A slow and regular idioventricular rate of 45 to 50 beats/min is reflected in the undulations (v, **curved arrows**) of the interventricular septum (IVS). Atrial contractions (a, **straight arrows**) cause regular undulations of the mitral valve (MV) at a rate of approximately 120 to 130 beats/min. There are brief episodes of atrial flutter at a rate of 300 beats/min. The atrial activity bears no fixed relation to the idioventricular rhythm. This patient had complete heart block.

postnatal electrocardiograms in the patients who had arrhythmias persisting beyond delivery, thus confirming the arrhythmia interpretation in these cases. A satisfactory 2-dimensional scan allowed structural analysis of the 4 cardiac valves and the interventricular and interatrial septa. Fifty-nine of the 71 patients were documented to have rhythm disturbances at the time of the echocardiographic study. Of these 59 patients, 48 had isolated premature beats, sinus pauses, or periods of bradycardia (Table I). Thirty-two patients were thought to have supraventricular ectopy (Fig. 1) and 2 had isolated ventricular premature contractions (Fig. 2). Six fetuses had regular bradycardia with heart rates of 90 to 100 beats/min in the absence of uterine contractions, and 1 fetus had a bradycardia of 60 beats/min. Sustained arrhythmias were noted in 11 patients: 2 with complete heart block, 1 with complex supraventricular and ventricular arrhythmia, 2 with atrial flutter, 3 with supraventricular tachycardia, the 1 patient with severe sinus bradycardia, and 2 patients with isolated supraventricular ectopic beats.

All patients discussed herein were subsequently delivered. Twenty-five of the fetuses with isolated ectopic beats (including 1 with atrial bigeminy (Fig. 3) and 1 of the 2 thought to have ventricular ectopy) demonstrated resolution of the arrhythmia before delivery. Eight patients had isolated atrial premature contractions and 1 patient had isolated ventricular premature contractions that spontaneously resolved on Holter monitoring by the fifth day of life. Two patients continued to have isolated supraventricular ectopy on discharge from the nursery. One has had resolution of the arrhythmia on Holter monitoring at 6 months of age; 1 continues to have isolated junctional ectopic beats at age 6 months.

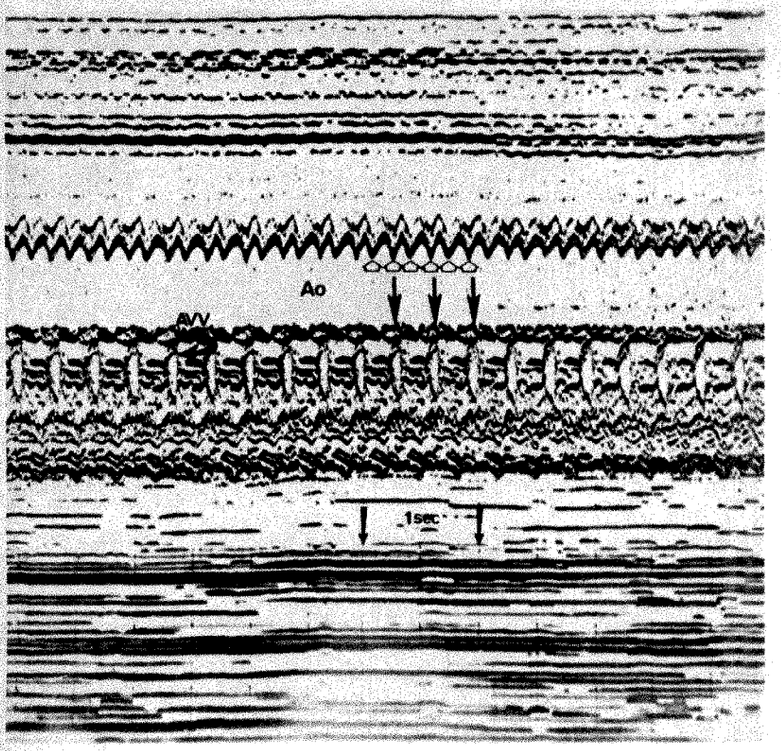



**FIGURE 5.** Atrial flutter with 2:1 atrioventricular block in a third-trimester fetus. The transducer beam was oriented from posterior to anterior in this fetus, who was oriented in an occiput anterior presentation. Rapid and regular atrial contractions are reflected on the posterior wall of the aorta (Ao, **open arrows**) at an atrial rate of 360 beats/min. The interventricular septum (**straight arrows**) and atrioventricular valve (AVV) respond to every other atrial contraction, resulting in a ventricular rate of approximately 180 beats/min. (The AVV is the tricuspid valve.)

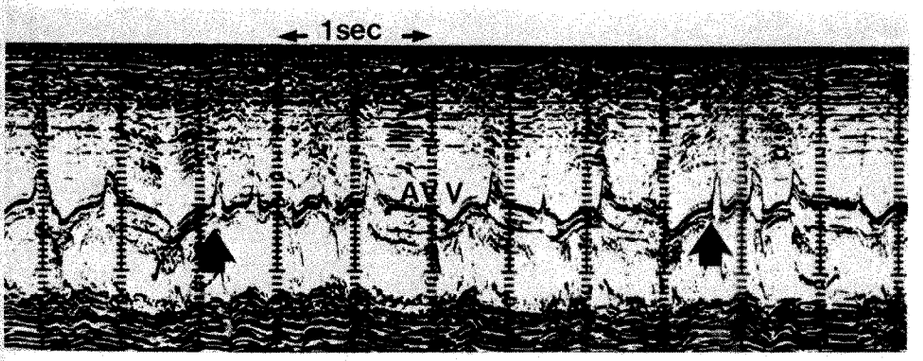



**FIGURE 6.** M-mode echocardiogram at the ventricular level in a third-trimester fetus. This fetus had been noted earlier in gestation to have isolated supraventricular premature contractions. On this scan, 2 self-limited episodes of supraventricular tachycardia are reflected in rapid undulations (**bold arrows**) of the atrioventricular valve (AVV). The first burst of tachycardia is of 5 beats' duration, the second burst of 3 beats' duration. This fetus developed a protracted episode of supraventricular tachycardia later in gestation.[2]

The arrhythmias of the 6 patients with mild bradycardia (90 to 100 beats/min) and the 8 patients with sinus pauses all resolved during gestation.

Table II summarizes the clinical information from our 11 patients with sustained fetal arrhythmias. In the first child found to have complete heart block (Patient 7) diagnosis was obtained by M-mode echocardiography at 28 weeks' gestation.[1] That child was followed throughout pregnancy and did well in the 3 years since birth, requiring no therapy for the persistent heart block. After diagnosis, a maternal history and serologic studies consistent with a diagnosis of systemic lupus erythematosus were documented.[19,20]

Several of the patients with sustained arrhythmias had associated nonimmune hydrops fetalis, structural heart disease, or both, as described in an earlier report from our laboratory.[2]

Fetal or immediate neonatal wastage was encountered when there was associated evidence of congenital cardiac malformation, severe hydrops fetalis, or both. This was the case in Patient 8, who was diagnosed as having complete heart block (Fig. 4) with associated isolated levocardia and congestive cardiac failure. Postmortem examination confirmed these diagnoses, in addition to polysplenia.[21]

Patient 6 had a chaotic rhythm with associated tetralogy of Fallot and polyhydramnios that was attributed to cardiomyopathy. This child died on the fifth day of life due to intractable ventricular arrhythmias.

Patient 1 was stillborn after the diagnosis of atrial flutter with high-grade atrioventricular block and hydrops fetalis was established. Due to the high degree of atrioventricular block and the resulting ventricular bradycardia, we had hoped to control the rhythm with

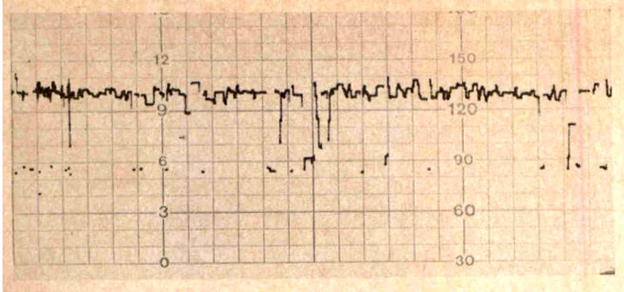


**FIGURE 7.** External fetal heart rate monitor recording from an hydropic fetus at 35 weeks' gestation. A regular rate of 125 beats/min was suggested.

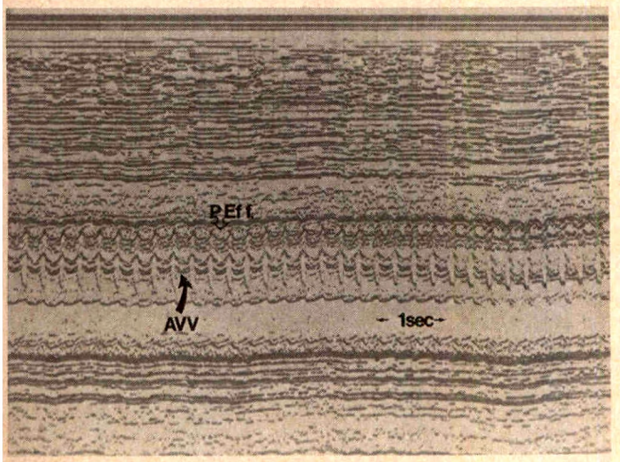



**FIGURE 8.** M-mode echocardiogram at the mid-ventricular level in the same fetus as in Figure 7. The cardiac rhythm is actually supraventricular tachycardia at 250 beats/min. P.Eff = pericardial effusion.

pacemaker therapy, electrical cardioversion, or both. The latter was successful in treating Patient 2, who, while also hydropic, had only 2 to 1 atrioventricular block (Fig. 5).

Patient 3 was initially evaluated due to auscultation of an irregular fetal cardiac rhythm. At the first examination, we noted frequent supraventricular ectopic beats with a protracted episode of bigeminy and several short (3 to 4 beat) runs of tachycardia (Fig. 6). Ten days later, a protracted episode of tachycardia was noted with evidence of early congestive heart failure (pericardial effusion).[22] Due to the extreme degree of prematurity, we elected to treat the arrhythmia through the administration of digoxin to the mother.[23–26] Within 48 hours, the paroxysmal tachycardia and associated effusion had resolved, although atrial ectopic beats did persist. Within 1 week, however, the rhythm was completely normal and remained so until 39 weeks' gestation when, against medical advice, the mother discontinued digoxin. The neonate had frequent atrial ectopic beats at birth and had multiple episodes of supraventricular tachycardia that were eventually controlled with digoxin and propranolol.

**TABLE II Clinical Profiles of Fetuses with Sustained Fetal Arrhythmias**

| Patient | Gestational Age (mo) | Arrhythmia | Clinical Data | Outcome |
|---|---|---|---|---|
| 1 | 34 | Atrial flutter with 5:1 and 6:1 AV block | Polyhydramnios; hydrops fetalis | Stillbirth |
| 2 | 38 | Atrial flutter with 2:1 AV block | Auscultated tachycardia; polyhydramnios; hydrops fetalis | Cesarean section; successful DC cardioversion; alive & well |
| 3 | 27 | Atrial ectopy, bigeminy, & sustained ST | Auscultated arrhythmia; fetal pericardial effusion (early CHF) on ultrasound | Successful transplacental digoxin therapy until 39th week; alive & well |
| 4 | 35 | ST | Fetal tachycardia auscultated | Successful transplacental digoxin therapy; alive & well |
| 5 | 35 | ST | Fetal tachycardia auscultated; polyhydramnios; hydrops fetalis | No reponse to transplacental digoxin & propranolol; cesarean delivery with DC cardioversion and drug therapy; alive and well |
| 6 | 28 | Complex arrhythmia | Polyhydramnios; hydrops fetalis; fetal echo: tetralogy of Fallot | Cesarean delivery 31 weeks, tetralogy of Fallot (cath); ventricular arrhythmias; death at 5 days |
| 7 | 28 | Complete heart block | Fetal bradycardia auscultated; structurally normal heart | Term birth; alive & well |
| 8 | 28 | Complete heart block | Polyhydramnios; hydrops fetalis; isolated levocardia; AV canal defect | Premature (34 weeks) birth; polysplenia syndrome; death at 10 min |
| 9 | 34 | Supraventricular ectopic beats | Arrhythmia auscultated | Term birth; atrial ectopic beats persist; alive & well |
| 10 | 32 | Supraventricular ectopic beats | Arrhythmia auscultated | Term birth; atrial ectopic beats persist; alive & well |
| 11 | 33 | Sinus bradycardia | Polyhydramnios; hydrops fetalis; dilated left atrium and ventricle | Premature delivery; death at 30 min; coronary artery embolus with myocardial infarction |

AV = atrioventricular; cath = cardiac catheterization; CHF = congestive heart failure; DC = direct current; echo = echocardiography; ST = supraventricular tachycardia.

Transplacental therapy with digoxin and propranolol failed to control the supraventricular tachycardia in Patient 5. This patient was delivered at 35 weeks' gestation due to increasing hydrops fetalis. The child had sinus rhythm with frequent atrial ectopic beats at birth

but soon developed reentrant supraventricular tachycardia at 250 to 260 beats/min. This was controlled, with difficulty, with direct-current countershock, digoxin, and verapamil. Over the first 24 hours of life, the arrhythmia was controlled and the child underwent vigorous diuresis. This child has recovered uneventfully and is receiving digoxin and propranolol maintenance therapy. The fetal cardiac rhythm was best demonstrated by M-mode echocardiography. Fetal heart tones in this polyhydramniotic woman were difficult to discern, and the external fetal heart rate monitor suggested that the fetal heart rate was a regular 125 beats/min (Fig. 7), while the echocardiogram correctly demonstrated the rate to be twice that (Fig. 8).

Fetal electrocardiography provided information regarding ventricular depolarization in 2 cases; however, atrial depolarization could not be detected against the background "noise" and the maternal electrocardiogram.[18,27–39]

## Discussion

Fetal cardiac rhythm disturbances are usually first suspected on the basis of auscultatory findings. Due to the inability of transabdominal fetal electrocardiograms to demonstrate atrial depolarization, this technique is unfortunately of limited value in the analysis of cardiac rhythm disturbances. The external fetal heart rate monitor, while accurate for regular rhythms in the "normal" range, may be inaccurate in the presence of fetal tachyarrhythmias (Patient 5).

The echocardiographic studies just described provide a noninvasive means of diagnosing rhythm disturbances and also provide a method of monitoring the response of the fetal rhythm to in utero therapy.[2] The use of 2-dimensional echocardiography in tandem with M-mode echocardiography allows analysis of associated structural cardiac abnormalities, may locate the appropriate planes for M-mode study,[40] and may be used for the detection of associated fetal congestive heart failure.[2]

Our initial studies are consistent with those of previous workers who have suggested that isolated ectopy in the fetus is almost always self-limited and carries a favorable prognosis.[15,16,28,41] Further study through pregnancy is warranted, however, due to the possibility that an isolated ectopic beat could trigger a reentrant tachyarrhythmia.[15,42] Sustained arrhythmias carry a more ominous prognosis, particularly if associated with structural heart disease or in utero congestive heart failure (hydrops fetalis), or both.

Supraventricular tachyarrhythmias associated with congestive heart failure,[24,42–51] when encountered early in gestation with evidence of pulmonary immaturity,[52] can and should be controlled with transplacental digoxin therapy.[15,23–26] Propranolol may be reserved for rhythm control if digoxin therapy alone is unsuccessful.[53,54] The direct administration of antiarrhythmic agents that do not readily cross the placenta (such as verapamil) may also be considered early in gestation. Later in gestation, with evidence of pulmonary maturity or, alternately, in the presence of increasingly severe congestive heart failure, bradyrhythmias, or high-grade atrioventricular block, premature delivery and electrical cardioversion or pacemaker therapy may be preferable.

The fetal echocardiogram, by providing information on heart rate as well as atrioventricular conduction and cardiac structure, may provide diagnostically and therapeutically useful information. The use of this tool for serial noninvasive monitoring of cardiac rhythm may increase the efficacy and safety of in utero therapy with antiarrhythmic agents.

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## References

1. **Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC, Talner NS.** Echocardiographic studies of the human fetus. Prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. Pediatrics 1980;65:1059–1067.
2. **Kleinman CS, Donnerstein RL, DeVore GR, Jaffe CC, Lynch DC, Berkowitz RL, Talner JS, Hobbins JC.** Fetal echocardiography for evaluation of in utero congestive heart failure: a technique for study of nonimmune fetal hydrops. N Engl J Med 1982;306:568–575.
3. **Allan LD, Tynan MJ, Campbell S, Wilkinson JL, Anderson RH.** Echocardiographic and anatomical correlates in the fetus. Br Heart J 1980;44: 444–451.
4. **Allan LD, Tynan MJ, Campbell S, Anderson RH.** Identification of congenital cardiac malformations by echocardiography in midtrimester fetus. Br Heart J 1981;46:358–362.
5. **Lange LW, Sahn DJ, Allen HD, Goldberg SJ, Anderson C, Giles H.** Qualitative real-time cross-sectional echocardiographic imaging of the human fetus during the second half of pregnancy. Circulation 1980;62:799–806.
6. **Baars AM, Merkus JMWM.** Fetal echocardiography: a new approach to the study of the dynamics of the fetal heart and its component parts. Eur J Obstet Gynaecol Reprod Biol 1977;7:91–100.
7. **Leandro I, Blandon R, Acuna EL.** Echocardiografia fetal en el 20 y 3er trimestre de gestacion. Rev Med Panama 1978;2:1–15.
8. **Crowley D.** Combined (2-D) and M-mode echocardiographic evaluation of fetal arrhythmia (abstr). Pediatr Res 1980;14:442.
9. **Hackeloer BJ.** The value of combined real-time and compound scanning in the detection of fetal heart disease. Contrib Gynecol Obstet 1979;6: 115–118.
10. **Harrison NA.** "Missed beats" in a fetus—a case report. S Afr Med J 1980;57:330–332.
11. **Henrion R, Aubry JP.** Fetal cardiac abnormality and real-time ultrasound study: a case of Ivemark syndrome. Contrib Gynecol Obstet 1979;6: 119–122.
12. **Kelley MJ, Jaffe CC, Kleinman CS.** Cardiac Imaging in Infants and Children. Philadelphia: WB Saunders, 1982:424–428.
13. **Madison JP, Sakhum P, Williamson D, Campion B.** Echocardiography and fetal heart sounds in the diagnosis of fetal heart block. Am Heart J 1979; 98:505–509.
14. **Silver TM, Wicks JD, Spooner EW, Cohen SM.** Prenatal ultrasonic detection of congenital heart block. AJR 1979;133:546–547.
15. **Kallfelz HC.** Cardiac arrhythmias in the fetus—diagnosis, significance and prognosis. In: Godman MJ, Marquis RM, eds. Paediatric Cardiology, vol. 2. Heart Disease in the Newborn. Edinburgh: Churchill Livingstone, 1979: 401–412.
16. **Southall DP, Richards J, Hardwick RA, Shinebourne EA, Gibbens GLD, Thelwell-Jones H, DeSwiet M, Johnston PGB.** Prospective study of fetal heart rate and rhythm patterns. Arch Dis Child 1980;55:506–511.
17. **Feigenbaum H.** Echocardiography. 3rd ed. Philadelphia: Lea & Febiger, 1981:222.
18. **DeVore GR, Donnerstein RL, Kleinman CS, Hobbins JC.** Real-time–directed M-mode echocardiography: a new technique for accurate and rapid quantitation of the fetal preejection period and ventricular ejection time of the right and left ventricles. Am J Obstet Gynecol 1981;141:470–471.
19. **McCue CM, Mantakas ME, Tingelstad JB, Ruddy S.** Congenital heart block in newborns of mothers with connective tissue disease. Circulation 1977;56:82–90.
20. **Reid RL, Pancham SR, Kean WF, Ford PM.** Maternal and neonatal implications of congenital complete heart block in the fetus. Obstet Gynecol 1979;54:470–474.
21. **VanMierop LHS, Gessner IH, Schiebler GL.** Asplenia and polysplenia syndrome. In: Bergsma D, ed. Congenital Cardiac Defects—Recent Advances. Birth Defects 1972;8:74–82.
22. **DeVore GR, Donnerstein RL, Lynch D, Kleinman CS, Hobbins JC.** The diagnosis and significance of fetal pericardial effusion using real-time-directed M-mode echocardiography (abstr). Proc Ann Meet AIUM 1981:29.
23. **Klein AM, Holzman IR, Austin EM.** Fetal tachycardia prior to the development of hydrops—attempted pharmacologic cardioversion: case report. Am J Obstet Gynecol 1979;134:347–348.
24. **Newburger JW, Keane JF.** Intrauterine supraventricular tachycardia. J

Pediatr 1979;95:780–786.
25. **Kerenyi TD, Meller J, Steinfeld L, Gleicher N, Brown E, Chitkara U, Raucher H.** Transplacental cardioversion of intrauterine supraventricular tachycardia with digitalis. Lancet 1980;2:393–395.
26. **Harrigan JT, Kargos JJ, Sikka A, Spisso KR, Natarajan N, Rosenfeld D, Lieman S, Korn D.** Successful treatment of fetal congestive heart failure secondary to tachycardia. N Engl J Med 1981;304:1527–1529.
27. **Larks SD, Longo L.** Fetal electrocardiogram showing cardiac malformation, including heart block. JAMA 1960;173:1217–1219.
28. **Kendall B.** Abnormal fetal heart rates and rhythms prior to labor. Am J Obstet Gynecol 1967;99:71–78.
29. **Blumenthal S, Jacobs JC, Steer CM, Williamson SW.** Congenital atrial flutter: report of a case documented by intrauterine electrocardiogram. Pediatrics 1968;41:659–661.
30. **Sokol RJ, Hutchison P, Krouskop RW, Brown EG, Reed G, Vasquez H.** Congenital complete heart block diagnosed during intrauterine fetal monitoring. Am J Obstet Gynecol 1974;120:1115–1117.
31. **Abinader EG, Klein A, Elbschitz I, Zilberman A, Pezeshk B, Shar M.** The significance of fetal electrocardiography in the diagnosis of intrauterine bradyarrhythmia. Am J Obstet Gynecol 1976;126:266–270.
32. **Goodlin RC.** Inappropriate fetal bradycardia. Obstet Gynecol 1976;48: 117–122.
33. **Harrigan JT, Acerra D, LaMagra R, Hoeveler J, Chandra N.** Fetal cardiac arrhythmia during labor. Am J Obstet Gynecol 1977;128:693–695.
34. **Komaromy B, Gaal J, Lampe L.** Fetal arrhythmia during pregnancy and labor. Br J Obstet Gynecol 1977;84:492–496.
35. **Sugarman RG, Rawlinson KF, Schifrin BS.** Fetal arrhythmia. Obstet Gynecol 1978;52:301–307.
36. **Garite TJ, Linzey EM, Freeman RK, Dorchester W.** Fetal heart rate patterns and fetal distress in fetuses with congenital anomalies. Obstet Gynecol 1979;53:716–720.
37. **Shenker L.** Fetal cardiac arrhythmias. Obstet Gynecol Surv 1979;34: 561–572.
38. **Young BK, Katz M, Klein SA.** Intrapartum fetal cardiac arrhythmias. Obstet Gynecol 1979;54:427–432.
39. **Sampayo F, Meleiro DeSousa L, Lima M, Telles E.** Foetal dysrhythmias. Proc Assoc Eur Pediatr Cardiol 1972;8:15–16.
40. **DeVore GR, Donnerstein RL, Kleinman CS, Platt LD, Hobbins JC.** Fetal echocardiography. I. Normal anatomy using real-time-directed M-mode ultrasound. Am J Obstet Gynecol, in press.
41. **Bernstine RL, Winker JE, Callagan DA.** Fetal bigeminy and tachycardia. Am J Obstet Gynecol 1968;101:856–857.
42. **Gillette PC.** The mechanisms of supraventricular tachycardia in children. Circulation 1976;54:133–140.
43. **Reygaerts J.** Un nouveau probleme de cardiologie foetale: la fibrillation auriculaire "in utero." Obstet et Gynecol 1959;58:208–219.
44. **Levkoff AH.** Perinatal outcome of paroxysmal tachycardia of the newborn with onset in utero. Report of 2 cases; review of the literature and a discussion of a clinical approach to fetal tachycardia. Am J Obstet Gynecol 1969;104:73–79.
45. **Silber DL, Durnin RE.** Intrauterine atrial tachycardia associated with massive edema in a newborn. Am J Dis Child 1969;117:722–726.
46. **Cowan RH, Waldo AL, Harris HB, Cassady G, Brans YW.** Neonatal paroxysmal supraventricular tachycardia with hydrops. Pediatrics 1975;55: 428–430.
47. **Hughey M, Elesh R.** Profound atrial tachycardia in utero. Am J Obstet Gynecol 1977;128:463–465.
48. **Pringsheim W, Windorfer A, Mross F.** Intrauterine herzinsuffizienz und hydrops congenitus. Monatsschr Kinderheilkd 1977;125:451–454.
49. **Valerius NH, Jacobsen JR.** Intrauterine supraventricular tachycardia. Acta Obstet Gynecol Scand 1978;57:407–410.
50. **Schreiner RL, Hurwitz RA, Rosenfeld CR, Miller W.** Atrial tachy-arrhythmias associated with massive edema in the newborn. J Perinat Med 1978;6: 274–279.
51. **Beitzke A, Winter R, Zach M, Grabbauer HM.** Kongenitales verhofflatero mit hydrops fetalis durch mutterliche tokolytikamedikation. Klin Paediatr 1979;191:410–417.
52. **Gluck L, Kulovich M, Borer RC, Brenner PH, Anderson GG, Spellacy WN.** Diagnosis of the respiratory distress syndrome by amniocentesis. Am J Obstet Gynecol 1971;109:440–445.
53. **Elbschitz I, Abinader EG, Klein A, Sharf M.** Intrauterine diagnosis and control of fetal ventricular arrhythmia during labor. Obstet Gynecol 1975;122: 597–600.
54. **Teascher A, Bossi E, Imhot P, Erb E, Stocker FB, Weber JW.** Effect of propranolol on fetal tachycardia in diabetic pregnancy. Am J Cardiol 1978;42:304–307.

# Assessment of Ventricular Size and Function in Congenitally Corrected Transposition of the Great Arteries

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**Twenty-four quantitative cineangiographic studies were performed in 19 patients with congenitally corrected transposition of the great arteries to assess right and left ventricular size and function. Ages ranged from 7 days to 44 years and associated lesions included ventricular septal defect (13 of 19), pulmonary stenosis (9 of 19), and systemic (tricuspid) valvular insufficiency (7 of 19). Systemic (anatomically right) ventricular end-diastolic volume was within normal limits in most patients and averaged 119% of predicted normal. Pulmonary (anatomically left) ventricular end-diastolic volume also was normal in most patients, averaged 112% of predicted, and was not different from systemic (right) ventricular end-diastolic volume. Systemic ventricular ejection fraction (RVEF) averaged 0.61 ± 0.02 and was not different from pulmonary ventricular ejection fraction (LVEF) (0.65 ± 0.02), but important differences were apparent when age was considered. With exclusion of 2 patients with hypoplastic systemic ventricles and 2 studies performed <6 months after open heart surgery, all 12 patients aged <10 years had a normal RVEF, whereas 2 of 5 patients aged >17 years had a definitely low RVEF and 1 of 5 had a value at the lower limit of normal. In children, systemic and pulmonary ventricular pump function is usually normal in congenitally corrected transposition of the great arteries and any deviation from normal should suggest ventricular hypoplasia or an increase in afterload. After childhood, systemic ventricular dysfunction is more common and may reflect the inability of the anatomic right ventricle to function as the systemic pumping chamber over a normal lifetime in most patients with congenitally corrected transposition of the great arteries.**

Although quantification of ventricular size and function in congenitally corrected transposition of the great arteries can be useful in assessing clinical status both before and after operation, angiocardiographic determination of ventricular volumes and ejection fractions in this condition has been reported previously in only 3 patients.[1] In congenitally corrected transposition of the great arteries there is discordance between the atrial and ventricular connections and between the ventricular and great arterial connections. Thus, the right atrium is connected through a mitral valve to the pulmonary (anatomic left) ventricle which is situated on the patient's right side (assuming normal atrial situs and levocardia). The left atrium receives the pulmonary venous return and is connected to the systemic (anatomic right) ventricle through a tricuspid valve. The systemic ventricle is located on the patient's left and is connected to the aorta, and the anatomic left ventricle is connected to the pulmonary artery. Thus, the anatomic right ventricle functions as the systemic pumping chamber. Frequently, there are associated defects, including ventricular septal defect, pulmonary stenosis, and tricuspid regurgitation as well as partial or complete heart block.

Clinically evident systemic ventricular dysfunction in congenitally corrected transposition of the great arteries is rare until adulthood[2,3] when congestive heart failure frequently associated with tricuspid regurgitation or complete heart block, or both, is a common presentation. Assessment of ventricular size and function not only is desirable for characterization of cardiac

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**TABLE I Patient Data**

| Case | Age (yr) | Weight (kg) | LVP (mm Hg) | RVP (mm Hg) | LV-PA (mm Hg) | Sys $O_2$ (%) | Qp/Qs | Associated Lesions |
|---|---|---|---|---|---|---|---|---|
| 1 AW | 7 days | 4.1 | 74/10 | 74/14 | NA | 98 | NA | VSD |
| 2 GW | 30 days | 2.4 | 68/14 | 80/15 | 22 | 98 | 2.1 | VSD, PS |
| 3a AJ | 45 days | 2.0 | 78/9 | 86/11 | 00 | 85 | 2.6 | VSD |
| 3b AJ | 3 | 11.9 | 95/6 | 100/10 | NA | 85 | . . . | VSD, PA Bd |
| 4a AWh | 2.8 mo | 4.5 | 80/6 | 125/15 | 16 | 100 | 2.6 | VSD |
| 4b AWh | 2.3 | 11.7 | 54/4 | 95/12 | 16 | 93 | 1.4 | Small VSD, moderate TI |
| 5 BB | 1.4 | 9.1 | 110/5 | 110/5 | NA | 71 | NA | VSD, PS |
| 6 DS | 2.7 | 15.4 | 120/5 | 120/5 | NA | 95 | NA | VSD, PS |
| 7a RR | 3.0 | 13.3 | 35/7 | 110/12 | 14 | 100 | 1.8 | VSD, mild TI |
| 7b RR | 8.5 | 26.9 | 38/3 | 100/10 | 14 | 97 | 1.0 | Severe TI |
| 8a MB | 3.6 | 14.6 | 100/3 | 105/6 | NA | 82 | NA | VSD, PAt, SHUNT |
| 8b BB | 3.9 | 14.7 | 66/10 | 85/12 | 38 | 93 | 1.7 | LV-PA conduit, VSD, moderate TI |
| 9 DW | 3.7 | 16.6 | 32/5 | 106/10 | 11 | 95 | 1.0 | Mild TI |
| 10 MW | 4.6 | 14.1 | 113/8 | 108/10 | NA | 71 | 0.73 | VSD, PA Bd, small RV |
| 11 JB | 4.6 | 18.9 | 100/6 | 100/6 | 92 | 76 | 1.20 | VSD, PS |
| 12 EB | 7.7 | 27.0 | 38/4 | 110/8 | 17 | 93 | 1.00 | Mild PS |
| 13 RV | 9.2 | 32.0 | 34/8 | 119/16 | 22 | 95 | 1.00 | Mild PS |
| 14 SM | 17.7 | 61.5 | 105/13 | 105/13 | 73 | 100 | 2.3 | VSD, PS |
| 15 RB | 18.0 | 68.5 | 100/15 | 100/15 | 100 | 90 | 0.8 | VSD, PS, shunt |
| 16a TJ | 18.0 | 60.0 | 100/15 | 135/28 | 0 | NA | 1.0 | TI, AI, 3° HB |
| 16b TJ | 18.5 | 64.0 | 90/23 | 115/40 | 0 | 93 | 1.0 | TVR, AI, PM |
| 17 MBy | 19.8 | 63.7 | 63/7 | 160/12 | 149 | 82 | 0.6 | VSD, PS, 2° HB |
| 18 BW | 23.0 | 49.9 | 40/2 | 130/10 | 10 | 97 | 1.0 | TVR |
| 19 DSw | 44.0 | 65.0 | 125/15 | 155/30 | 5 | NA | 1.0 | Moderate TI |
| Mean ± SEM | . . . | . . . | 82 ± 8/ 8 ± 1 | 110 ± 5 13 ± 2 | 33 ± 12 | 90 ± 2 | 1.4 ± 0.4 | . . . |

AI = aortic insufficiency; 2° HB = second-degree heart block; 3° HB = third-degree heart block; LV-PA pulmonary artery to LV systolic pressure gradient; LVP = left (pulmonary) ventricular peak systolic/end-diastolic pressure; PA Bd = pulmonary artery banding; PAt = pulmonary atresia; PM = pacemaker; PS = pulmonary stenosis; Qp/Qs = pulmonary/systemic flow ratio; RVP = right (systemic) ventricular peak systolic/end-diastolic pressure; shunt = Blalock-Taussig shunt; SEM = standard error of the mean; Sys $O_2$ = systemic oxygen saturation; TI = tricuspid (systemic atrioventricular valvular) insufficiency; TVR = tricuspid valve replacement; VSD = ventricular septal defect.

performance in congenitally corrected transposition of the great arteries but also could be useful for comparison with the large number of patients with complete transposition of the great arteries who have undergone intraatrial repair.

In these patients the right ventricle also functions as the systemic pumping chamber, and right ventricular dysfunction has been reported in such patients.[4–6]

The purpose of this investigation was to determine systemic and pulmonary ventricular volumes and ejection fractions during diagnostic cardiac catheterization in patients with congenitally corrected transposition of the great arteries using quantitative cineangiocardiographic techniques and to attempt to relate these variables to other hemodynamic abnormalities.

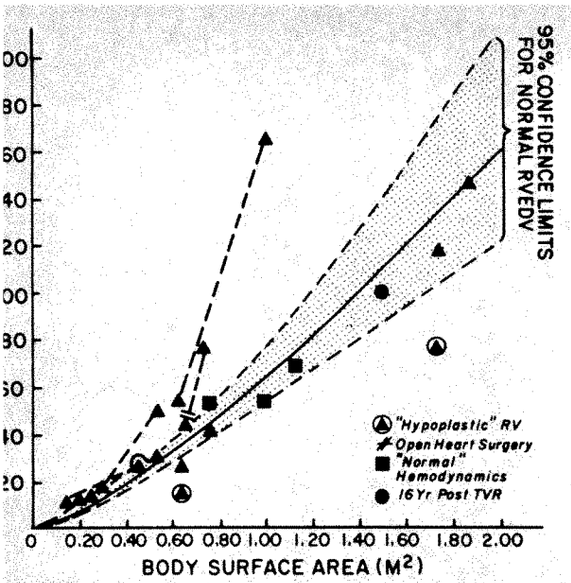
## Methods

All patients studied at Vanderbilt Hospital from 1971 through 1981 were included in the study. Data were obtained at diagnostic catheterization. Nineteen patients were studied, with 5 patients studied on 2 occasions for a total of 24 studies (Table I). Ages ranged from 7 days to 44 years. Pressures were obtained with fluid-filled catheters with zero referenced to mid-chest. Oxygen saturation was measured by reflectance oximetry and Qp/Qs ratio calculated in patients in whom the pulmonary artery could be entered.

Patient data and hemodynamics are shown in Table I. Thirteen (68%) had ventricular septal defects, 9 (41%) had pulmonary stenosis, and 1 had pulmonary atresia at a preoperative study and a left ventricular to pulmonary artery conduit at the second study with a conduit gradient of 38 mm Hg. One patient had second degree block and 1 had complete heart block at the initial study with a ventricular pacemaker at the second study. The remaining patients were in sinus rhythm with either a normal or a prolonged P-R interval. Tricuspid insufficiency was present in 7 patients (37%) and was graded by the following angiographic criteria. Mild tricuspid insufficiency was defined as minimal atrial opacification during systemic ventricular angiocardiography with filling of only part of the atrium and clearing of contrast within 2 to 3 beats. Moderate tricuspid insufficiency was defined as filling the entire left atrium with clearing of contrast within 3 to 5 beats. Severe tricuspid insufficiency was defined as dense opacification of the left atrium and pulmonary veins which did not clear completely during 5 beats. With these criteria, 1 patient had severe tricuspid insufficiency, 4 had moderate tricuspid insufficiency, and 2 had mild tricuspid insufficiency (Table I). In addition, 1 patient (Patient 18) had tricuspid valve replacement 16 years before the present study, and 1 patient (Patient 16) had significant aortic insufficiency both before and after tricuspid valve replacement. Clinical cyanosis was present in 4 patients with mild desaturation in 2 additional patients.

In this report left ventricle refers to the anatomic left (pulmonary) ventricle and right ventricle refers to the anatomic right (systemic) ventricle. Left ventricular peak systolic pressure was elevated when compared with normal right (pulmonary) ventricular pressure in all but 5 patients. These 5 patients had pressure near the upper limit of normal (32 to 40 mm Hg). End-diastolic pressure in the pulmonary ventricle was ≥12 mm Hg in 5 patients, and end-diastolic pressure in the right (systemic) ventricle was ≥12 mm Hg in 11 patients.

Right and left ventricular volume determinations were performed using angiocardiographic techniques described previously.[7,8] Sixteen patients had levocardia and 3 had dextrocardia. Anteroposterior and lateral views were used in all patients. The area-length method was used for the pul-




**RE 1.** Right (systemic) ventricular end-diastolic volume (ml) as a on of body surface area. The **shaded area** indicates the 95% dence limits for patients previously studied with normal right cles (RV). **Triangles** indicate patients with associated lesions. TVR uspid valve replacement.

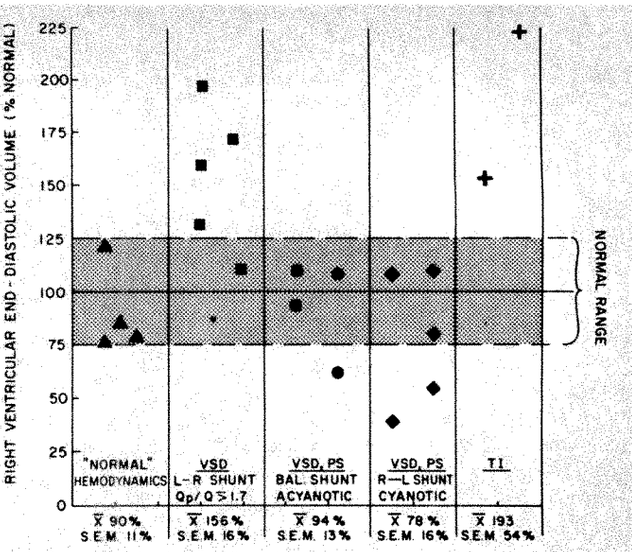



**FIGURE 2.** Right (systemic) ventricular end-diastolic volume as a function of percentage of predicted normal for patients grouped according to hemodynamic lesions. BAL. = balanced; L = left; PS = pulmonary stenosis; R = right; VSD = ventricular septal defect; S.E.M. = standard error of the mean; TI = tricuspid insufficiency; X = mean.

ary ventricle[7] and Simpson's rule method for the systemic icle.[8] All data were calculated during sinus rhythm, and ic or immediate postectopic beats were not used. In 20 e 24 studies, angiograms were suitable for analysis of both icles. In 4 studies, only right ventricular angiograms were n and in 3 of these studies a magnification grid was not so that only ejection fraction data were available. Two nts with hypoplastic right ventricles[1] are included in the hic analyses and in the tables but were excluded from the stical analyses as indicated in the results.

mparison of right and left ventricular data from patients nom both were available was performed by paired $t$ test $p < 0.05$ considered the lower level of significance. Linear ession analysis was performed to determine correlates of diastolic volume and ejection fraction in terms of age, ee of shunt, and degree of cyanosis.

## Results

gure 1 shows systemic ventricular end-diastolic me as a function of body surface area, with normal es from previous data[8] shown for comparison. teen of 21 studies (62%) are within the 95% confie limits of normal. Three patients have values w normal; all have ventricular septal defect plus re pulmonary stenosis and 2 (indicated by circled ngles) have been reported on previously as examples ypoplastic systemic ventricles.[1] Five values are inased, and all of these patients had ventricular septal ct with large systemic to pulmonary shunts or lerate to severe tricuspid insufficiency.

Figure 2, systemic ventricular end-diastolic volume own as a percentage of predicted normal[8] with pats grouped by the major hemodynamic lesion or ns at the time of study. Four patients had insigant hemodynamic defects. Two had trivial pulary stenosis (left ventricle-pulmonary artery gradient 17 to 22 mm Hg), 1 had mild tricuspid insufficiency, and a 23 year old girl had had tricuspid valve replacement 16 years previously. At the time of this study, she had no tricuspid insufficiency and no significant wedge to right ventricular end-diastolic pressure gradient. These patients had normal volumes.

The second group shown in Figure 2 had ventricular septal defects with large left to right shunts, and 4 of 5 patients had a large systemic ventricle.

The third group of patients had ventricular septal defect plus pulmonary stenosis with a balanced shunt resulting in no significant cyanosis, defined here as a systemic oxygen saturation ≥85% (range 85 to 100%, mean 93%). Three of 4 patients have normal-sized right ventricles and 1 patient has a small chamber, 63% of the predicted normal size. The fourth group in Figure 2 consists of patients with ventricular septal defect plus severe pulmonary stenosis resulting in clinical cyanosis and a systemic oxygen saturation ≤82% (range 71 to 82%, mean 76%). These patients have normal or small

**TABLE II Comparison of Pulmonary and Systemic Volume Variables in Patients for Whom Both Variables Were Calculated (17 Studies in 14 Patients)***

| | LV | RV | |
|---|---|---|---|
| End-diastolic volume (% of normal) | 112 ± 7 | 119 ± 11 | NS |
| Ejection fraction | 0.65 ± 0.02 | 0.61 ± 0.02 | NS |

* Excluded from comparison were 2 patients with a hypoplastic right ventricle, 2 studies performed within 6 months after open heart surgery, and 4 studies in 3 patients with no left ventricular angiograms.

Values are mean ± standard error of the mean. LV = left (pulmonary) ventricle; NS = not significant ($p > 0.05$); RV = right (systemic) ventricle.

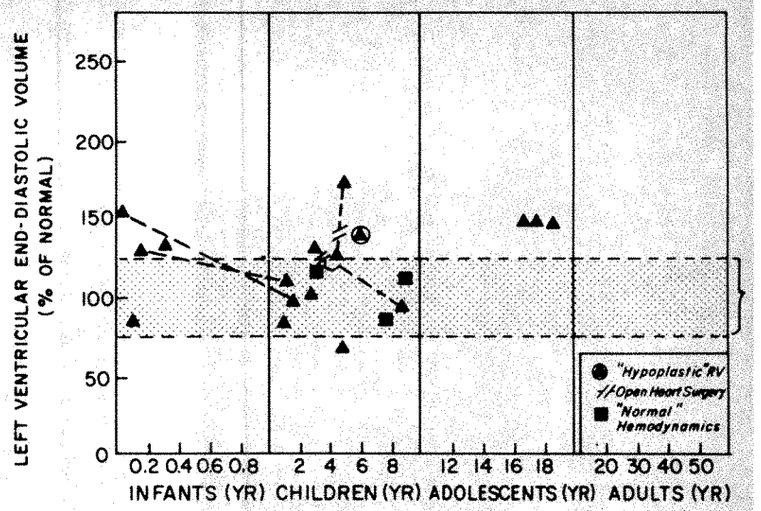



**FIGURE 3.** Left (pulmonary) ventricular end-diastolic volume as a function of percentage of predicted normal. The normal range indicates the values for patients with normal left ventricles. RV = right ventricle.

ventricles, with the 2 patients with hypoplastic right ventricles previously reported[1] shown here. The fifth group consists of 2 patients with significant tricuspid insufficiency. These patients have markedly enlarged ventricles, as would be predicted.

Figure 3 shows pulmonary (anatomic left) ventricular end-diastolic volume plotted as a percentage of predicted normal values. Nine patients who ranged in age from infancy to adolescence had definite enlargement of the left ventricle. Enlargement appeared to be related to systemic to pulmonary shunting at the ventricular level in 6 patients with Qp/Qs $\geq$1.7 in 5 of 6 in whom oximetry data were available and with all patients showing clinical evidence of increased Qp. The 2 patients with hypoplastic right ventricles also had enlarged left ventricles. One of these patients (aged 5) had a tight pulmonary artery band and 1 patient (aged 19) had severe pulmonary stenosis with systemic hypertension and left and right ventricular peak systolic pressure of 165 mm Hg. Enlargement of the left ventricle in these patients was undoubtedly related to the small systemic ventricle and to the pulmonary to sys temic shunting, with the left ventricle supplying par of the systemic output. In addition, these patients ha chronic, severe pressure overload which also possibl contributed to the left ventricular enlargement.

Table II shows a comparison of left and right end diastolic volumes in 17 studies in 14 patients in whor both variables could be calculated. The 2 patients wit hypoplastic systemic ventricles as well as 1 patien studied 4 months after open heart surgery were ex cluded from this analysis. Mean values for both pul monary (left) and systemic (right) ventricular volume were slightly increased above normal, but compariso of the 2 ventricles showed no significant difference i size.

Systemic ventricular ejection fraction in all 24 studie is shown in Figure 4. The ejection fraction was withi normal limits in 19 of the 24 studies. Only 2 patient aged <10 years had an ejection fraction less than nor mal. One child was studied for pulmonary atresia an ventricular septal defect <6 months after open hear

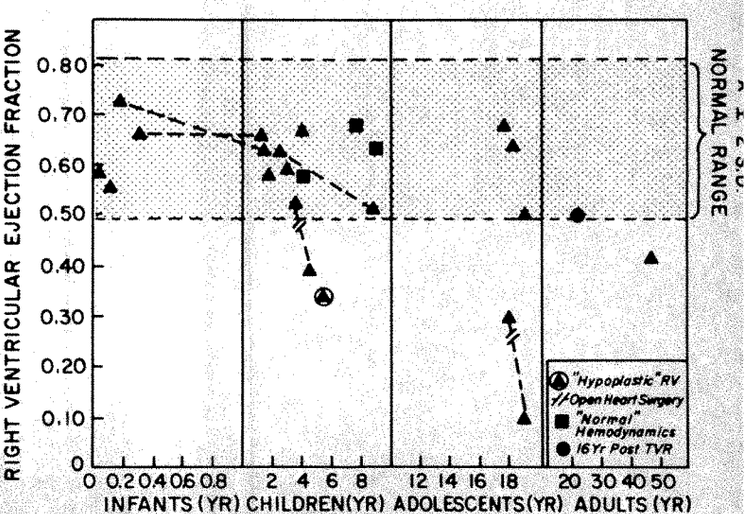
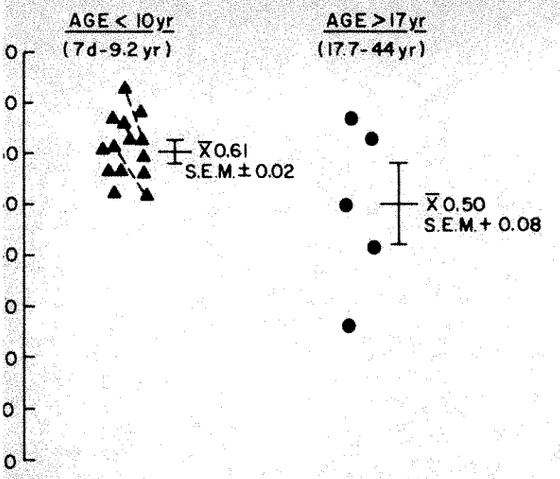



**FIGURE 4.** Right (systemic) ventricular ejection fraction shown for 4 age groups. Normal range is for patients with a normal right ventricle functioning as the pulmonary ventricle. Abbreviations as in preceding figures.




**5.** Right (systemic) ventricular ejection fraction in congenitally d transposition shown for patients aged <10 years versus those 17 years. Patients excluded from this figure include those with lastic right ventricle and those with recent open heart surgery. iations as in preceding figures.

y. This child had an open ventricular septal defect ıoderate tricuspid insufficiency at the time of The recent open heart surgery may have con- ed to the low ejection fraction. The only other ıt with a low ejection fraction in the young age was the patient with severe hypoplasia of the right cle.[1]

ong adolescents and adults, 3 studies in 2 patients d a low ejection fraction, and 2 additional patients n ejection fraction at the lower limit of normal. patient with a markedly low ejection fraction was ·d originally at another hospital at 6 years of age ›und to have no hemodynamic abnormalities. He n athletic young man in whom signs of severe ·stive heart failure developed when he was 18 years , and he was found to have a markedly enlarged ventricle and heart block. The tricuspid valve was ·ed and a pacemaker implanted. He continued to ·igns of severe congestive heart failure and at re- 6 months later (at 18.5 years of age) showed a ·r decrease in the ejection fraction.

ure 5 compares right ventricular ejection fraction ients <10 years of age with that in 5 patients >17 at the time of study. Again, the 2 patients with ›lastic right ventricles were excluded from analysis ·ll as 2 studies performed within 6 months ›pen heart surgery. Younger patients have a higher ejection fraction than do older patients, although is considerable overlap between the 2 groups. A for unpaired data showed a significant difference, 02.

lmonary (left) ventricular ejection fraction (Fig. s normal in 14 of 20 studies. Low left ventricular on fractions were present before and after at- ·ed repair in the 3 year old with pulmonary atresia ı the 19 year old with a small right ventricle and ·e left ventricular pressure overload. This variable was greater than normal in 4 studies in 3 children aged 3.5 to 8.5 years.

Left and right ventricular ejection fractions (Table II) in the 17 studies in 14 patients in whom both variables could be calculated were not significantly different. Right ventricular ejection fraction calculated in 20 patients, including 3 in whom left ventricular studies were unavailable, was 0.58 ± 0.02 (mean ± standard error of the mean). The latter data again exclude patients with hypoplastic right ventricles as well as patients with open heart surgery performed in the 6 months before study.

Attempts to determine possible correlations of the volume determinations and ejection fraction data with other variables also were made. No significant linear relation was found between right ventricular end-diastolic volume and oxygen saturation or age. There was a significant correlation between right ventricular end-diastolic volume and Qp/Qs ratio in patients with no significant tricuspid insufficiency. The r value for this relation was 0.645. In addition, the right ventricular stroke index/left ventricular stroke index calculated from the angiographic studies also was compared with the Qp/Qs ratio. Again in the same group of patients, the correlation was significant: r = 0.648. These data indicate that right ventricular size and right ventricular/left ventricular output ratios do show a significant correlation with pulmonary blood flow when patients with severe tricuspid insufficiency are excluded from analysis. An attempt also was made to determine if there were significant correlations of right ventricular ejection fraction with age, right ventricular end-diastolic volume, or systemic oxygen saturation. No significant correlations were found using regression analysis techniques.

## Discussion

Our data demonstrate that the majority of patients up to their young adult years with congenitally corrected transposition of the great arteries have systemic ventricles that are normal or near normal in size. In addition, 4 patients with relatively normal hemodynamics showed values that were well within the normal range.

Patients who did have abnormalities of volume fell into 2 categories. Patients with ventricular septal defects and large systemic to pulmonary shunts as well as patients with moderate to severe tricuspid (systemic) atrioventricular valvular insufficiency had large systemic ventricles. Patients with congenitally corrected transposition of the great arteries plus ventricular septal defect and large left to right shunts have analogous hemodynamic loads on the systemic ventricles as do patients with normally related great arteries and ventricular septal defects who demonstrate left ventricular enlargement which correlates well with the degree of left to right shunt.[9,10] In addition, patients with congenitally corrected transposition of the great arteries plus tricuspid insufficiency have systemic ventricular hemodynamic loads that are analogous to those of patients without congenitally corrected transposition of the great

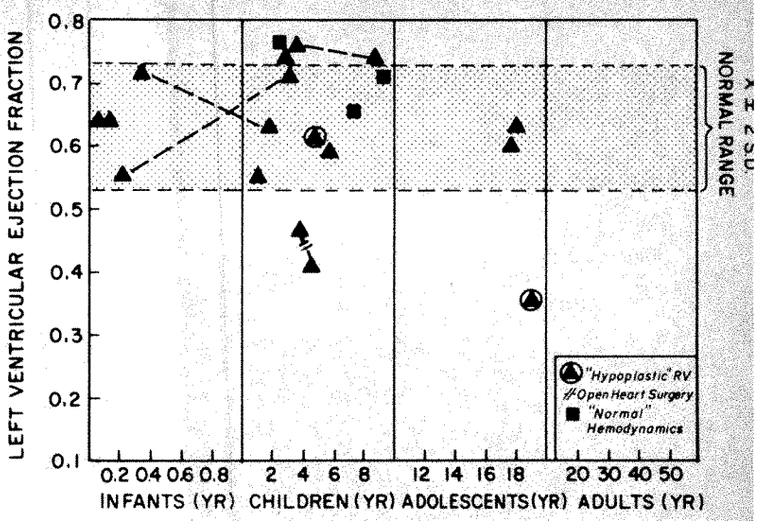



**FIGURE 6.** Left (pulmonary) ventricular ejection fraction in patients with congenitally corrected transposition of the great arteries. Normal ranges for patients with a normal left ventricle. RV = right ventricle; S.D. = standard deviation.

arteries who have mitral insufficiency and left ventricular enlargement.

Patients with congenitally corrected transposition of the great arteries and ventricular septal defect plus pulmonary stenosis had normal or decreased systemic ventricular volume. These patients have analogous hemodynamics to patients without congenitally corrected transposition of the great arteries who have tetralogy of Fallot and who have normal or mildly decreased left ventricular volumes with left ventricular size showing a direct correlation with pulmonary blood flow.[11,12] Finally, 2 of 19 patients (10.5%) showed definitely small or hypoplastic right ventricles. Both of these patients have been reported on previously[1] and had decreased pulmonary flow due to pulmonary stenosis or pulmonary artery banding. A similar degree of left ventricular hypoplasia has been reported in tetralogy of Fallot.[13]

The anatomic left or pulmonary ventricle of patients with congenitally corrected transposition was also normal or near normal in size in the majority of patients studied. Most of these pulmonary ventricles were under high pressure (Table I). In our laboratory, values for normal left or normal right ventricular end-diastolic volume are not significantly different. In addition, the right ventricle in children with high pressure secondary to pulmonary stenosis is not enlarged.[8] Therefore, the mean values for systemic and pulmonary ventricular volume in patients with congenitally corrected transposition will be normal or near normal whichever ventricle is chosen for comparison. In this study, only patients with large ventricular systemic to pulmonary shunts or hypoplastic systemic ventricles had enlarged pulmonary ventricles.

The ejection fraction for left (pulmonary) ventricles in patients with corrected transposition was within normal limits with 2 exceptions. This value was decreased preoperatively in a patient with pulmonary atresia and continued to be decreased postoperatively. In addition, 1 other patient with severe pulmonary stenosis had a low left ventricular ejection fraction. Thus, in the majority of patients with congenitally corrected transposition without ventriculotomy or a severely increased afterload, the ejection fraction of the pulmonary ventricle was normal.

Although the systemic or right ventricular ejection fraction was normal in most patients, it was abnormal only in 2 of 13 patients (15%) who were <10 years of age but was abnormal in 2 of 6 patients (33%) >17 years of age and at the lower limit of normal in 2 additional older patients. Moreover, the 2 children with a low ejection fraction had a hypoplastic right ventricle and recent open heart surgery, conditions that could explain the decreased ejection fraction. These data suggest that an increasing incidence of systemic ventricular dysfunction may be present in older patients with congenitally corrected transposition.

A number of reports have documented adults usually aged 20 to 40 years with congenitally corrected transposition of the great arteries who present with congestive heart failure frequently associated with tricuspid (systemic atrioventricular valvular) insufficiency, complete heart block, or atrial arrhythmias, or a combination of these.[2,3,14–22] Most of these patients were asymptomatic earlier in life. Our data suggest that such patients probably have a normal ejection fraction in childhood which gradually worsens with progressive deterioration of the systemic ventricle in adult life.

The contribution of progressive tricuspid insufficiency to systemic ventricular dysfunction in congenitally corrected transposition of the great arteries is unclear. The structure and muscular configuration of the systemic ventricle may predispose to tricuspid insufficiency when it is forced to function in the systemic circuit. Most patients who have isolated mitral insufficiency and do not have corrected transposition can tolerate moderate to severe mitral insufficiency for extended periods before ventricular dysfunction occurs. The patient in our study who had a normal cardiac catheterization at 6 years and presented with severe

ongestive heart failure at 18 years had the development of both ventricular dysfunction as well as tricuspid insufficiency between the 2 studies.

These data are of considerable interest in terms of follow-up study of patients who have had intraatrial repair of complete transposition and who also have the anatomic right ventricle function as the systemic ventricle after operation. Many of these children have systemic ventricular dysfunction on angiographic measurements, and the overall mean value for right ventricular ejection fraction in patients with no significant hemodynamic abnormalities after surgery is approximately 45%[4–6,23] as compared with the 61% ejection fraction found in this study in patients with congenitally corrected transposition. Thus, the 45% right ventricular ejection fraction in children with complete transposition is clearly abnormal when compared with "nature's model" for a right ventricle functioning as the systemic pumping chamber. These patients with postoperative transposition deserve careful follow-up study to determine the incidence of clinically significant systemic ventricular dysfunction in adolescence and early adulthood and the correlates of such dysfunction.

Several potential methodologic problems arise with the studies presented. The ventricular volume data were obtained using angiographic methods that have been validated for normal left and right ventricles. Postmortem ventricular casts from patients with congenitally corrected transposition were unavailable for in vitro volume determinations. However, the shape of the pulmonary ventricle in congenitally corrected transposition of the great arteries is similar to that of the normal left ventricle, suggesting that the area-length method is applicable.

Right ventricular volume studies have been applied in patients with various congenital abnormalities including complete transposition before and after repair.[4–6,23] Comparison of cineangiographic right and left ventricular outputs with indicator dilution output in such patients shows an excellent correlation, and thus an in vivo validation of volume-derived output has been performed.[5] In addition, we compared angiographic right ventricular ejection fractions with radionuclide data in postoperative transposition as well as in congenitally corrected transposition and found an excellent correlation ($r = 0.98$, standard error of the estimate $\pm 0.03$) with no significant difference between the values obtained by the 2 methods.[24]

A second potential problem is the use of the ejection fraction as a measurement of ventricular performance. The ejection fraction is determined not only by contractile state but also by preload and afterload. In the 3 patients with small ventricles in this study, a depressed ejection fraction could be due to the small volumes and would not necessarily indicate ventricular muscle dysfunction. In the remaining patients with normal or increased volume, afterload must be considered. Systemic vascular resistance could be calculated in 21 of the 24 studies reported. This variable was greater than the upper limit of normal in our laboratory (>30 units/m$^2$) in only 3 of the 21 studies. One abnormal value for systemic vascular resistance (32 units/m$^2$) was in the 23 year old woman who had had tricuspid valve replacement 13 years previously. Her ejection fraction was slightly above normal. The other 2 values for elevated systemic vascular resistance were in the 18 year old man with a severely decreased ejection fraction (0.26 and 0.07) in 2 studies. The systemic vascular resistance at the first study was 37 and at the second study, 62. Because of the patient's low cardiac indexes (2.0 and 1.0) calculated at both studies, these values for systemic vascular resistance may be falsely high. At such low cardiac indexes, the error in calculation can be considerable. Nevertheless, this patient's low systemic ventricular ejection fractions may have been related in some measure to the elevated systemic vascular resistance. In addition, the decrease in ejection fraction from 0.26 and 0.07 after tricuspid valve replacement may have been largely due to the elimination of a low resistance pathway for systemic ventricular ejection into the left atrium.

In contrast, only 1 patient had a systemic resistance that was less than our lower limit of normal (<15 units/m$^2$). That patient was a 9 year old girl with severe tricuspid insufficiency and marked ventricular dilation whose ejection fraction was within normal limits. Thus, neither an abnormally low nor an abnormally high systemic vascular resistance appears to have been related to the overall results in terms of systemic ventricular ejection fraction.

**Conclusions:** (1) Systemic (right) ventricular size and ejection fraction are with normal limits in most infants and children with congenitally corrected transposition. Patients in this age group who have an increase in systemic ventricular size usually have significant systemic to pulmonary shunting or tricuspid insufficiency. (2) Evidence suggests that systemic ventricular ejection fraction may decrease with age. Further longitudinal data are needed in this regard. (3) The systemic ventricular ejection fraction is considerably higher in young patients with congenitally corrected transposition than in children studied after intraatrial repair of complete transposition of the great arteries. This difference implies that other factors such as preoperative myocardial hypoxia or intraoperative myocardial ischemia may contribute to the abnormal systemic ventricular function in patients with complete transposition. (4) Left (pulmonary) ventricular size and ejection fraction are normal in the majority of infants and children. Increases in left ventricular size usually are associated with ventricular septal defect, hypoplastic right ventricle, or a marked increase in ventricular afterload.

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## References

1. **Erath JG, Graham TP Jr, Hammon JW Jr, Smith CW.** Hypoplasia of the systemic ventricle in congenitally corrected transposition of the great arteries. J Thorac Cardiovasc Surg 1980;1979:770–775.
2. **Masden RR, Franch RH.** Isolated congenitally corrected transposition of the great arteries. In: Hurst JW ed., Update III: The Heart. New York: McGraw-Hill, 1980:59–83.
3. **Bliddal J.** Congenitally corrected transposition: a review of the world literature. Dan Med Bull 1976;23:168–183.

4. **Jarmakani JM, Canent RV Jr.** Preoperative and postoperative right ventricular function in children with transposition of the great vessels. Circulation 1974;49:Suppl II:II-39–II-45.
5. **Graham TP Jr, Atwood GF, Boucek RJ Jr, Boerth RC, Bender HW Jr.** Abnormalities of right ventricular function following Mustard operation for transposition of the great arteries. Circulation 1975;52:678–684.
6. **Hagler DJ, Ritter DG, Mair DD, Tajik AJ, Seward JB, Fulton RE, Ritman EL.** Right and left ventricular function after the Mustard procedure and transposition of the great arteries. Am J Cardiol 1979;44:279–283.
7. **Graham TP Jr, Jarmakani MM, Canent RV Jr, Morrow MD.** Left heart volume estimation in infancy and childhood: re-evaluation of methodology and normal values. Circulation 1971;43:895–904.
8. **Graham TP Jr, Jarmakani MM, Atwood GF, Canent RV Jr.** Right ventricular volume determination in children: normal values and observation with value or pressure overload. Circulation 1973;47:144–152.
9. **Jarmakani MM, Graham TP Jr, Spach MS, Canent RV, Capp MP.** Effect of site of shunt on left heart volume characteristics in infants and children with ventricular septal defect and patent ductus arteriosus. Circulation 1969;40:411.
10. **Graham TP Jr, Atwood GF, Boucek RJ Jr, Cordell D, Boerth RC.** Right ventricular volume characteristics in ventricular septal defect. Circulation 1976;54:800–804.
11. **Jarmakani JM, Graham TP Jr, Canent RV Jr, Jewett PH.** Left heart function in children with tetralogy of Fallot before and after palliative or corrective surgery. Circulation 1972;46:478–490.
12. **Graham TP Jr, Cordell D, Atwood GF, Boucek RJ Jr, Boerth RC, Bender HW, Nelson JH, Vaughn WK.** Right ventricular volume characteristics before and after palliative and reparative operation in tetralogy of Fallot. Circulation 1976;54:417–422.
13. **Graham TP Jr, Faulkner S, Bender HW Jr, Wender CM.** Hypoplasia of the left ventricle: rare cause of postoperative mortality in tetralogy of Fallot. Am J Cardiol 1977;40:454–457.
14. **Schiebler GL, Edwards JE, Burchell HB, DuShane JW, Ongley PA, W EA.** Congenital corrected transposition of the great vessels: a study o cases. Pediatrics 1961;27:851–888.
15. **Cumming GR.** Congenital corrected transposition of the great ves without associated intracardiac anomalies. Am J Cardiol 1962;10:6 614.
16. **Roberts WC, Ross RS, Davis FW Jr.** Congenital corrected transpos of the great vessels in adulthood simulating rheumatic valvular disease. Johns Hopkins Hosp 1964;114:157–159.
17. **Rotem CE, Hultgren HN.** Corrected transposition of the great vessels wit associated defects. Am Heart J 1965;70:305–318.
18. **Friedberg DZ, Nadas AS.** Clinical profile of patients with corrected tr position of the great arteries. N Engl J Med 1970;282:253–359.
19. **Nagle JP, Cheitlin MD, McCarthy RJ.** Transposition of the great ves without associated anomalies: report of a case with congestive failu age 45. Chest 1971;60:367–370.
20. **Dodek A, Neill WA.** Corrected transposition of the great arteries m querading as coronary artery disease. Am J Cardiol 1972;30:910–91
21. **Bjarke BB, Kidd BSL.** Congenitally corrected transposition of the g arteries. Acta Paediatr Scand 1976;65:153–160.
22. **Selden R, Schaefer RA, Kennedy BJ, Neill WA.** Transposition of the g arteries simulating coronary heart disease in adults. Chest 1976 188–190.
23. **Bender HW Jr, Graham TP Jr, Boucek RJ Jr, Walker WE, Boerth** Comparative operative results of the Senning and Mustard procedure transposition of the great arteries. Circulation 1980;62:Suppl I:I-19 203.
24. **Parrish MD, Graham TP Jr, Born ML, Jones J.** Radionuclide validatio right and left ventricular function in children: validation of methodology. J Cardiol 1982;49:1241–1247.

# ediatric Population: Evaluation by Radionuclide ngiocardiography

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**e ability to quantitate aortic (AR) or mitral gurgitation (MR), or both, by radionuclide angio- rdiography was evaluated in children and young lults at rest and during isometric exercise. gurgitation was estimated by determining the tio of left ventricular stroke volume to right ven- cular stroke volume obtained during equilibrium ntriculography. The radionuclide measurement as compared with results of cineangiography, with od correlation between both studies in 47 of 48 tients. Radionuclide stroke volume ratio was used classify severity: the group with equivocal gurgitation differed from the group with mild gurgitation ($p < 0.02$); patients with mild regurgi- tion differed from those with moderate regurgita- n ($p < 0.001$); and those with moderate regurgitation differed from those with severe regurgitation ($p < 0.01$). The stroke volume ratio was responsive to isometric exercise, remaining constant or increasing in 16 of 18 patients. After surgery to correct regurgitation, the stroke volume ratio significantly decreased from preoperative measurements in all 7 patients evaluated. Results from the present study demonstrate that a stroke volume ratio >2.0 is compatible with moderately severe regurgitation and that a ratio >3.0 suggests the presence of severe regurgitation. Thus, radionuclide angiocardiography should be useful for noninvasive quantitation of AR or MR, or both, helping define the course of young patients with left-side valvular regurgitation.**

rdiac catheterization is frequently necessary to aluate the degree of MR or AR in children, because ese lesions are difficult to quantitate by noninvasive ethods. Furthermore, it may be helpful to evaluate ch patients during drug intervention, during exercise, by serial investigations, thus increasing the desirility for a noninvasive technique. Such evaluation is ost important when managing younger patients, in om surgical treatment should be considered at a time en preservation of long-term myocardial function can accomplished. However, early surgical intervention these lesions is seldom recommended because valve placement is often required to significantly reduce gurgitation.

Noninvasive laboratory evaluation of adults with lvular regurgitation has recently been supplemented echocardiography, exercise testing, and radionuclide giocardiography.[1–3] The radionuclide technique has en useful in evaluating systolic pump function, wall otion, and regurgitation fraction.[4–7] The purpose of e present study is to investigate the role of radionude angiocardiography in quantitation of AR or MR in young patients by (1) a comparison of the radionuclide estimate of regurgitation with the estimate by cineangiography; and (2) an evaluation of possible change in regurgitation during isometric exercise and after cardiac surgery to correct regurgitation.

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## Methods

**Patient population:** The study group consisted of 48 children and young adults referred to the Division of Nuclear Medicine at Children's Hospital Medical Center (CHMC) and Riley Hospital for Children at Indiana University (IU) for further evaluation of documented aortic or mitral valve abnormalities, or both, including some degree of regurgitation. Patients shown by cardiac catheterization to have intra- or extracardiac shunting, tricuspid regurgitation, or pulmonary regurgitation were excluded. The radionuclide estimate of valvular regurgitation was compared with the cineangiographic estimate; only patients with both studies performed within 4 months were included. The age range of the 19 CHMC patients was 0.5 to 26 years (median 13) and of the 29 IU patients 1 to 16 years (median 7). The valvular abnormality was congenital in 42 patients and rheumatic in 6. At the time of radionuclide study the aortic valve was predominantly involved in 29 patients and the mitral valve in 19. Of the total group, 37 patients had previous cardiac surgery and 26 had defects in addition to the valvular regurgitation (Table I). Seven patients were evaluated by radionuclide angiocardiography before and after operation to relieve regurgitation, but not all 7 had postoperative cineangiography. Eighteen patients underwent radionuclide angiocardiography while performing isometric exercise. Three of these had clinical

diagnosis of AR or MR but no current, confirmatory cardiac catheterization; 15 had resting studies included in the initial comparison between radionuclide and cineangiographic estimate of regurgitation.

**Radionuclide angiocardiography:** All 48 patients had estimation of resting left ventricular ejection fraction by gated equilibrium ventriculography. At CHMC, red blood cells were labeled in vivo using 1 to 2 mg stannous pyrophosphate (Pyrolite, New England Nuclear) followed in 20 minutes by 200 μCi/kg technetium-99m as pertechnetate labeled onto 2 to 3 ml of the patient's own red blood cells.[8] Radionuclide ventriculograms were obtained using an Anger scintillation camera and a high-sensitivity, straight-bore collimator slanted at 30°. Five minutes after injection of the radiopharmaceutical, the camera was positioned in a modified left anterior oblique projection (30° caudal tilt).[9] Ten million counts were acquired in matrix mode, using a matrix size of 64 × 64 elements. Data were acquired on magnetic disk using a standard digital computer and nuclear medicine software (PDP 11/34 and Gamma-11 system, Digital Equipment), with a 15% window centered on the technetium-99m photo-peak. Data acquisition was gated to the patient's electrocardiogram. Initially, left ventricular ejection fraction was calculated. The cardiac cycle was divided into 57 frames, with data acquisition triggered by the patient's R wave.

The end-diastolic left ventricular perimeter was drawn manually, and left ventricular background regions were defined automatically.[10] Briefly, this entails estimation of the left ventricular background per cell as the mean counts per cell in 3 background regions surrounding the left ventricle and calculated on the end-systolic frame. This background value was then subtracted from each cell of the end-diastolic and end-systolic frames. Occasional changes in background regions were necessary to avoid excessive splenic activity, or, in smaller children, to keep the "septal" background region out of the right ventricular cavity by narrowing the region. End-systolic and end-diastolic images were selected from time activity curves; these images were derived by adding frames (usually 2 or 3) to most closely approximate a summed 50 ms interval.

At IU, red blood cells were labeled in vitro; after withdrawal of 2 to 3 ml of the patient's blood, 200 μCi/kg technetium-99m as pertechnetate was labeled onto a small bolus of blood (less than 0.5 ml) and then injected. Imaging was performed in a left anterior oblique projection to obtain best septal delineation. A mild caudal tilt (15 to 20°) was employed. Images were acquired with an Anger camera and a medium-sensitivity, parallel-hole collimator. Data were collected on a magnetic disk and interpolated to 64 × 64 matrix. Acquisition was terminated when 1 of the 28 frames from each cardiac cycle had 250,000 counts. Analysis was performed using commercial software programs (Medical Data Systems).[11] Semiautomatic regions of interest were generated over the left ventricle, and background was automatically generated lateral and inferior to the left ventricle. From these regions of interest, time activity curves were derived.

A stroke volume ratio (left ventricular counts to right ventricular counts) was calculated from activity ejected from each ventricle by a similar technique at both institutions. This ratio was determined from the stroke volume image and was not background-corrected.[4–7] The stroke volume image itself was obtained by subtracting the end-systolic frame (or frames) from the end-diastolic frame (or frames). Separate ventricular regions of interest were then drawn from this image. An attempt was made to include all right ventricular activity, including the outflow area (Fig. 1). Boundaries could be established with reasonable certainty using the paradox image, which provided atrial and great vessel contours by subtracting end-diastolic frames from end-systolic frames. Thus, remaining activity was presumably nonventricular when present at the upper or outer margin of the cardiac area (ventricular aneurysms might also have paradoxic activity).

**TABLE I Associated Lesions in All Patients With Radionuclide and Cineangiographic Comparison**

| Lesion | CHMC | IU | Total |
|---|---|---|---|
| AS | 4 | 4 | 8 |
| Co A | 1 | . . . | 1 |
| PO AS | 8 | 9 | 17 |
| PO AVR | 2 | . . . | 2 |
| PO VSD; AR | 2 | 2 | 4 |
| PO MVR | 2 | 3 | 5 |
| PO ECD | . . . | 10 | 10 |
| PO VSD, TGA | . . . | 1 | 1 |
| Total | 19 | 29 | 48 |

AS = aortic stenosis; AVR = aortic valve replacement; Co A = coarctation of the aorta; ECD = endocardial cushion defect; MVR = mitral valve replacement; PO = postoperative; VSD, AR = ventricular septal defect and aortic regurgitation; VSD, TGA = ventricular septal defect and transposition of the great arteries (Rastelli procedure).

The effects of isometric exercise were analyzed in 20 patients. A hand-grip dynamometer was constantly squeezed at 25 to 33% of single maximal effort for a 2-minute warm-up, with the collection of data for 2 to 3 minutes in the same projection as that used for the resting study. Count acquisition was 20 to 25% of that in the resting study, and provided sufficient data to allow stroke volume images to be clearly discernible in 18 of the 20 patients. Pulse, blood pressure, and electrocardiogram were monitored during and after isometric exercise.

**Data analysis:** Stroke volume ratio, defined as counts ejected from the left ventricular region by counts ejected from the right ventricular region, was compared with the cineangiographic degree of regurgitation routinely classified by the staff cardiologist and radiologist as slight, mild, moderate, or severe. This cineangiographic estimate is subjective, being based on a visual interpretation of regurgitation. The interpretation adopted at both CHMC and IU is a modification of the classification proposed by Sellers et al,[12] with present grading as follows: *slight* (or trace) has minimal opacification, with clearing of the proximal chambers in 1 beat, and may be only artifactual; *mild* has opacification not clearing in 1 cycle, is not progressive, but is definitely abnormal; *moderate* has progressive filling of the proximal chamber and is of considerable significance; *severe* occurs when the proximal chamber fills within 1 or 2 cycles, allowing complete visualization with opacity as great as the distal chamber. Individual stroke volume ratios were placed into these angiographic classifications, with compilation of mean and standard deviations for each group. These values were then compared by Student's *t* test

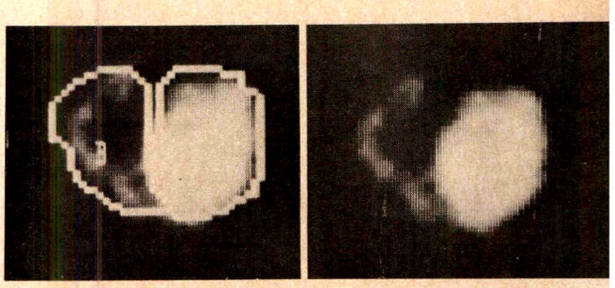
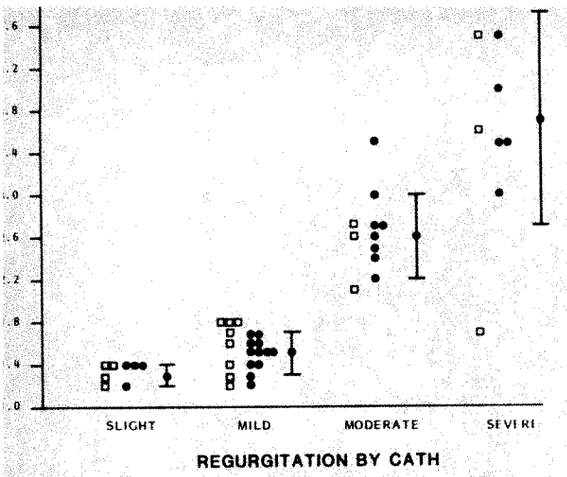


**FIGURE 1.** Stroke volume image with ventricular regions of interest. Note small right ventricular (B) stroke volume activity compared with that of left ventricle (A) in a 10-year-old with moderate to severe AR.

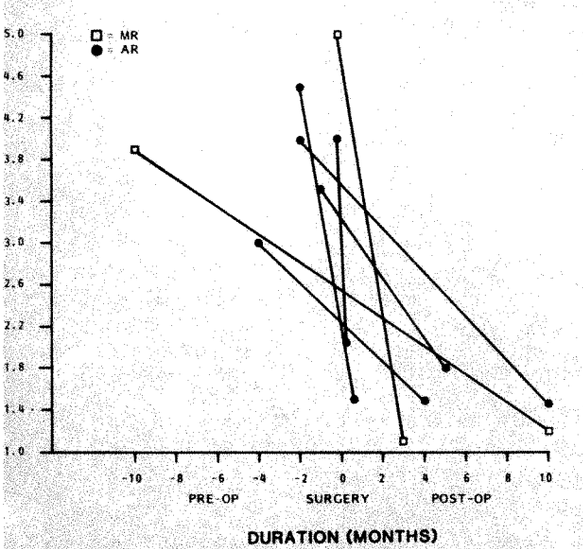



**IE 2.** Stroke volume ratio (SVR) plotted against degree of valvular gitation assessed by angiography performed during cardiac terization (cath). AR and MR = aortic and mitral regurgitation, ctively.

ıpaired data. When isometric exercise was performed, volume ratios at rest and during exercise were com- using Student's *t* test for paired data. Regression sis was used to test a possible relation between stroke ıe ratios and ejection fraction.

## Results

**timate of regurgitation by stroke volume ratio:** /-eight patients had comparison of AR or MR, or estimated by radionuclide techniques and cine- ıgraphy. Previously, the left ventricular to right icular stroke volume ratio in children without ılar regurgitation was calculated up to 1.4 at CHMC g a slant-hole collimator) and up to 1.5 at IUMC g a parallel-hole collimator). When classified ac-




**RE 3.** Stroke volume ratio (SVR) in 7 patients studied by radio- le angiocardiography before (pre-op) and after (post-op) surgery rect valvular regurgitation.

stroke volume ratio of patients with slight (equivocal) regurgitation was 1.3 ± 0.1; with mild regurgitation, 1.5 ± 0.2; with moderate regurgitation, 2.6 ± 0.4; and with severe regurgitation, 3.7 ± 1.0. The group with slight regurgitation was not statistically different from our patients without regurgitation, but was significantly different from those with definite but mild regurgitation ($p < 0.02$). The group with mild regurgitation differed from the group with moderate regurgitation ($p < 0.001$); the moderate group also differed from the group with severe regurgitation ($p < 0.01$). Generally, any patient with a stroke volume ratio >2.0 had at least moderate regurgitation, and if the ratio were >3.0, severe regurgitation was likely (Fig. 2). The radionuclide estimate of regurgitation correlated well with cineangiographic estimate in 47 of 48 patients.

**Isometric exercise:** Isometric exercise resulted in a group heart rate increase of 6.2% (range 3 to 12), systolic blood pressure increase of 14.8% (range 5 to 32), and diastolic blood pressure increase of 5.5% (range 0 to 18). Isometric exercise increased mean stroke volume ratio from 2.5 ± 0.8 to 2.8 ± 1.0 ($p < 0.05$) in the 18 patients. The stroke volume ratio remained constant or increased in 16 of 18 patients during exercise.

**Effect of surgery:** Seven patients (5 with aortic and 2 with mitral valve disease) were studied before and after surgery. One patient had aortoplasty, and the other 6 underwent valve replacement. The stroke volume ratio decreased significantly in each patient (Fig. 3). This change could be seen as early as 2 weeks postoperatively.

## Discussion

Management of asymptomatic patients with AR or MR remains imprecise, because the goal is often preservation of long-term myocardial function. Valve replacement in children is dangerous; during the first 20 years of open-heart surgery, aortic or mitral valve replacement carried a 30% risk in the pediatric population,[13] and current reports cite perioperative mortality of 10%.[14] Also, progressive valvular obstruction may occur with growth, necessitating repeat valve replacement.[15] To lessen the possibility of embolization and the necessity for anticoagulation, homo- and heterograft valves were considered logical prostheses for children. Unfortunately, in a significant number of these valves tissue degeneration or calcification developed, especially in children.[14,16]

Accurate noninvasive quantitation of regurgitation would help determine an optimal management schedule for children with aortic or mitral valvular lesions. Recently, estimation of valvular regurgitation in adults by radionuclide ventriculography showed good correlation when compared with estimation by cardiac catheterization.[4–7] The radionuclide estimate, based on ventricular count output, correlated well with both hemodynamic and angiographic estimate of regurgitation. Therefore, we applied these radionuclide techniques to study children and young adults. Analysis of the radionuclide study was performed without knowledge of the severity of deformity suspected clinically or estimated by cardiac catheterization.

The stroke volume ratio was used to estimate regurgitation. Theoretically, this ratio should be unity. However, complex right ventricular anatomy, magnified in the left anterior oblique projection, makes it difficult to accurately image the entire right ventricle. When totally eliminating the right atrium, a segment of pulmonary outflow may be sacrificed. Also, the extension of right ventricle curving posteriorly around the septum in this projection may be amputated. Normal adults, our normal patients, and those in this study with equivocal valvular regurgitation have a stroke volume ratio of 0.9 to 1.5.[9,10] Thus, a stroke volume ratio >1.4 to 1.5 must be present to diagnose definite regurgitation. There was overlap between estimated stroke volume ratios of normal patients and those with slight regurgitation. However, the radionuclide technique was capable of identifying those with more significant regurgitation and also of providing quantitative classification. Accuracy of quantitation appeared similar for patients with either aortic or mitral valve regurgitation, although the smaller subgroups precluded statistical verification.

Overall, there was excellent correlation between radionuclide and cardiac catheterization estimate of regurgitation in all but 1 patient, who had previous aortic valvotomy. He also had a bizarre left ventricle, long segment subaortic stenosis, and intermittent atrial fibrillation and was considered clinically to have congestive heart failure despite a high left ventricular ejection fraction determined by both cardiac catheterization and radionuclide angiocardiography. The inconsistency in the estimation of regurgitation was not totally unexpected, because previous work has shown that when discrepancy between catheterization and radionuclide quantitation occurs, it is usually in those patients with arrhythmia or severe congestive heart failure.[6]

Stroke volume ratio was also responsive to apparent surgical intervention. Radionuclide evaluation of 7 postoperative patients demonstrated significantly less regurgitation and correlated with cineangiographic results in the 4 patients studied postoperatively by cardiac catheterization. A decrease in stroke volume ratio was documented in 1 patient at the first radionuclide test 2 weeks after surgery. Stroke volume ratio often changed before any measurable increase in left ventricular ejection fraction. This alteration in regurgitation before improvement in myocardial function is common after valve replacement in adults.[17]

The role of isometric exercise as an adjunct in the evaluation of patients with AR or MR was investigated. Generally, the stroke volume ratio was sensitive to the increased afterload imposed by isometric exercise. After stress, the left ventricular ejection fraction significantly decreased in 2 patients with normal resting values. However, the total group of patients showed no statistical relation between resting or stress stroke volume ratio and ejection fraction. This negative relation could be expected because resting myocardial function is usually preserved in patients with left-sided valvular regurgitation until late in the disease.[18] Despite large ventricular dimensions, a large stroke volume may result in a normal cardiac output and ejection fraction. When an abnormal ejection fraction is found, function is usually severely impaired. Thus, candidates for surgery might be those whose ventricular function or degree of regurgitation shows a significant change during serial studies or in response to exercise, because abnormal response to stress has been demonstrated in adults requiring valve replacement.[19] Furthermore, there are data suggesting that even mild congestive heart failure significantly alters the surgical prognosis.[20]

The present study demonstrates that radionuclide angiocardiography is safe and effective in quantitating regurgitation during evaluation of ventricular ejection fraction in children with AR or MR. Serial resting studies using this technique, coupled with evaluation during stress, may help define the course of such patients, providing objective data in a relatively noninvasive manner.

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## References


1. **Henry WL, Bonow RO, Borer JS, Ware JH, Kent KM, Redwood DR, McIntosh CL, Morrow AG, Epstein SE.** Observations on the optimum time for operative intervention for aortic regurgitation. Circulation 1981;61:471–483.
2. **Henry WL, Bonow RO, Rosing DR, Epstein SE.** Observations on the optimum time for operative intervention for aortic regurgitation: serial echocardiographic evaluation of asymptomatic patients. Circulation 1980;61:484–495.
3. **Borer JS, Bachrach SL, Green MV, Kent KM, Henry WL, Rosing DR, Seides SF, Johnston GS, Epstein SE.** Exercise induced left ventricular dysfunction in symptomatic and asymptomatic patients with aortic regurgitation: assessment with radionuclide cineangiography. Am J Cardiol 1978;42:351–357.
4. **Sorensen SG, O'Rourke RA, Chavdhuri TK.** Noninvasive quantitation of valvar regurgitation by gated equilibrium radionuclide angiography. Circulation 1980;62:1089–1098.
5. **Bough EW, Gandsman EJ, North DL, Shulman RS.** Gated radionuclide angiographic evaluation of valve regurgitation. Am J Cardiol 1980;46:423–428.
6. **Lam W, Pavel D, Byrom E, Sheikh A, Best D, Rosen K.** Radionuclide regurgitant index: value and limitations. Am J Cardiol 1981;47:292–298.
7. **Urquhart J, Patterson RE, Pacer M, Goldsmith SJ, Horowitz SF, Litwack R, Gorlin R.** Quantitation of valve regurgitation by radionuclide angiography before and after valve replacement surgery. Am J Cardiol 1981;47:287–291.
8. **Jones AG, Davis MA, Uren RF, Shulkin P.** In vivo red cell labeling with TC-99m (abstr). J Nucl Med 1977;18:637.
9. **Parker JA, Uren RF, Jones AG, Maddox DE, Zimmerman RE, Neil JM, Holman BL.** Radionuclide left ventriculography with the slant hole collimator. J Nucl Med 1977;18:848–851.
10. **Maddox DE, Holman BL, Wynne J, Idoine J, Parker JA, Uren R, Neill JM, Cohn PF.** Ejection fraction image: a noninvasive index of regional left ventricular wall motion. Am J Cardiol 1978;41:1230–1238.
11. **Slutsky R, Karliner J, Ricci D, Kaiser R, Pfisterer M, Gordon D, Peterson KJ, Ashburn W.** Left ventricular volumes by gated equilibrium radionuclide angiography: a new method. Circulation 1979;60:556–564.
12. **Sellers RD, Levy MJ, Amplatz K, Lillehei CW.** Left retrograde cardioangiography in acquired cardiac disease. Am J Cardiol 1964;14:437–447.
13. **Freed MD, Bernhard WF.** Prosthetic valve replacement in children. Prog Cardiovasc Dis 1975;17:475–487.
14. **Sanders SP, Levy RJ, Freed MD, Norwood WI, Castaneda AR.** Use of Hancock porcine zenografts in children and adolescents. Am J Cardiol 1980;46:429–438.
15. **Friedman S, Edmunds LH Jr, Cusao CC.** Long term mitral valve replacement in young children. Circulation 1978;57:981–986.
16. **Weesner KM, Rocchini AP, Rosenthal A, Behrendt D.** Intravascular hemolysis associated with porcine mitral valve calcification in children. Am J Cardiol 1981;47:1286–1288.
17. **Clark DG, McAnulty JH, Rahimtoola SH.** Valve replacement in aortic insufficiency with left ventricular dysfunction. Circulation 1980;61:411–421.
18. **Fowler NO, Van Der Bel-Kahn JM.** Indications for surgical replacement of the mitral valve. Am J Cardiol 1979;44:148–157.
19. **Peter CA, Jones RH.** Radionuclide measurements of left ventricular function their use in patients with aortic insufficiency. Arch Surg 1980;115:1348–1352.
20. **Samuels DA, Curfman GD, Friedlich AL, Buckley MJ, Austen WG.** Valve replacement for aortic regurgitation: long-term follow-up with factors influencing the results. Circulation 1979;60:647–654.

# ıupravalvular Aortic Stenosis

## . 20-Year Clinical Perspective and Experience With Patch Aortoplasty

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ıd CHARLES WOOLEY, MD

**ıpravalvular aortic stenosis has a wide range of inical and morphologic expression. Since 1961, ; patients (aged 1 to 49 years) with documented ıpravalvular aortic stenosis have been evaluated. even (28%) had Williams' syndrome, 5 (20%) had familial form of supravalvular aortic stenosis, and 3 (52%) had a sporadic form. A blood pressure fference of >10 mm Hg between the arms was ted in 65% of the patients. Angiographically, 19 6%) had segmental supravalvular narrowing; 6 4%) had diffuse narrowing of the ascending rta.**

**Sixteen patients underwent patch aortoplasty. At ırgery, portions of the aortic valve cusps were equently attached to supravalvular tissue. This cusp tuck" resulted in distinctive angiographic atures and influenced the results of corrective ırgery. Three surgical deaths occurred in the early 960s—2 with diffuse narrowing of the aorta. Of the remaining 12 patients, followed for 1 to 12 years, 10 are asymptomatic, 1 has angina, and 1 died from cancer. All 8 patients who underwent postoperative catheterization had a thick band between the left and right coronary sinus which represented persistent attachment of portions of the aortic valve cusps to residual supravalvular tissue (cusp tuck). This resulted in aortic valvular gradients (23 to 48 mm Hg) in 4 patients and aortic valvular insufficiency in 2 patients. No significant supravalvular gradient was noted.**

**The 20-year experience with supravalvular aortic stenosis reported herein emphasizes a wide range of clinical and morphologic expression, the benefits and limitations of patch aortoplasty, and the importance of postoperative cardiac catheterization, and furthers the understanding of a complex clinical syndrome.**

ıpravalvular aortic stenosis is an unusual form of left ntricular outflow tract obstruction which has been cognized with increasing frequency during the last 30 ars. Little is known about the natural history and ng-term follow-up of this disorder. Since 1961, 25 ıtients with supravalvular aortic stenosis were evalıted at the Ohio State University Hospital and at the olumbus Children's Hospital. The present study reews our clinical, hemodynamic, angiographic, surgical, ıd follow-up experience with this group over the last ) years.

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### Clinical Material

**Patient population:** Twenty-five patients with documented supravalvular aortic stenosis were included in this study, 15 male and 10 female. Their ages at the time of diagnosis ranged from 1 to 49 years (average 18). Twelve of the patients were 16 years or older at the time of diagnosis. Of the 25 patients, 15 are still followed up on a regular basis. Seven patients have died. Three patients were lost to follow-up immediately after an initial evaluation and cardiac catheterization.

Three clinical groups were recognized. A sporadic form occurred in 13 patients. These patients had normal growth and development and no family history of supravalvular aortic stenosis. Seven patients had Williams' syndrome, defined as entailing a characteristic elfin face and mental retardation associated with supravalvular aortic stenosis. The remaining 5 patients had a familial form in which a parent or a sibling had documented supravalvular aortic stenosis.

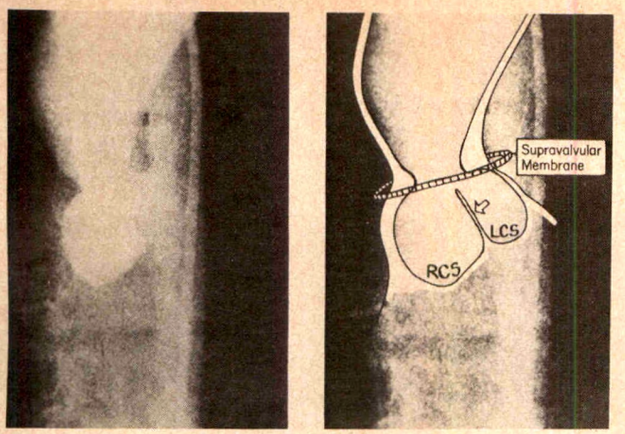



**FIGURE 1.** Aortic root injection in the anteroposterior projection demonstrating an hourglass form of supravalvular aortic stenosis. A band (**arrow**) is seen between the left (LCS) and right (RCA) coronary sinuses, extending to the supravalvular stenosis.

**Clinical evaluation:** All patients had an aortic systolic ejection murmur without an aortic valve ejection click. Blood pressure was recorded in both arms in 20 patients. Thirteen had a blood pressure difference of >10 mm Hg between the arms. In 11, blood pressure was higher in the right arm; in 2, the left arm had a higher reading.

The electrocardiogram showed left ventricular hypertrophy in 14, and a chest x-ray showed an enlarged heart in 9 of the 25 patients.

**Cardiac catheterization:** All patients had gradients between the left ventricle and the ascending aorta ranging from 7 to 170 mm Hg (average 88). The gradient was higher in the older age group, with an average gradient of 100 mm Hg in patients >16 years of age. Five patients had 2 cardiac catheterizations before surgery. Four had a progressive increase in gradient between the left ventricle and ascending aorta over a 4- to 12-year period, with the remaining patient's gradi unchanged over a 9-year period.

Angiographically, 2 types of supravalvular aortic sten were observed: an hourglass deformity and a hypoplastic ty In the hourglass deformity, seen in 19 of our patients, s mental narrowing of the ascending aorta just above the ao valve was noted. The aortic arch and descending aorta w of normal caliber. Six of our patients had the hypoplastic fo in which there was diffuse narrowing of the entire ascend aorta, aortic arch, and descending aorta.

In addition to the narrowing above the aortic valve, we a noted angiographic abnormalities in the aortic valve its Figure 1 is an aortic root angiogram in the anteroposter projection of an hourglass type of supravalvular aortic s nosis. A thick band exists between the right and left coron sinuses and was present in all preoperative angiograms. T band represents the apposition of the right and left ao valve cusps due to traction on the cusps by the supravalvu tissue. The band is a very important feature of supravalvu aortic stenosis and is discussed in detail later in this repo

Several associated cardiac lesions were noted. Two patie had angiographic evidence of severe peripheral pulmon artery stenosis. Two had a patent ductus arteriosus. Otl defects included subaortic membrane, atrial septal defe ventricular septal defect, mitral regurgitation, mitral va prolapse, and coarctation of the aorta.

**Follow-up: nonsurgical patients:** Nine patients have undergone surgery. Three have died: a 3-year-old boy fr Wilms' tumor, a 13-year-old girl suddenly after experienc syncope, and a 37-year-old male from subacute bacterial docarditis after resection of bowel cancer. Three other patie continue to be followed up: a teenaged girl who cannot u dergo an operation because of severe peripheral pulmon artery stenosis, a 34-year-old man with exertional chest p who refused surgery, and a 4-year-old boy who is awaiti surgery. Three patients were lost to follow-up after an init evaluation and cardiac catheterization.

**Follow-up: surgical patients:** Sixteen patients underw operative repair. Eleven surgical patients had an hourgl type of supravalvular aortic stenosis; 5 had a hypoplastic ao

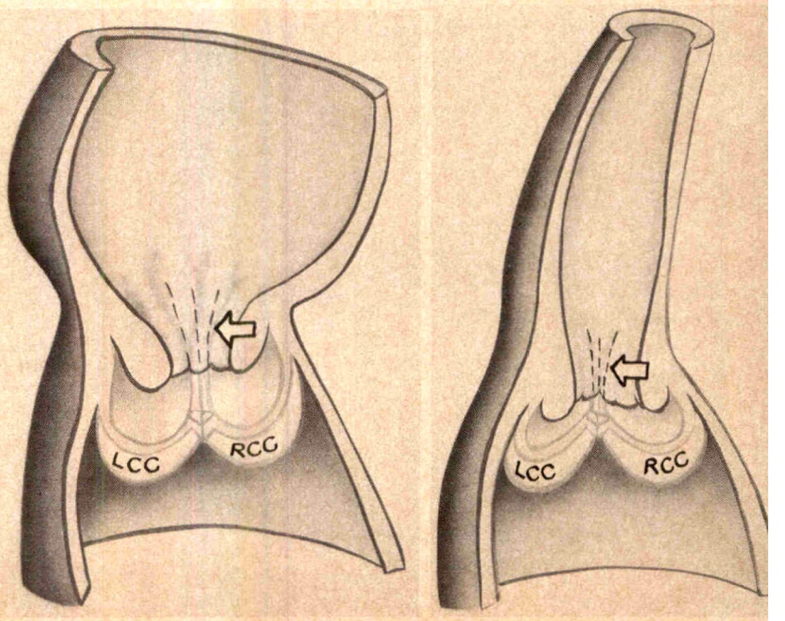
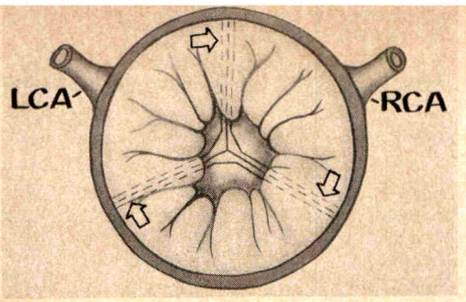



**FIGURE 2.** Hourglass (**left**) and hypoplastic (**right**) forms of supravalvular aortic stenosis. The **arrows** point to an area of apposition between the left coronary cusp (LCC) and right coronary cusp (RCC) which is tucked beneath the supravalvular stenosis.

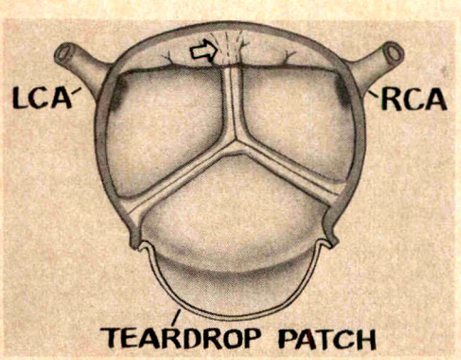



**GURE 3.** Preoperative cross-sectional view from above the supra-lvular stenosis. The **arrows** point to the aortic valve commissures lich are tucked under the supravalvular tissue. LCA = left coronary ery; RCA = right coronary artery.

ne left ventricular-aortic gradients ranged from 40 to 170 m Hg. At surgery, a lateral aortotomy was performed ex-nding across the supravalvular stenosis into the noncoronary sp. Figure 2 demonstrates the supravalvular constriction both the hourglass (left panel) and hypoplastic forms (right nel). The posterior wall of the aorta and the noncoronary sp were removed for illustrative purposes. Note that the left d right coronary cusps are tucked under the stenosing su-avalvular ring (arrows). This cusp tuck results in apposition the margins of these cusps, which is seen angiographically the thick band during diastole. This band was present in preoperative angiograms in patients with supravalvular rtic stenosis. Figure 3 is a cross-sectional view from above e supravalvular constriction. The left and right coronary teries are labeled. Portions of the aortic valve cusps and the rtic valve commissures are tucked under the supravalvular embrane, as depicted by the arrows. Surgical repair included tensive resection of the supravalvular obstruction and in-rtion of a Dacron patch over the aortotomy. Figure 4 shows e results after surgery. The patch effectively relieved the pravalvular obstruction and mobilized the noncoronary sp. However, persistent anterior supravalvular tissue re-ained with portions of the left and right aortic cusps tucked der this tissue (arrow).

The completed external repair is shown in Figure 5.

**Surgical results:** Thirteen surgical survivors have been llowed up for 1 month to 12 years. Eleven patients, aged 15 28 years, are currently asymptomatic. One patient with an




**GURE 4.** Postoperative cross-sectional view demonstrating portions



**FIGURE 5.** Completed external repair illustrating the teardrop-shaped Dacron patch.

84 mm Hg gradient and normal coronary arteries underwent surgery at age 45. Exertional chest pain developed postoperatively. A stress thallium scan indicated an inferior perfusion defect immediately after exercise which resolved 4 hours later. Postoperative cardiac catheterization showed a reduction in gradient to 23 mm Hg. The right coronary artery could not be entered for selective injection and did not fill on aortic root injection, suggesting coronary ostial occlusion. Another patient who underwent surgery at age 49 had chest pain and shortness of breath postoperatively. She died from cancer at age 57.

There were 3 surgical deaths; all occurred in the early 1960s. Two of these patients had the hypoplastic form of supravalvular aortic stenosis.

Postoperative cardiac catheterization was performed in 8 patients 6 months to 12 years after surgery; all had reduction in the gradient between the left ventricle and aorta (Fig. 6). No significant supravalvular gradients were found. However, 4 patients had persistent gradients of 23 to 48 mm Hg at the

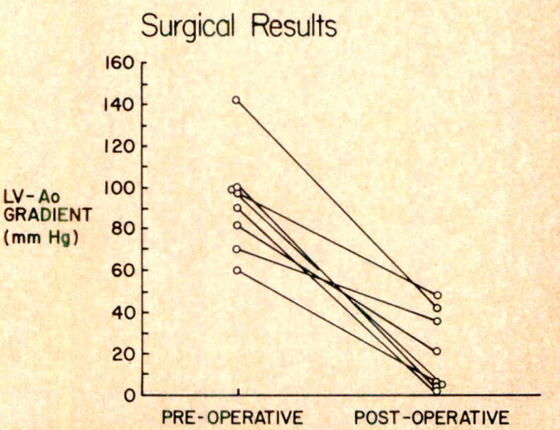



**FIGURE 6.** Pre- and postoperative gradients between the left ventricle

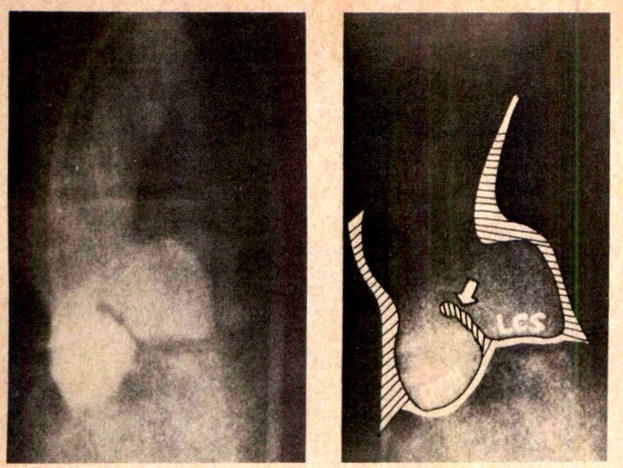



**FIGURE 7.** Postoperative aortic root angiogram in the anteroposterior projection demonstrating the thick band (**arrow**) between the right coronary sinus (RCS) and left coronary sinus (LCS). This patient had a 48 mm Hg gradient across the aortic valve but no supravalvular gradient.

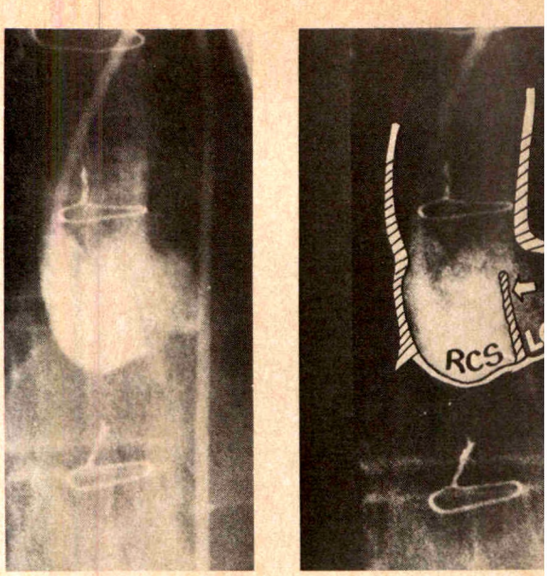



**FIGURE 8.** Postoperative aortic root angiogram in the anterop projection. The thick band is noted. This patient did not have a valve or a supravalvular gradient. LCS = left coronary sinus; right coronary sinus.

aortic valve level. Two of these patients had mild aortic insufficiency. All postoperative patients had a thick band between the right and left coronary sinuses, which was present preoperatively. This band was due to cusp tuck—the persistent attachment of portions of the aortic cusps to residual anterior supravalvular tissue. The band was present in all patients postoperatively, including those patients without a gradient between the left ventricle and aorta (Fig. 7 and 8).

## Discussion

Supravalvular aortic stenosis is a complex form of left ventricular outflow tract obstruction with distinctive morphologic features which influence the results of corrective surgery. Our study demonstrates that patch aortoplasty provides good postoperative results with asymptomatic patients for up to 12 years. However, residual abnormalities may remain, including gradients across the aortic valve and aortic valve insufficiency. These abnormalities appear related to the amount of attachment between the aortic valve cusps and residual anterior supravalvular tissue.

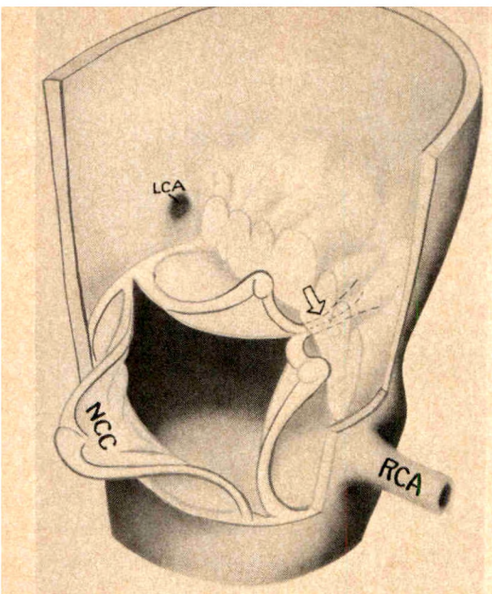
This attachment of the aortic valve leaflets to the supravalvular membrane—cusp tuck—has been recognized for years. In 1957, Cheu et al[1] described a crescent-shaped fibrous membrane above the aortic valve in a 37-year-old man. The right posterior aortic cusps were attached to the undersurface of the membrane. One year later, Burry[2] noted commissural fusion with a supravalvular ridge in a patient with morphologic features of Marfan's syndrome. Denie and Verheught[3] described a 25-year-old patient with angina who had fusion between all 3 aortic cusps at the very outer edge near the commissures. The left coronary artery originated from a blind pouch which was formed from the free margin of the left aortic cusp with the aortic wall. This pouch communicated with the free aortic lumen by a very narrow opening. Edwards,[4] in his classification of the pathology of supravalvular aortic stenosis, mentioned that up to one fourth of the cases have associated changes of the aortic valve cusps, most notably sions of portions of the cusps to the supravalvul nosis.

As surgical techniques improved, it became important to differentiate supravalvular aortic st from other forms of outflow tract obstruction. W viously emphasized the familial predisposition disorder, the clinical significance of the blood pr difference in the arms, and the attachment of the cusps to the supravalvular tissue.[5]

Patch aortoplasty has been the surgical proced choice for supravalvular aortic stenosis; howev modynamic abnormalities have been noted in p erative studies. Rastelli et al[6] observed that gra persisted after patch aortoplasty in 14 of 16 pa but the site of the gradient was not mentioned. et al[7] studied 6 patients postoperatively and did n a supravalvular gradient, but recorded pressu ferences between the left ventricle and aorta cons with valvular or possibly subvalvular stenosis. et al[8] found residual gradients in 5 postoperati tients, 2 of which occurred at the valvular level.

Doty et al[9] pointed out that patch aortoplasty in an asymmetric surgical repair and occasionall not relieve outflow tract obstruction. They desig symmetric form of reconstruction in which the ste supravalvular ring is divided at 2 points, all lengthening of 2 aortic cusps with better valve fur A reduction in the gradient between the left ve and the aorta was noted on intraoperative me ments; however, postoperative cardiac catheteriz were not reported. This type of repair may be n in some cases with marked fusion of the coronary to the supravalvular tissue.

There may be other reasons for valvular gra after surgical repair. Thirty % of aortic valves




**RE 9.** Artist's depiction of persistent attachment of portions of the valve (**arrow**) to residual anterior supravalvular tissue which has partly resected. The noncoronary cusp (NCC) has been mobilized e Dacron patch (not shown), which is inserted posteriorly. LCA = oronary artery; RCA = right coronary artery.

ed to be thickened in patients with supravalvular ic stenosis. Cheevers, in the original description of avalvular aortic stenosis, noted that the aortic valve be calcified; hence, valvular gradients may be due ntrinsic valvular disease.[10] Patients with a combi- on of supravalvular aortic stenosis and intrinsic ic valve disease represent a more complex form of disease, and patch aortoplasty combined with val- tomy or aortic valve replacement may be necessary chieve satisfactory results.

he results of this study show that patch aortoplasty fective in reducing supravalvular obstruction but portions of the aortic valve remain attached to re- al anterior supravalvular membrane (Fig. 9). This tuck causes traction on the aortic valve leaflets and osition of the valve margins, which has the angio- hic appearance of a thick band between the right left coronary cusps (Fig. 7 and 8). This results in ic valvular abnormalities manifested by persistent lients across the aortic valve with or without aortic e insufficiency.

valvular gradient was operated on 12 years ago. The patients operated on within the last few years have minimal, if any, aortic valvular gradients despite angiographic evidence of cusp tuck. Whether there is progressive aortic valve dysfunction due to the persistent attachment of the anterior portions of the aortic valve to the residual anterior supravalvular membrane or whether surgery has improved with more aggressive resection of the anterior tissue is not known at this time. Serial catheterizations, precise intraoperative observations, and detailed pathologic examinations will be needed to provide more information.

*In summary*, our 20-year experience with supravalvular aortic stenosis demonstrates a wide range of clinical features which allow differentiation from other forms of left ventricular outflow tract obstruction. Attachment between the supravalvular tissue and portions of the aortic valve—cusp tuck—causes distinctive angiographic abnormalities and influences the results of corrective surgery. Patch aortoplasty for supravalvular aortic stenosis produces good clinical results and a reduction in the pressure difference between the left ventricle and ascending aorta. However, residual valvular abnormalities remain, including aortic stenosis and aortic insufficiency. These abnormalities need to be recognized to assist in the long-term management of these patients.

**Acknowledgment:** We thank J. Thomas Targoss, MS, DDS, for illustrations, and Ruth Long and Karen Hibbard for their assistance in the preparation of this manuscript.

## References

1. **Cheu S, Fiese M, Hatayama E.** Supra-aortic stenosis. Am J Clin Pathol 1957;28:293–300.
2. **Burry AF.** Supra-aortic stenosis associated with Marfan's syndrome. Br Heart J 1958;20:143–146.
3. **Denie J, Verheught A.** Supravalvular aortic stenosis. Circulation 1958; 18:902–908.
4. **Edwards J.** Pathology of left ventricular outflow tract obstruction. Circulation 1965;31:586–599.
5. **Wooley CF, Hosier DM, Booth RW, Molnar W, Sirak HD, Ryan JM.** Supravalvular aortic stenosis. Clinical experience with four patients including familial occurrence. Am J Med 1961;31:717–725.
6. **Rastelli GC, McGoon DC, Ongley PA, Mankin HT, Kirklin JW.** Surgical treatment of supravalvular aortic stenosis. J Thorac Cardiovas Surg 1966;51:873–882.
7. **Weisz D, Hartmann AF, Weldon CS.** Results of surgery for congenital supravalvular aortic stenosis. Am J Cardiol 1976;37:73–77.
8. **Keane JF, Fellows KE, LaFarge CG, Nadas AS, Bernhard WF.** The surgical management of discrete and diffuse supravalvular aortic stenosis. Circulation 1976;54:112–117.
9. **Doty DB, Polansky DB, Jenson GB.** Supravalvular aortic stenosis. Repair by extended aortoplasty. J Thorac Cardiovas Surg 1977;74:362–371.
10. **D'Cruz IA, Miller RA.** Norman Cheevers: a description of the congenital absence of pulmonary valves and supravalvular aortic stenosis in the 1840s. Br Heart J 1964;26:723–725.

# Radionuclide Stroke Count Ratios for Assessment of Right And Left Ventricular Volume Overload in Children

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**The ratio of left ventricular to right ventricular stroke counts measured by radionuclide angiography has been used in adults to estimate the severity of left-sided valvular regurgitation. The validation of this technique in children for assessment of right and left ventricular volume overload is reported herein. Radionuclide stroke count ratios in 60 children aged 0.5 to 19 years (mean 11) were determined. Based on their diagnoses, the patients were divided into 3 groups: (1) normal—40 patients with no shunts or valvular regurgitation, (2) left ventricular volume overload—13 patients with mitral or aortic regurgitation, or both, and (3) right ventricular volume overload—7 patients, 2 with severe tricuspid regurgitation, 3 with atrial septal defects, and 2 with total anomalous pulmonary venous drainage. The radionuclide stroke count ratio clearly differentiated these groups ($p < 0.05$): normal patients had a stroke count ratio of 1.04 ± 0.17 (mean ± 1 standard deviation), the left ventricular volume overload group had a stroke count ratio of 2.43 ± 0.86, and the right ventricular volume overload group had a stroke count ratio of 0.44 ± 0.17. In 22 of our 60 patients, radionuclide stroke count ratios were compared with cineangiographic stroke volume ratios, resulting in a correlation coefficient of 0.88. It is concluded that radionuclide ventriculography is an excellent tool for qualitative and quantitative assessment of valvular regurgitation in children.**

The ratio of the left ventricular stroke output to right ventricular stroke output (stroke volume ratio) provides an index of left ventricular volume overload in patients with aortic or mitral regurgitation.[1–6] This ratio has been estimated noninvasively in adults with radionuclide ventriculography.[3–6] However, the use of this radionuclide technique in assessing right ventricular volume overload in children is unknown. For these reasons, we now report our experience with the radionuclide stroke count ratio in children for the assessment of right and left ventricular volume overload. The radionuclide stroke count ratio is validated by comparison with the cineangiographic stroke volume ratio.

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## Methods

From June 1980 to August 1981, we obtained equilibrium radionuclide ventriculograms in 88 children. Twenty-eight of these patients were excluded from the study for the following reasons: (1) inadequate blood pool labeling, septal definition, or both (6 patients); (2) single ventricle anatomy (5 patients); and (3) bidirectional shunts, regurgitant lesions, or both, affecting both ventricles (17 patients). The remainder of our patients (60 children) were included in this study. These children were assigned to 1 of 3 categories based on clinical and catheterization findings: (1) Normal—40 children were assigned to this category because they had no shunts or valvular regurgitation. (2) Left ventricular volume overload—13 children were assigned to this category based on clinical and catheterization findings of aortic or mitral regurgitation. (3) Right ventricular volume overload—7 children were assigned to this category based on clinical and catheterization findings of tricuspid regurgitation, atrial septal defect, or total anomalous pulmonary venous drainage.

Table I further characterizes our patients. The diagnoses are diverse, with most children in the normal group having postoperative repair of cardiac defects (tetralogy of Fallot,

**BLE I Patient Diagnoses by Category in the 60 Patients Studied***

| Diagnoses | n |
|---|---|
| Normal (40 patients)† | |
| ralogy of Fallot (PO) | 12 |
| ransposition (PO) | 6 |
| tic stenosis | 5 |
| monary stenosis | 4 |
| hythmia | 4 |
| ial septal defect (PO) | 3 |
| tus excavatum | 2 |
| cellaneous‖ | 4 |
| Left Ventricular Volume Overload (13 Patients)‡ | |
| tic regurgitation | 8 |
| diomyopathy (mitral regurgitation) | 5 |
| Right Ventricular Volume Overload (7 Patients)§ | |
| ial septal defect | 3 |
| uspid regurgitation | 2 |
| al anomalous pulmonary venous drainage | 2 |

Ages 0.5 to 19 years (mean 11), weight 6 to 70 kg (mean 36).
Ages 1 to 19 years (mean 11), weight 10 to 70 kg (mean 36).
Ages 0.5 to 19 years (mean 11), weight 6 to 70 kg (mean 41).
Ages 0.5 to 15 years (mean 10), weight 5 to 43 kg (mean 28).
Miscellaneous patients: partial anomalous pulmonary venous inage (PO), Type II hyperlipidemia, atrioventricular canal (PO), and ral stenosis.
O = postoperative.

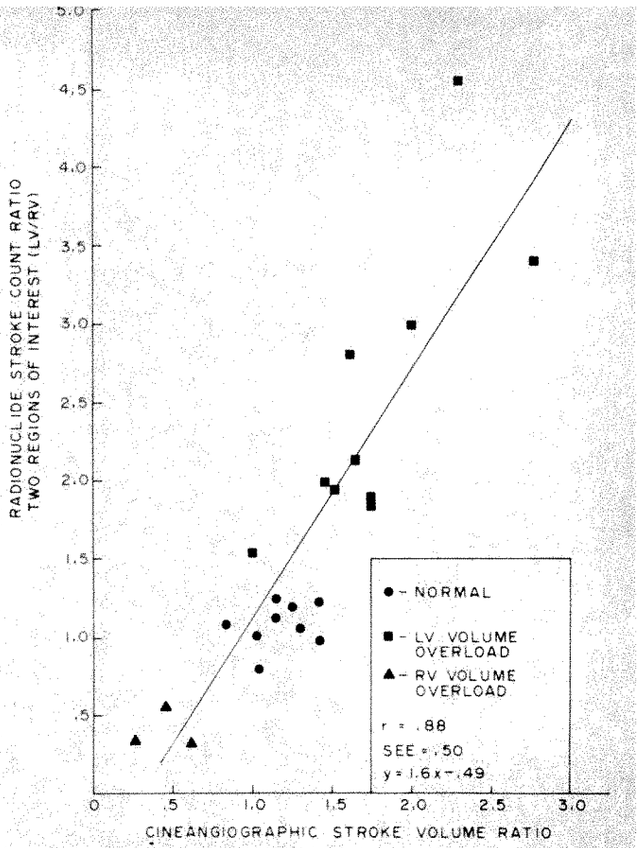



**FIGURE 1.** Cineangiographic stroke volume ratios are compared with radionuclide stroke count ratios using 2 separately determined regions of interest (end-diastole and end-systole). LV = left ventricle; r = correlation coefficient; RV = right ventricle; SEE = standard error of the estimate.

ransposition of the great arteries, and atrial septal defect). e right and left ventricular volume overload groups were nprised of patients who had not undergone previous sury. Although we had a few 19-year-old patients, the mean for the total group of 60 children was 11 ± 4.9 years (mean tandard deviation).

Multiple-gated equilibrium radionuclide studies were formed for diagnostic purposes in all patients. Informed nsent was obtained before performing these studies. Diagtic cardiac catheterizations were done in 22 of our 60 pants within 1 week of the radionuclide study, allowing ranuclide-cineangiographic correlations.

Standard techniques were used for collection of radionule studies, with in vivo labeling of red blood cells using an ult dose of 20 mCi, adjusted downward for children based their body surface area.[7,8] We have previously described collection and analysis methods.[9] Right and left ventricr regions at end-diastole and end-systole were identified hand using criteria similar to that described by Maddahi l.[10] The following formula was used to calculate the stroke nts: Ventricular stroke counts = (end-diastolic counts − kground counts) − (end-systolic counts − background nts). The ratio of left ventricular stroke counts to right tricular stroke counts was then determined for each ge.

From cineangiograms, right and left ventricular stroke ume ratios were determined using previously published thods. Volumes were calculated from biplane images for patients, using the area-length method for the left ventri-[11] and Simpson's rule for the right ventricle.[12] The ratio of left ventricular to right ventricular stroke volume was then culated.

Radionuclide ventricular stroke count ratios were determed in 5 patients by 1 observer on 2 different occasions to ess intraobserver variability. In addition, a second observer ependently performed the region identification for the e 5 patients (interobserver variability). All observers were blinded to each other's results as well as to the cineangiographic results.

Stroke count ratios from the radionuclide images were statistically compared to cineangiographic stroke volume ratios using linear regression analysis. Intraobserver and interobserver variation was assessed by calculating the absolute difference between observer 1's first determination, and each subsequent determination (observer 1's second determination and observer 2's determination). These absolute differences for each patient were then expressed as a percentage of observer 1's first determination. The mean values for stroke count ratios in each of our 3 patient groups were compared by 1-way analysis of variance followed by Student-Neuman-Keul's test. The level of statistical significance was chosen as $p < 0.05$.

## Results

Assessment of intra- and interobserver variability in the determination of radionuclide stroke count ratios disclosed differences of 24 ± 14% and 32 ± 19%, respectively. Despite this variability, we demonstrated a good correlation between radionuclide studies and cineangiographic studies. Figure 1 shows the radionuclide cineangiographic comparison (r = 0.88). The radionuclide technique generally overestimated the actual (cineangiographic) stroke volume ratio (radionuclide

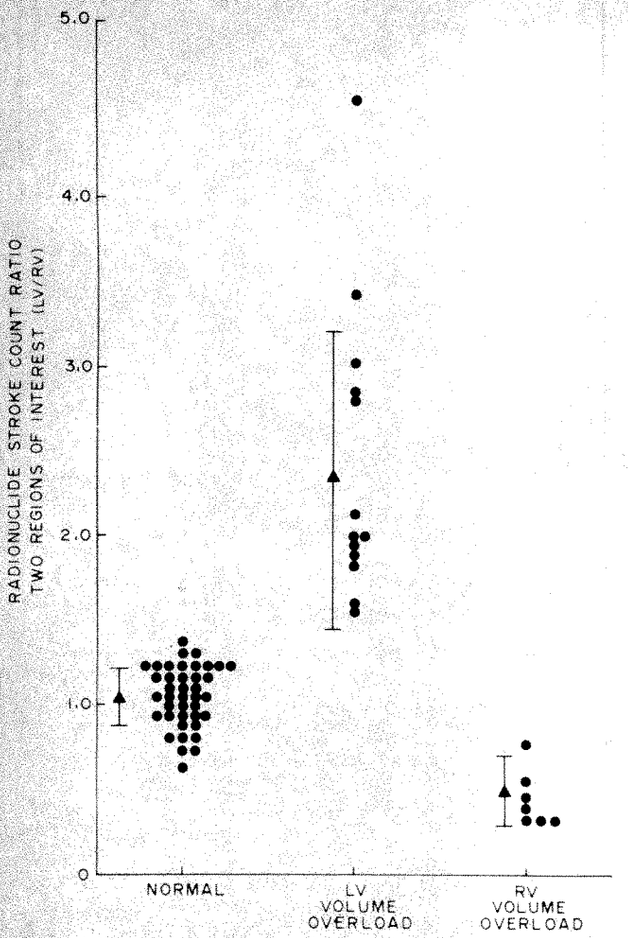



**FIGURE 2.** Radionuclide stroke count ratios in our 3 patient groups. **Error bars** encompass 1 standard deviation above and below the mean. **Circles** represent individual values, **triangles** mean values. LV = left ventricle; RV = right ventricle.

stroke count ratio = 1.6 × cineangiographic stroke volume ratio − 0.49) (Fig. 1).

Figure 2 shows the radionuclide stroke count ratios for our 3 patient groups. The mean stroke count ratio for the normal group was 1.04 ± 0.17 (mean ± standard deviation). The mean stroke count ratio for the left ventricular volume overload group (2.43 ± 0.86) was significantly greater than the normal group ($p < 0.05$). Furthermore, the mean stroke count ratio for the right ventricular volume overload group (0.44 ± 0.17) was significantly less than for the normal group ($p < 0.05$).

Table II summarizes the normal range for radionuclide stroke counts. From the data in Figure 2, we defined a normal stroke count ratio as ranging from 0.70 to 1.38 (2 standard deviations below and above the mean). Only 1 of the 40 normal patients fell outside this range. This patient had had Mustard repair of D-transposition of the great vessels, and had a radionuclide stroke count ratio of 0.62. The right ventricular-right atrial border was difficult to define on the radionuclide image in this patient and may have led to inaccuracy in the estimation of the stroke count ratio.

**TABLE II Radionuclide Stroke Count Ratios**

| Groups | Patients Outside Normal Range* | Patients Within Normal Range* |
|---|---|---|
| Normal | 1/40 | 39/40 |
| LV volume overload | 13/13 | 0/13 |
| RV volume overload | 6/7 | 1/7 |

* Normal range 0.70 to 1.38 (2 standard deviations to either side of the mean). LV = left ventricle; RV = right ventricle.

All patients in the left ventricular volume overload group had radionuclide stroke count ratios >1.38. In 1 patient from this group, the cineangiographic stroke volume ratio was 1.0 despite the subjective impression from the left ventricular angiogram of moderate mitral regurgitation and a large left atrium. The radionuclide stroke count ratio was 1.56, leading us to question the accuracy of the cineangiography determined stroke volume ratio in this particular patient.

Only 1 of the 7 patients with right ventricular volume overload had a radionuclide stroke count ratio within the normal range (0.77). This patient had total anomalous pulmonary venous drainage.

## Discussion

Both echocardiography and nuclear angiography have been used extensively for the evaluation of cardiac size and function in patients with left-sided valvular regurgitation.[13–17] However, only recently have there been attempts to actually quantitate the severity of valvular regurgitation by noninvasive techniques. Bommer et al[18] found that pulsed Doppler 2-dimensional echocardiography can be used to quantitate aortic regurgitation. In addition, several workers[6,19–21] have validated the equilibrium radionuclide technique for quantitation of valvular regurgitation, finding radionuclide-cineangiographic correlation coefficients of 0.72 to 0.95. This radionuclide technique estimates right and left ventricular stroke volumes by measuring the change in regional counts from end-diastole to end-systole. The severity of valvular regurgitation is then assessed by calculating a regurgitant index (left ventricular stroke counts divided by right ventricular stroke counts).

The previous work with radionuclide assessment of valvular regurgitation has been limited entirely to adult patients with left-sided valvular regurgitation. We now report our validation of this technique in children. In addition, we have used this method to evaluate several patients with right-sided volume overload.

Several potential methodologic problems and sources of error are inherent in this radionuclide technique. The major difficulty centers around the appropriate identification of the ventricular regions of interest. Adequate septal visualization must be obtained in order to separate and identify each ventricle. Variable red blood cell labeling, motion artifact, and unusual ventricular geometry and position in children with congenital heart disease can make septal identification more difficult than in adult patients. Six patients with inadequate septal visualization were excluded from this study.

Separation of ventricular from atrial activity may be difficult with the equilibrium radionuclide technique. This problem is of additional concern in the current study, because some diseases we are interested in evaluating (tricuspid and mitral regurgitation) may increase right or left atrial size and thus increase overlap of atrial and ventricular activity. If atrial overlap is greatest on the end-systolic image, this error would tend to decrease the estimated stroke counts for the affected ventricle, resulting in an underestimation of the severity of valvular regurgitation. In our patients, we attempted to improve atrial-ventricular separation by collecting studies from a left anterior oblique view with 5 to 15° caudal tilt. Careful study of playback images was also quite helpful in identifying the atrial ventricular border. We do not believe that there was any systematic error in the estimation of the stroke counts from right or left ventricle, because the normal group had a mean stroke count ratio near unity (1.04). There is, however, a moderate degree of intra- and interobserver variability in this measurement, which may reflect the multiple regions of interest one must identify in order to derive the stroke count ratio.

Lam et al[22] validated stroke count ratios in normal patients and those with left-sided volume overload. They found discordant radionuclide-cineangiographic results in 12 of 100 patients, and correlated this discrepancy with severe left ventricular dysfunction or mitral valve prolapse. We found discrepant results in 2 patients (Table II). One of these patients had had Mustard repair of D-transposition and had a radionuclide stroke count ratio of 0.62, despite clinical and catheterization findings indicating no significant shunt or valvular insufficiency. No distinct atrial-ventricular disorder could be appreciated in this patient, and we hypothesize that atrial activity overlapped with the left ventricle, reducing the stroke count ratio. Five other patients with D-transposition and poor atrial separation had stroke count ratios within the normal range. The second patient with discordant results had total anomalous pulmonary venous drainage. Although the radionuclide stroke count ratio was 0.77, it was within the normal range. A large portion of right atrial activity in this patient may have been included in the right ventricular end-systolic frame and excluded from the end-diastolic frame, artificially increasing the stroke count ratio. We had 1 patient with mitral valve prolapse, and 5 patients with severe cardiomyopathy. Radionuclide, catheterization, and clinical findings were in agreement in these patients.

Despite these methodologic considerations, we found good correlation between radionuclide and cineangiographic estimates of the stroke volume ratio ($r = .88$). Furthermore, the radionuclide technique clearly identified and separated patients with left ventricular volume overload from patients with no volume overload. Severe right ventricular volume overload could also be detected in 6 of 7 patients. We have not attempted to evaluate children with volume overload of both ventricles. In this situation, the radionuclide technique might provide an indication of which ventricle was more severely overloaded.

We conclude that the equilibrium radionuclide technique provides a useful noninvasive tool for qualitative and quantitative assessment of right and left ventricular volume overload in children with congenital heart disease.

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## References

1. **Boucher C, Okada R, Pohost G.** Current status of radionuclide imaging in valvular heart disease. Am J Cardiol 1980;46:1153–1163.
2. **Baxter R, Becker L, Alderson, P. Rigo P, Wagner H, Weisfeldt M.** Quantification of aortic valvular regurgitation in dogs by radionuclide imaging. Circulation 1979;60:Suppl II:II-267.
3. **Henze E, Wisenberg G, Schelbert H.** Changes in regurgitant fraction and right and left ventricular function in aortic and mitral insufficiency in response to exercise. Circulation 1980;62:Suppl III:III-230.
4. **Konstam M, Wynne J, Holman L, Brown E, Neill J, Kozlowski J.** Quantitation of left ventricular output in patients with and without left-sided valvular regurgitation using equilibrium radionuclide ventriculography. Am J Cardiol 1981;47:454.
5. **Gandsman E, Baugh E, North D, Shulman R.** The ventricular stroke volume ratio: requirements for accurate quantitation. Circulation 1979;60:Suppl II:II-62.
6. **Rigo P, Alderson PO, Robertson RM, Becker LC, Wagner HN.** Measurement of aortic and mitral regurgitation by gated cardiac blood pool scans. Circulation 1979;60:306–312.
7. **Hegge F, Hamilton G, Larson S, Ritchie J, Richards P.** Cardiac chamber imaging: a comparison of red blood cells labeled with Tc-99m in vitro and in vivo. J Nucl Med 1978;19:129–134.
8. **Webster E, Alpert N, Brownell G.** Radiation dose in pediatric nuclear medicine and diagnostic x-ray procedures. In: James AE, Wagner H, Cooke R, eds. Pediatric Nuclear Medicine, New York: WB Saunders, 1974:34.
9. **Parrish M, Graham T, Born M, Jones J.** Radionuclide evaluation of right and left ventricular function in children: validation of methodology. Am J Cardiol 1982;49:1241–1247.
10. **Maddahi J, Berman DS, Matsuoka DT, Wadman AD, Forrester JS, Swan HJC.** Right ventricular ejection fraction during exercise in normal subjects and in coronary artery disease patients: assessment by multiple gated equilibrium scintigraphy. Circulation 1980;62:133–140.
11. **Sandler H, Dodge H.** Use of single plane angiocardiograms for the calculation of left ventricular volume in man. Am Heart J 1968;75:325–337.
12. **Graham T, Jarmakani J, Canent R, Morrow M.** Right ventricular volume determination in children. Circulation 1973;47:144–156.
13. **Boucher C, Bingham J, Osbakken M, Okada R, Strauss H, Block P, Levine F, Phillips H, Pohost G.** Early changes in left ventricular size and function after correction of left ventricular volume overload. Am J Cardiol 1981;47:991–1003.
14. **Dehmer G, Firth B, Hillis L, Corbett J, Lewis S, Parkey R, Willerson J.** Alterations in left ventricular volumes and ejection fraction at rest and during exercise in patients with aortic regurgitation. Am J Cardiol 1981;48:17–27.
15. **Lawrence R, Mena I, Jengo J, Walkinshaw M, Nelson R.** Noninvasive evaluation of late left ventricular function after aortic valve replacement. J Thorac Cardiovasc Surg 1980;79:504–512.
16. **Borer J, Rosing D, Kent K, Bacharach S, Green M, McIntosh C, Morrow A, Epstein S.** Left ventricular function at rest and during exercise after aortic valve replacement in patients with aortic regurgitation. Am J Cardiol 1979;44:1297–1305.
17. **Kotler M, Mintz G, Parry W, Segal B.** M-mode and two dimensional echocardiography in mitral and aortic regurgitation: pre- and postoperative evaluation of volume overload of the left ventricle. Am J Cardiol 1980;46:1144–1152.
18. **Bommer W, Mapes R, Miller L, Mason D, Demaria A.** Quantitation of aortic regurgitation with two-dimensional Doppler echocardiography. Am J Cardiol 1981;47:412.
19. **Urquhart J, Patterson R, Packer M, Goldsmith S, Horowitz S, Litwak R, Gorlin R.** Quantification of valve regurgitation by radionuclide angiography before and after valve replacement surgery. Am J Cardiol 1981;47:287–291.
20. **Bouch E, Gandsman E, North D, Shulman R.** Gated radionuclide angiographic evaluation of valve regurgitation. Am J Cardiol 1980;46:423–428.
21. **Sorensen S, O'Rourke R, Chaudhuri T.** Noninvasive quantitation of valvular regurgitation by gated equilibrium radionuclide angiography. Circulation 1980;62:1089–1097.
22. **Lam W, Pavel D, Byrom E, Sheikh A, Best D, Rosen K.** Radionuclide regurgitant index: value and limitations. Am J Cardiol 1981;47:292–298.

# Pulmonary Vascular Disease in Secundum Atrial Septal Defect in Childhood

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**Pulmonary vascular structure was analyzed in the lungs of 10 patients with a secundum atrial septal defect (ASD) in whom pulmonary hypertension had developed. Four patients were aged 6 months or less, 5 were aged 2 to 9 years, and 1 was 21 years old. Pulmonary vascular structure was analyzed using lung biopsy tissue in 5 and autopsy material in the other 5. All the infants presented with heart failure and all had a marked increase in pulmonary arterial smooth muscle; only 1 infant survived surgery. Of the 5 older children, 1 presented with cyanosis, but in the rest the ASD was incidental to the presentation. Three patients had severe pulmonary vascular disease, similar to that seen in adults with a hypertensive ASD. Only 2 older children underwent successful surgery. In 1 child and in the 1 adult, the severity of the pulmonary vascular disease precluded surgery. The ASD was closed in 8 patients, but only 3 survived. Pulmonary hypertension develops rarely in secundum ASD in childhood.**

Most children with a secundum ASD are asymptomatic. Rarely, cardiac failure develops in young children; in such cases the severity of pulmonary hypertension is frequently greater than that found in the asymptomatic older child.[1–4] Conservative management may not be successful and the operative mortality is greater than in older children with an ASD.[2] In the pulmonary circulation, the structural changes found in older patients are usually restricted to medial hypertrophy and slight intimal proliferation, although plexiform lesions can occur in the presence of severe pulmonary hypertension.[5] To understand the structural basis of pulmonary hypertension in ASD and its relation to age, the clinical findings and pulmonary vascular changes were studied in 10 patients aged 3.5 months to 21 years.

## Methods

Six male and 4 female patients were studied (Table I). Six patients presented during the first 6 months of life and all except Patient 7 had signs of congestive heart failure and failure to thrive (Table I). Patient 1 was cyanotic when he presented at 6 weeks of age. All had an ejection systolic murmur at the left sternal border, and in all except Case 7 the pulmonary component of the second heart sound was accentuated. Patient 6 also had the soft continuous murmur of a small patent ductus arteriosus in the left infraclavicular region. The remaining 4 patients presented between 2 and 16 years of age. Patient 5 presented with cyanosis at 2 years, but in the other patients the presence of an ASD was incidental. All these older patients had an ejection systolic murmur in the pulmonary area and wide splitting of the second heart sound with accentuation of the pulmonary component, but only 2 had an rsR′ pattern in the right precordial leads of the electrocardiogram. In all 10 patients the electrocardiogram showed sinus rhythm with right ventricular hypertrophy. The chest radiogram showed slight cardiac enlargement with pulmonary plethora in all except Cases 5, 7, and 10. In Cases 5 and 10, the proximal pulmonary arteries appeared dilated with pruning of the peripheral arteries.

All patients underwent a cardiac catheterization study except Patient 9, in whom the diagnosis was established by 2-D echocardiography (Table II). All patients had pulmonary hypertension, but this was most severe in the 5 patients catheterized during the first 2 years of life and in the 19-year-old man. Case 9 had significant pulmonary hypertension after closure of the ASD. In all except Case 10 there was a left-to-right shunt at the atrial level with a pulmonary: systemic flow ratio of 1.3 to 3.3:1. Pulmonary arteriolar resistance was 4 to 16 units/$m^2$.

An open lung biopsy was performed in 5 patients, immediately after the cardiac catheterization study in 2 patients, 2 years after the study in Patient 10, and at operation in the remaining 2 patients (Table I).

The 5 symptomatic infants were given intensive medical treatment, but only Patient 6 responded satisfactorily. For the entire group, the ASD was closed in 8 patients. The time between presentation and operation was <6 months except in Cases 6 and 7. The ASD was closed successfully in only 3 children aged 7 months, 7 years, and 9 years. Five children died at or soon after operation. The 2 remaining patients did not undergo surgical treatment because the lung biopsy showed severe obliterative pulmonary vascular disease.

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**TABLE I Clinical Data**

| Case | Sex | Age at Presentation | Presentation | Post-Catheter Diagnosis | Age at Biopsy or Death | Source of Lung Tissue |
|---|---|---|---|---|---|---|
| 1 | M | 6 wk | Cyanosis, CF, FT | ASD | 3 mo | A |
| 2 | F | 12 days | CF | ASD | 5 mo | B |
| 3 | M | 5 mo | CF, RTI | ASD | 6 mo | A |
| 4 | F | 6 days | CF, FT, RTI | ASD, small VSD | 5 mo | A+I |
| 5 | F | 2 yr | Cyanosis | ASD | 2 yr | A+I |
| 6 | F | 3 mo | CF, FT | ASD, small PDA | 5 yr | A |
| 7 | M | 1 wk | Phocomelia | ASD | 5 yr | B |
| 8 | M | 7 yr | Incidental | ASD | 7 yr | B |
| 9 | M | 9 yr | RTI | ASD | 9 yr | B |
| 10 | M | 16 yr | Bonnevie-Ullrich syndrome | ASD | 21 yr | B |

A = uninjected autopsy material; A+I = uninjected and injected autopsy material; B = biopsy; CF = cardiac failure; FT = failure to thrive; RTI = respiratory tract infections.

No patient had coarctation of the aorta and none had an obstructive left heart abnormality. The mitral valve was normal at autopsy in 5 cases and at operation in 3. In the remaining 2 cases, there was no auscultatory evidence of mitral valve dysfunction; left ventricular cineangiography was normal in both.

Thus, in 8 patients an isolated secundum ASD was the only congenital malformation of the heart or great vessels and in the remaining 2 patients it was the only significant malformation.

**Pathologic preparation and examination:** The lung tissue examined was obtained by biopsy in 5 cases and at autopsy in the remaining 5 (Table I). Uninjected tissue was analyzed using quantitative morphometric techniques in all 10 cases. In 2 of the autopsied cases, a piece of lung tissue was removed from the specimen and the pulmonary arteries were then injected with a barium-sulfate gelatin mixture; in these cases, both injected and uninjected tissue was analyzed.[6,7] The lungs of the 2 injected specimens were radiographed, and on the arteriograms the lumen diameter of the preacinar arteries was measured at 25% intervals along the pathway from hilus to pleural surface. Paraffin-embedded 4 $\mu$m sections were stained with Miller's elastic stain, with hematoxylin and eosin, and with Perls' stain for iron. In the injected specimen of Case 5, the artery of the anterior segment of the left upper lobe was reconstructed from hilus to pleural surface by analysis of step and serial sections. Microscopically, the following features of peripheral arterial structure were studied: (1) The external diameter and medial thickness was measured in approximately 100 vessels in each injected specimen and in all the arteries present in a biopsy specimen, and the percent arterial medial thickness was calculated for each vessel: Percent arterial medial thickness = (2 × wall thickness/external diameter) ×100. The arteries were then divided into size ranges and the mean percent medial thickness was calculated for each size range. (2) Where a small artery accompanies a small airway it can be characterized by reference to the type of airway it accompanies. In each uninjected specimen, the structure of the arterial wall, whether muscular, partly muscular, or nonmuscular, was described at each airway level; in this way the degree of extension of muscle along the arterial pathway was established. Also, the external diameter of all arteries at each airway level was measured and the mean calculated. (3) The number of arteries and alveoli were counted in the same area of lung section and the result expressed as a ratio: this made allowance for any difference in the degree of inflation in various lungs. (4) A qualitative assessment of the appearance of the arteries at each airway level was made.

**TABLE II Cardiac Catheterization Data**

| | | Pressure (mm Hg) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Case | Age at Catheter | RA Mean | LA Mean | PA | LV | Qp/Qs | Rp (units/m$^2$) | Age at Operation | Outcome | Diameter of Defect (cm) |
| 1 | 3 mo | 4 | 4 | 70/30 | 80/0 | 2:1 | 4 | 3 mo | Died | 1 |
| 2 | 5 mo | 8 | 9 | 66/21 | 80/18 | 1.5:1 | 9.4 | 7 mo | Well | . . . |
| 3 | 5 mo | 6 | 6 | 65/20 | 65/5 | 2.6:1 | 5.6 | 6 mo | Died | 1.5 |
| 4 | 5 mo | 4 | 4 | 70/20 | 90/0 | 2.0:1 | * | 5 mo | Died | 1.5 |
| 5 | 2 yr | . . . | 5 | 68/35 | 86/8 | 3.3:1 | 16.5† | 2 yr | Died | 1.8 |
| 6 | 4 yr | 2 | 2 | 40/20 | 100/8 | 2.0:1 | 4.5 | 5 yr | Died | 1.8 |
| 7 | 5 yr | 5 | 5 | 61/32 | 92/0 | 1.3:1 | 15.5 | . . . | Alive | . . . |
| 8 | 7 yr | 6 | 6 | 60/25 | 110/6 | 1.6:1 | 4 | 8 yr | Well | 2 |
| 10 | 19 yr | 6 | 7.5 | 80/25 | 100/0 | 0.66:1 | 9.5 | . . . | Alive | . . . |
| | | | | | Postoperative | | | | | |
| 9 | . . . | 5 | 3 | 60/35 | 100/0 | . . . | . . . | 9 yr | Alive | 3 |

* Calculations unreliable due to pulmonary venous desaturation. † Rp decreased to 8 units/m$^2$ on inhalation of 100% oxygen. This was the only patient in whom pulmonary blood flow was measured. LV = left ventricular; PA = pulmonary arterial; RA = right atrial; Rp = pulmonary arteriolar resistance.

Normal data on uninjected lung tissue was obtained by analyzing postmortem material from 13 children who died without cardiopulmonary disease at 3 months to 9 years of age. Mean percent arterial medial thickness did not differ significantly in children of different ages, and therefore for this assessment the results were pooled. The mean external diameter and the proportion of nonmuscularized, partly muscularized, and entirely muscularized arteries accompanying each type of peripheral airway was determined in 9 normal cases and the alveolar-arterial ratio in 7.

## Results

**Arteriograms:** In Patient 4, aged 6 months, the lumen diameter of the preacinar arteries was increased from the hilus to the pleural surface and was greater than is normal at 2 years of age. The subsegmental and more peripheral arteries were tortuous. The background haze of small arteries was normal. By contrast, in Patient 5, aged 2 years, the arteries were smaller than is normal at 10 months of age. The peripheral arteries were tortuous and many anastomoses between the pulmonary arteries were seen at the pleural surface. An abnormal, fluffy haze surrounded each subsegmental artery and there were intervening zones without a haze, suggesting failure of small lateral branches to fill with contrast material.

### Qualitative Assessment

**Arterial wall structure:** The microscopic appearance of the pulmonary arteries was similar in the 4 patients aged 3 to 6 months (Cases 1 to 4), and consisted of an increase in muscularity of both pre- and intraacinar arteries. The normally muscularized preacinar, terminal, and respiratory bronchiolar arteries showed an increase in wall thickness, and muscle was present in more peripheral arteries than normal—in arteries accompanying alveolar ducts and lying within the alveolar walls (Fig. 1). Intimal proliferation was seen in several respiratory bronchiolar arteries in Case 2.

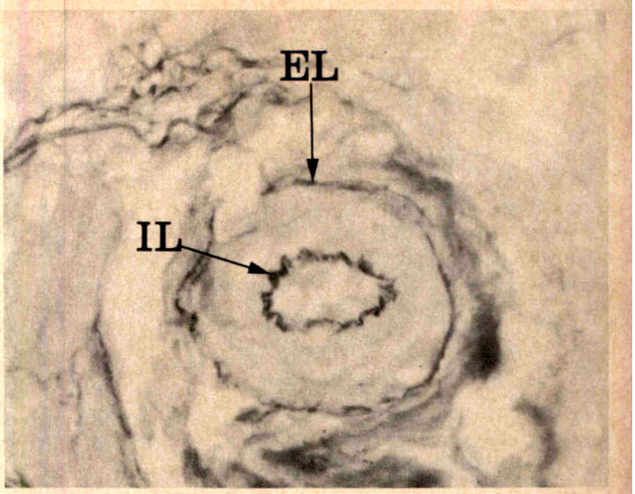



**FIGURE 1.** Photomicrograph of an artery accompanying an alveolar duct in Case 1, showing a thick media lying between internal (IL) and external (EL) elastic laminae. (Magnification ×982, reduced 22%.) Stain for this and subsequent photomicrographs: Miller's elastic stain counterstained with van Gieson's stain.

In the 6 older children, the structural changes were less uniform. Changes were least severe in Cases 6 and 8.

In Patient 5, severe pulmonary vascular disease was present at 2 years of age. In random and serial sections muscular preacinar arteries with intimal proliferation and fibrosis gave rise to dilated, thin-walled saccular branches whose lumens were almost obstructed by intimal proliferation at origin from the parent branches (Fig. 2, left). Terminal and respiratory bronchiolar ar-

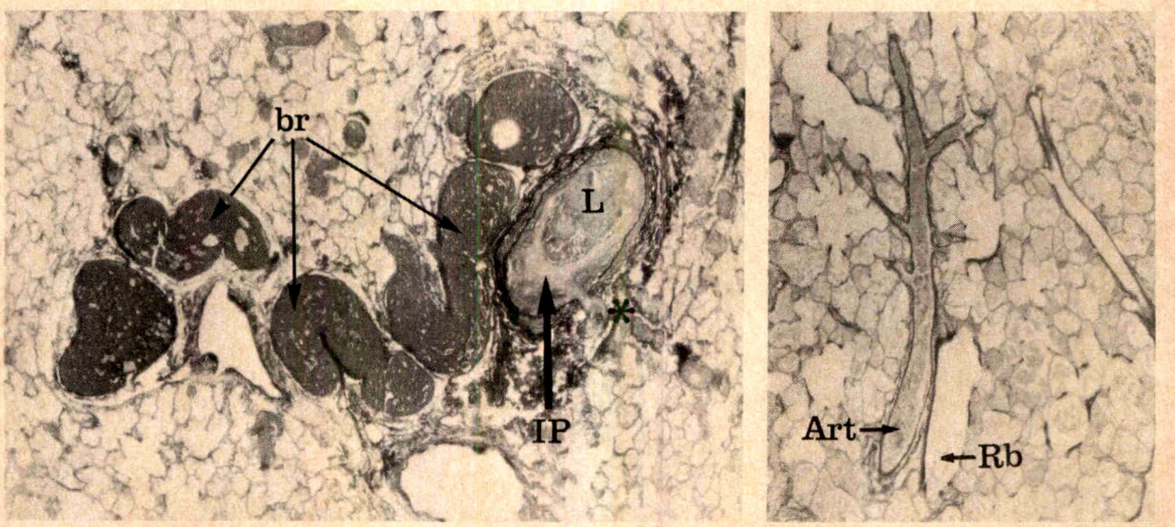



**FIGURE 2.** Photomicrographs of 2 sections of a serial reconstruction of the injected pulmonary artery to the anterior segment of the left upper lobe in Case 5. **Left,** a preacinar artery, with a lumen (L) narrowed by intimal proliferation and thin-walled branches (br). One branch (**asterisk**) is obstructed at its origin by intimal proliferation (IP). **Right,** the preacinar artery on the **left** has become a thin-walled artery (Art) accompanying a respiratory bronchiolus (Rb). (Magnifications ×61.7, reduced 36%.)

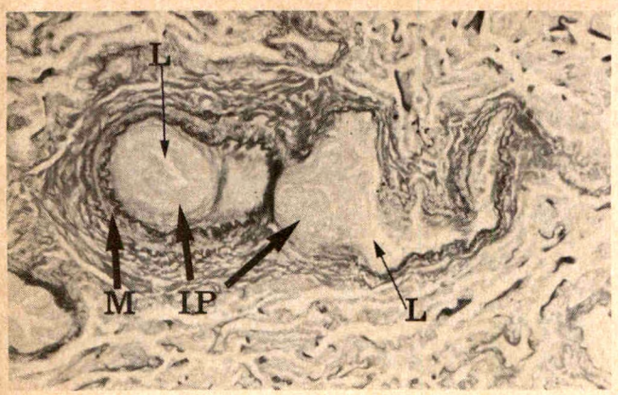



**FIGURE 3.** Photomicrograph of a small preacinar artery in Case 7, showing narrowing of the lumen (L) by intimal proliferation (IP). M = media. (Magnification ×216, reduced 40%.)

teries contained only a thin layer of muscle cells (Fig. 2, right). The more peripheral alveolar duct and alveolar wall arteries did not generally contain muscle and appeared fragile, dilated, and thin-walled. The lumens of a few intraacinar arteries were obliterated by intimal fibrosis.

Three of the older patients (Cases 7, 9, and 10) also had changes of severe pulmonary vascular disease. Intimal fibrosis occurred more frequently than in Case 5 and was more severe the older the child.

In Case 7, the preacinar arteries were abnormally thick-walled and many branches were occluded at their origin by concentric intimal proliferation (Fig. 3). Terminal and respiratory bronchiolar and alveolar duct arteries showed medial atrophy and, unlike in Case 5, intimal proliferation and fibrosis occluded the lumens of many of these small vessels. Within the alveolar walls some arteries were occluded by fibrosis while others showed medial atrophy and dilatation.

The changes were similar in Case 9, but less severe (Fig. 4). In Patient 10, aged 21 years, the picture differed from that seen in the children because of the greater atrophy of the media in large preacinar and intraacinar arteries, and in the greater severity of intimal fibrosis. Elastosis, a thickening of internal and external elastic laminae and increase in elastic fibers within the media, was severe. The media was fibrotic in some arteries, with collagen appearing between the muscle cells and elastic fibers. In Cases 5, 7, 9, and 10 the adventitia was abnormally thick and the collagen appeared dense.

**Vein wall structure:** In 4 patients aged 2 years or more (Cases 5, 6, 7, and 10) the veins were abnormally thick-walled and the small veins were "arterialized." Intimal fibrosis occurred in Cases 6 and 10 and was severe in the latter. In 1 infant, Patient 3, vein wall thickness was slightly increased.

Siderophages were scattered in clumps throughout the sections of tissue in Cases 7 and 10, with some deposition of iron in the arterial walls.

### Quantitative Assessment

**Percent arterial medial thickness:** *Uninjected material:* In patients 1 to 4, aged 3 to 6 months, percent arterial medial thickness was greater than normal in arteries of all sizes (Fig. 5). Of the 6 older children, in 3 (Cases 6, 7, and 9) muscularity was greater than normal in arteries <450 μm in diameter, but was below that seen in the 4 younger children with an ASD (Fig. 6). In Case 8 the percent medial thickness was normal. In Case 10, muscle was greater than normal in arteries of ≥250 μm, and the normal percent arterial medial thickness in the smaller arteries was associated with the appearance of medial atrophy. In Case 5, the percent medial thickness in arteries <700 μm in diameter was high and similar to that seen in the 4 younger cases, but was below normal in arteries <350 μm in diameter.

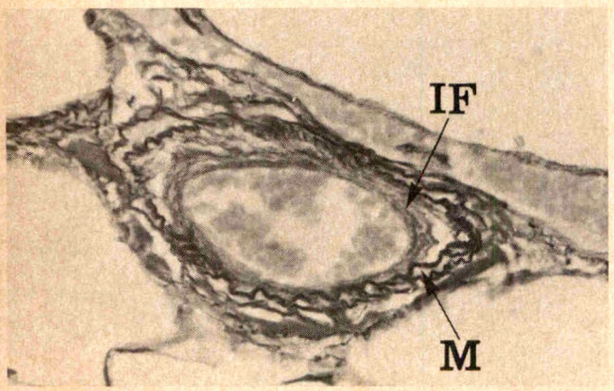



**FIGURE 4.** Photomicrograph of a respiratory bronchiolar artery in Case 9, showing a layer of intimal fibrosis (IF) within the media (M). (Magnification ×540, reduced 37%.)

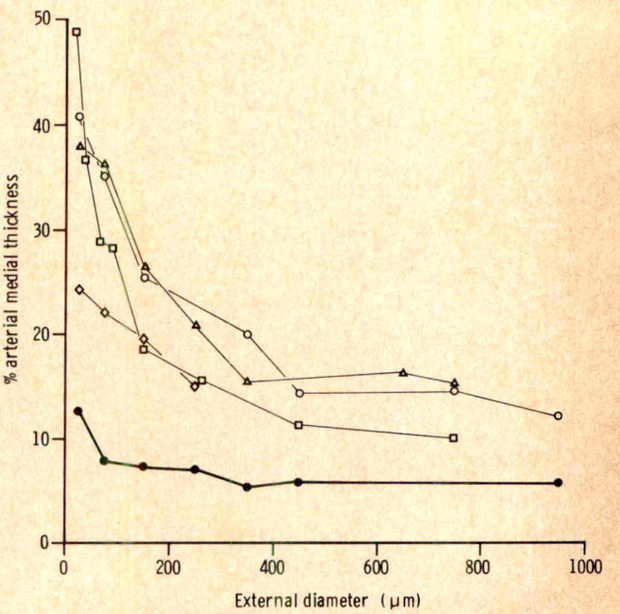



**FIGURE 5.** Mean percent arterial medial thickness related to external diameter (μm) in uninjected tissue from 4 infants, showing a considerable increase in muscularity above the normal level. **Open circles** indicate Case 1; **diamonds,** Case 2; **squares,** Case 3; **triangles,** Case 4; **closed circles,** normal, 3 months to 9 years.

*Injected material:* The more precise measurements of the percent arterial medial thickness made on the injected lung tissue from Cases 4 and 5 confirmed the observations made on the uninjected tissue (Fig. 7).

**Structure of arteries accompanying peripheral airways:** In the 4 youngest patients (Cases 1 to 4) the proportion of partially muscularized and muscularized arteries at alveolar duct and alveolar wall level was greater than normal. In the normal child of similar age, the proportion of entirely muscularized alveolar duct arteries is <60% and it is unusual to find many muscularized arteries within the alveolar wall. In these 4 infants, 64 to 100% of alveolar duct arteries were entirely muscularized and 40 to 100% of alveolar wall arteries contained muscle cells. Of the 6 older patients, the proportion of partly muscularized alveolar wall arteries was increased in Case 7 at the expense of nonmuscularized vessels, from a normal value of approximately 60% to 80%. Muscularization was most severe in Case 9, where almost half the alveolar wall arteries were entirely surrounded by a coat of muscle cells. Cases 5 and 10 showed a reduction in the proportion of partly muscularized and muscularized arteries at the respiratory bronchiolar, alveolar duct, and alveolar wall level; in Case 10 this was due to medial atrophy. There was no abnormal extension of muscle in Cases 6 and 8.

**Size and number of intraacinar arteries:** In 6 cases, the mean external diameter of intraacinar arteries was normal for age (Table III). Only in Case 4 were the arteries larger than normal; in this instance the luminal diameter of the preacinar arteries was also greater than normal on the postmortem arteriogram. The arteries were smaller than normal in Cases 6, 7, and 10; in all these 3, aged 5, 5, and 21 years, respectively, the arteries were similar to the normal at <2 years of age. In Case 10, intimal fibrosis was severe and many arteries appeared shrunken and fibrotic.

The alveolar/arterial ratio was determined in 7 cases (Table III). It was not possible to determine the ratio in Case 7 because the alveoli were not well expanded and in Cases 5 and 10 many alveolar wall arteries were either occluded by fibrotic change or replaced by thin-walled dilated arteries or both. The ratio was markedly increased in Cases 1 and 2, suggesting a reduction in the number of intraacinar arteries, and slightly increased in Case 9. The alveolar/arterial ratio was normal in the remaining 4 cases.

**Relation to the Heath and Edwards Classification of pulmonary vascular disease:** Had the Heath and Edwards Classification[8] been used, the pulmonary vascular changes in the 4 infants would have been classified as grade I at all levels along the arterial pathway. Using the modification of the Heath and Edwards Classification proposed by Rabinovitch et al,[9] the changes in Cases 3 and 4, extension of muscle into more peripheral arteries than normal plus medial hypertrophy in normally muscularized arteries, indicated grade Ib disease. In addition to both these changes, Cases 1 and 2 also had a reduction in intraacinar arterial number, indicating grade Ic disease.

Of the 6 older children, Cases 6 and 8 showed only grade I pulmonary vascular disease. In Cases 5, 7, and

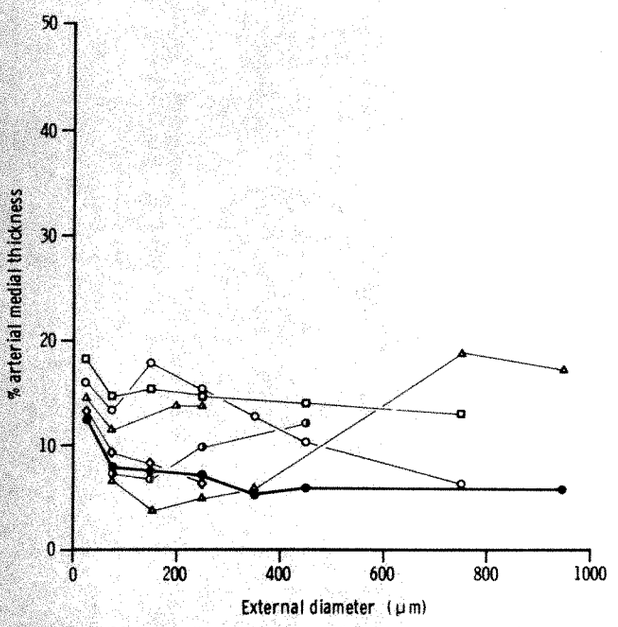



**FIGURE 6.** Mean percent arterial medial thickness related to external diameter (μm) in uninjected tissue from 5 children and 1 young adult, compared with normal findings. **Triangles,** indicate Case 5; **open circles,** Case 6; **squares,** Case 7; **diamonds,** Case 8; **half-shaded triangles,** Case 9; **half-shaded circles,** Case 10; **closed circles,** normal, 3 months to 9 years.

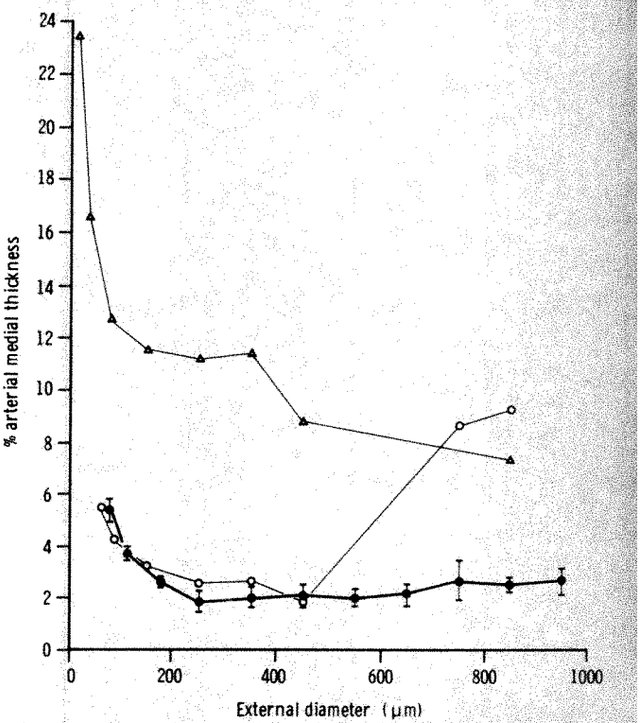



**FIGURE 7.** Mean percent arterial medial thickness related to external diameter (μm) in injected tissue from Cases 4 and 5, and from normal patients. **Triangles** indicate Case 4; **open circles,** Case 5; **closed circles,** normal, 4 months to 10 years, ±1 standard deviation.

**TABLE III Size and Number of Arteries Accompanying Peripheral Airways**

| Case | Age at Biopsy/ Death | Mean External Diameter (μm) | | | | Alveolar/ Arterial Ratio |
|---|---|---|---|---|---|---|
| | | TB | RB | AD | AW | |
| 1 | 3 mo | 66 | 37 | 17 | 15 | 14 |
| 2 | 5 mo | . . . | 44 | 23 | 14 | 17 |
| 3 | 6 mo | 63 | 38 | 26 | 15 | 10 |
| 4 | 5 mo | 88 | 55 | 35 | 23 | 10 |
| 5 | 2 yr | 80 | 58 | 34 | 24 | . . . |
| 6 | 5 yr | 81 | 52 | 37 | 25 | 10 |
| 7 | 5 yr | 85 | 45 | 31 | 20 | . . . |
| 8 | 7 yr | 147 | 76 | 41 | 23 | 10 |
| 9 | 9 yr | 120 | 71 | 42 | 20 | 12 |
| 10 | 21 yr | 71 | 59 | 38 | . . . | . . . |
| | | Normal Values | | | | |
| 4–6 mo | 3 | 66 | 44 | 26 | 18 | 10 |
| 2 yr | 2 | 95 | 62 | 42 | 23 | . . . |
| 5 yr | 2 | 109 | 74 | 41 | 22 | 10 |
| 8–9 yr | 2 | 109 | 76 | 47 | 23 | 10 |

AD = alveolar duct; AW = alveolar wall; RB = respiratory bronchiolus; TB = terminal bronchiolus.

9, the severe intimal fibrosis with occlusive change would have been classified as grade III disease. In Case 10, the severe fibrotic occlusive change with dilatation of alveolar duct and alveolar wall arteries indicated advanced stage III or early grade IV disease.

## Discussion

Four infants with a secundum ASD presented in cardiac failure; all had severe pulmonary hypertension and a marked increase in pulmonary arterial muscularity (Table IV). Only 1 infant survived closure of the defect, and he had the least increase in muscularity. In 4 children aged 5 to 9 years, pulmonary hypertension was less severe than in the infants and none had symptoms attributable to ASD. Nevertheless, in 2 patients examination of lung tissue showed severe obliterative pulmonary vascular disease, and of these 4 patients only 2 have had the defect closed successfully. One additional child did not fall into either group. Presentation was delayed until 2 years of age and was due to cyanosis, not heart failure. Only the preacinar arteries showed medial hypertrophy, but they also showed obliterative change; the more peripheral arteries were abnormally thin-walled. This child also did not survive surgery. Two patients, including the 21-year-old man, will not undergo surgery because of the severity of the pulmonary vascular disease. Thus, in only 3 of the 10 patients was it possible to close the defect successfully.

The present series of children with a secundum ASD and pulmonary hypertension is unusual because most such patients have, in addition, an obstructive left heart abnormality.[10] In most infants with a large isolated se-

**TABLE IV Summary of Results**

| Case | PAP/SAP | Pulmonary Arterial Muscularity | | Intraacinar Arteries | | Outcome |
|---|---|---|---|---|---|---|
| | | Preacinar | Intraacinar | Size | Number | |
| | | Infants | | | | |
| 1 | 0.88 | ↑ | ↑ | N | ↓ | + |
| 2 | 0.83 | . . . | ↑ | N | ↓ | Op |
| 3 | 1.0 | ↑ | ↑ | N | N | + |
| 4 | 0.78 | ↑ | ↑ | ↑ | N | + |
| 5 | 0.79 | ↑OB | ↓ | N | . . . | + |
| | | "Older" Children | | | | |
| 6 | 0.4 | ↑ | ↑ | ↓ | N | + |
| 7 | 0.7 | ↑IF, OB | ↑IF, OC | ↓ | . . . | No op |
| 8 | 0.54 | ↑ | N | N | N | Op |
| 9 | Postoperative 0.6 | ↑IF | ↑IF, OC | N | N/↓ | Op |
| | | Adult | | | | |
| 10 | 0.8 | A, IF, OB | A, IF, OC | ↓ | ↓ | No op |

A = medial atrophy; IF = intimal fibrosis; OB = obstructed branches; OC = occlusive fibrosis; Op = ASD closed successfully; PAP/SAP ratio of systolic pressures; ↑ and ↓ indicate increase and decrease with respect to normal for age; + = dead.

cundum ASD, pulmonary arterial pressure and resistance decrease normally after birth.[11] Pulmonary hypertension rarely develops before the third decade of life. During the last 10 years at the Hospital for Sick Children in London, an isolated secundum ASD was closed in 80 patients whose pulmonary arterial pressure was normal. Only 4 additional patients had pulmonary hypertension, 2 of whom are included in this study. The normotensive patients were 5 to 14 years old, and those with pulmonary hypertension were 6 months to 7 years of age. Also, pulmonary vascular resistance was elevated in all patients in the present study (including 3 infants); other series have included some infants in whom the resistance was not increased.[1,2]

Five of the 6 infants in the present study failed to respond to intensive medical therapy. Symptomatic infants can usually be managed conservatively, deferring surgery until the child is older,[1,4,12] but there are exceptions.[1,2]

Presentation of an ASD in infancy has been attributed to a primary abnormality of the pulmonary vasculature causing persistence of the fetal circulation, the ASD being incidental. In the present study, however, the presentation and clinical findings were unlike those seen in babies with persistent fetal circulation. The symptoms in the infants with an ASD were attributable to a high pulmonary blood flow due to a left-to-right shunt, whereas in babies with persistence of the fetal circulation, pulmonary blood flow is not increased. Instead, there is pulmonary hypoperfusion, and cyanosis is due to a right-to-left shunt through persistent fetal channels.[13] However, a prenatal increase in medial thickness and in the medial surface area of pulmonary vascular smooth muscle has been found in 3 fetuses with an ASD, suggesting that in some children the pulmonary circulation may be structurally abnormal before birth.[14] In the same study, a greater increase in muscularity occurred in 2 children who resembled the infants in the present series, dying in cardiac failure at 7 and 28 weeks of age.[14] After birth, it is probable that at least part of the increase in pulmonary arterial smooth muscle is secondary to an increase in pulmonary blood flow. The immature lung is more susceptible to an increase in flow than is the mature lung.[15–17]

In the present study the infants whose intrapulmonary arteries showed only medial hypertrophy were more sick and had a higher pressure than did most of the older patients, some of whom had more advanced pulmonary vascular disease. But the muscularized intraacinar arteries of the hypertensive lung have a different appearance in the first months of life from that seen in older patients. In the infant the smooth muscle cells are particularly large and plump, and the muscle coat is extremely thick relative to external diameter and severely narrows and sometimes even obstructs the lumen. It is not difficult to imagine that such change could produce greater elevation of resistance and a more labile pulmonary circulation than the less exuberant change found in older patients.

In this series the relation between the clinical and pathologic findings in the symptomatic infants and the relatively asymptomatic older children is not clear. One child did, however, present with heart failure at 3 months; at 4 years of age the child was clinically and pathologically similar to children of similar age, suggesting that with growth a high pulmonary arterial pressure and pulmonary arterial medial thickness may decrease. Other clinical studies suggest that this is so.[1,4,12] Perhaps in some children the hypertrophy of the media is too abundant to allow this to happen, and a hyperreactive pulmonary vascular bed is associated with uncontrolled heart failure and a higher operative mortality than is to be expected in the presence of a relatively simple cardiac defect. In 2 of the older children and in the man whose lung was biopsied at 21 years, the clinical and pathologic findings were similar to those seen in adults with an atrial septal defect and pulmonary hypertension, suggesting an accelerated progression of pulmonary vascular obliterative disease in these patients.

Vein wall thickness was increased in 5 cases in the present series. An increase in venous muscularity is frequently seen in the presence of arterial medial hypertrophy, and the relation is not understood. Left atrial pressure is frequently normal, as in the present study in which only Patient 2 showed a slight increase in mean pressure with respect to age.

The absence of pulmonary hypertension in the vast majority of patients with a secundum ASD is attributed to dilatation of the pulmonary arterial circulation, particularly of the proximal elastic pulmonary arteries. However, the arteries were dilated in only 1 child in the present study; despite the increase in arterial size, in this patient pulmonary hypertension was also severe. Of the remaining cases, in 6 the intraacinar arteries were reduced in either size or number. The same features of a restricted pulmonary vascular bed are found in infants and young children with a ventricular septal defect and pulmonary hypertension.[18]

The variation in response shown by different individuals to the presence of a large ASD is not understood. Individual susceptibility to the development of pulmonary hypertension is known to vary considerably.[19] Genetic factors are probably important in determining the amount of pulmonary vascular smooth muscle.[20] In the present series of children with a secundum ASD and pulmonary hypertension, there was no predominance of female patients. In a series of adult patients with an ASD who developed the Eisenmenger reaction, the female to male ratio, was 4 to 1.[21] Women also have a greater tendency than men to develop primary pulmonary hypertension in adult life. The greater tendency of female patients to develop the Eisenmenger reaction in ASD has been attributed to an underlying abnormality of the pulmonary vasculature akin to that present in women with primary pulmonary hypertension. There is no evidence to support this hypothesis in children.

The structural findings in the present study illustrate the difficulties of classifying pulmonary vascular disease in young children. In older patients, an increase in pulmonary arterial muscularity as the only structural

abnormality is associated with a mild increase in pulmonary arterial pressure and a favorable surgical outcome.[8] In infants, however, this is not always so, as the present study shows. Also, the same end result of increased muscularity and reduction in arterial size and number may represent a different type of structural change at different ages. Classification of pulmonary vascular change is necessary when describing the pathologic findings in a large population and when relating structural to hemodynamic findings. Particularly in childhood, however, it is preferable to describe precisely what is seen, rather than to use any system of classification which has certain clinical and prognostic associations.

**Clinical implications:** The rarity of pulmonary hypertension developing in children with an isolated secundum ASD is emphasized. Also, the majority of infants who do develop pulmonary hypertension and cardiac failure respond satisfactorily to medical treatment. The present study indicates that unfortunately it is the sick infants who have potentially reversible pulmonary vascular disease, while some asymptomatic older patients have more advanced disease which is less likely to reverse completely when the defect is closed.[22] Despite the high mortality in the present series, in symptomatic infants who fail to respond to intensive medical therapy the defect is best closed immediately, both to improve the clinical condition and to prevent the development of further pulmonary vascular damage.[4] In asymptomatic older children, if a diagnosis of a secundum ASD is made by 2-dimensional echocardiography alone, closure of the defect should not be postponed if there is any doubt that pulmonary arterial pressure is normal.

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## References

1. **Hunt CE, Lucas RV.** Atrial septal defect in infancy. Circulation 1973;47: 1042–1048.
2. **Bull C, Deanfield J, de Leval M, Stark J, Taylor JFN, Macartney FJ.** Correction of isolated secundum atrial defect in infancy. Arch Dis Child 1981;56:784–786.
3. **Ainger LE, Pate JW.** Ostium secundum atrial septal defects and congestive heart failure in infancy. Am J Cardiol 1965;15:380–385.
4. **Phillips SJ, Okies JE, Henken D, Sunderland CO, Starr A.** Complex of secundum atrial septal defect and congestive heart failure in infants. J Thorac Cardiovasc Surg 1975;70:696–700.
5. **Wagenvoort CA, Wagenvoort N.** Pathology of Pulmonary Hypertension. London: John Wiley & Sons, 1977:138.
6. **Davies G, Reid L.** Growth of the alveoli and pulmonary arteries in childhood. Thorax 1970;25:669–681.
7. **Hislop A, Reid L.** New pathological findings in emphysema of childhood. I. Polyalveolar lobe with emphysema. Thorax 1970;25:682–690.
8. **Heath D, Edwards JE.** The pathology of hypertensive pulmonary vascular disease. A description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation 1958;18:533–547.
9. **Rabinovitch M, Haworth SG, Castaneda AR, Nadas AS, Reid LM.** Lung biopsy in congenital heart disease: a morphometric approach to pulmonary vascular disease. Circulation 1978;58:1107–1122.
10. **Tandon R, Edwards JE.** Clinicopathologic correlations. Atrial septal defect in infancy: common association with other anomalies. Circulation 1974; 49:1005–1010.
11. **Rudolph AM.** Congenital Diseases of the Heart. Chicago: Year Book Medical, 1974:42.
12. **Spangler JG, Feldt RH, Danielson GK.** Secundum atrial septal defect encountered in infancy. J Thorac Cardiovasc Surg 1976;71:398–401.
13. Avery ME, Fletcher BD, Williams RG, eds. The Lung and Its Disorders in the Newborn Infant. Vol I in series: Major Problems in Clinical Pediatrics. London: WB Saunders 1981:318.
14. **Wagenvoort CA, Neufeld HN, DuShane JW, Edwards JE.** The pulmonary arterial tree in atrial septal defect. A quantitative study of anatomic features in fetuses, infants and children. Circulation 1961;23:733–739.
15. **Rudolph AM, Neuhauser EBD, Golinko RJ, Auld PAM.** Effects of pneumonectomy on pulmonary circulation in adult and young animals. Circ Res 1961;9:856–861.
16. **Vogel JHK, Averill KH, Pool PE, Blount GS.** Experimental pulmonary arterial hypertension in the newborn calf. Circ Res 1963;13:557–571.
17. **Haworth SG, de Leval M, Macartney FJ.** Hypoperfusion and hyperperfusion in the immature lung. Pulmonary arterial development following ligation of the left pulmonary artery in the newborn pig. J Thorac Cardiovasc Surg 1981;82:281–292.
18. **Haworth SG, Sauer, U, Bühlmeyer K, Reid L.** The development of the pulmonary circulation in ventricular septal defect: a quantitative structural study. Am J Cardiol 1977;40:781–788.
19. **Grover RF, Vogel JHK, Averill KH, Blount SG.** Pulmonary hypertension. Individual and species variation relative to vascular reactivity. Am Heart J 1963;66:1–3.
20. **Vogel JHK, McNamara DG, Hallman G, Rosenberg H, Jamieson G, McCrady JD.** Effects of mild chronic hypoxia on the pulmonary circulation in calves with reactive pulmonary hypertension. Circ Res 1967;21:661–669.
21. **Wood P.** Disease of the Heart and Circulation. 3rd ed. London: Eyre & Spottiswoode, 1968:977.
22. **Braunwald NS, Braunwald E, Morrow AG.** The effects of surgical abolition of left to right shunts on the pulmonary vascular dynamics of patients with pulmonary hypertension. Circulation 1962;26:1270–1278.

# Clinical Follow-Up Study of Paroxysmal Supraventricular Tachyarrhythmias After Operative Repair of a Secundum Type Atrial Septal Defect in Adults

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**Adults with isolated secundum atrial septal defect (ASD) may present with paroxysmal atrial tachyarrhythmias. The clinical course of these rhythmic disturbances after correction of the ASD is unknown. Of 188 patients aged 44 years old or older with isolated ASD, 27 (14%) (mean age 52.7 years, range 44 to 71) had documented paroxysmal atrial tachyarrhythmias *preoperatively:* 16 had paroxysmal atrial fibrillation, 2 had atrial flutter, and 9 had supraventricular tachycardia. Among these 3 groups, there were no differences in age, sex, New York Heart Association class, duration of preoperative symptoms, mean right atrial and pulmonary arterial pressures, shunt size, atrial size, or follow-up period. After operative repair, follow-up data were available in all patients for a mean of 12 years (range 1.5 to 25). Of the 16 patients with preoperative paroxysmal atrial fibrillation, 14 (88%) continued to have increasingly frequent paroxysmal atrial fibrillation, culminating in sustained atrial fibrillation. In 1 of the 2 patients with paroxysmal atrial flutter, sustained atrial fibrillation developed. Of the 9 patients with preoperative paroxysmal supraventricular tachycardia, 5 had no further episodes of this arrhythmia postoperatively.**

Atrial septal defects (ASD) in adults may have various presentations ranging from no symptoms with abnormal findings on chest roentgenography or electrocardiography to severe disability with congestive heart failure and pulmonary hypertension. In addition, paroxysmal supraventricular tachyarrhythmias (atrial fibrillation, atrial flutter, and supraventricular tachycardia) are relatively common, particularly in older patients,[1–3] and may be the only presenting symptom. Operative repair of ASD has been well established as optimal treatment. Although improvement in hemodynamic and functional status after closure of an ASD is documented, the clinical course of paroxysmal supraventricular tachyarrhythmias after operation is not well known. To assess this condition, adult patients with secundum ASD who had documented paroxysmal tachyarrhythmias preoperatively were studied to determine the clinical course of the arrhythmias after operation.

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## Methods

The records of all adult patients aged 44 years or older with ASD seen at the Mayo Clinic from 1955 to 1980 were reviewed. Patients with atrial defects other than the secundum type were excluded, as were patients with other accompanying congenital cardiac anomalies. Also excluded were patients with other possible causes of atrial arrhythmia, including mitral valve prolapse, hypertrophic cardiomyopathy, mitral or tricuspid regurgitation, pericarditis, Wolff-Parkinson-White syndrome, severe hypertension, and hyperthyroidism. Thirty-eight patients with chronic persistent atrial fibrillation before operation were also excluded. After these exclusions, there were 188 patients, 31 of whom had had paroxysmal supraventricular tachyarrhythmia (17%). Four of the 31 patients had no electrocardiographic documentation of the arrhythmia by the referring physician or at the Mayo Clinic before operation and they were excluded. The records of the remaining 27 patients form the basis of this report.

There were 7 men (aged 45 to 54 years at operation, mean 49) and 20 women (aged 44 to 71 years, mean 54). Ten patients (37%) were in class I, with paroxysmal tachycardia the only symptom; the remaining patients were in functional class II. As a group, the patients had had 2 to more than 400 subjective episodes of tachycardia (approximate mean 30 episodes per patient) from 1 month to more than 20 years before operation.

**TABLE I Preoperative Electrocardiographic Findings in Secundum Atrial Septal Defect***

| Case | Age (yr) & Sex | RBBB | | | RAD | Prolonged P-R Interval | RVH | RAE | LAE | MI | EAP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Present | I | C | | | | | | | |
| **Atrial Fibrillation** | | | | | | | | | | | |
| 1 | 52M | + | + | ... | ... | ... | ... | ... | ... | ... | ... |
| 2 | 45F | + | + | ... | + | ... | ... | ... | ... | ... | ... |
| 3 | 50M | + | + | ... | ... | ... | ... | ... | ... | ... | ... |
| 4 | 45M | + | + | ... | + | + | ... | ... | ... | ... | ... |
| 5 | 63F | + | + | ... | ... | + | ... | ... | ... | ... | ... |
| 6 | 59F | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ... | ... |
| 7 | 59F | ... | ... | ... | + | + | ... | ... | ... | ... | ... |
| 8 | 48F | + | 0 | + | ... | + | ... | ... | ... | ... | ... |
| 9 | 51F | ... | ... | ... | + | ... | ... | ... | ... | ... | ... |
| 10 | 71F | ... | ... | ... | + | ... | + | ... | ... | ... | ... |
| 11 | 51M | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ... | ... |
| 12 | 51F | ... | ... | ... | + | ... | ... | ... | ... | ... | ... |
| 13 | 66F | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ... | ... |
| 14 | 57F | + | ... | + | ... | ... | ... | ... | ... | ... | ... |
| 15 | 53F | + | ... | + | ... | ... | ... | ... | ... | ... | ... |
| 16 | 49F | + | + | ... | + | ... | ... | ... | ... | ... | ... |
| **Supraventricular Tachycardia** | | | | | | | | | | | |
| 17 | 47F | + | + | ... | ... | ... | ... | + | ... | ... | ... |
| 18 | 50F | + | + | ... | ... | ... | ... | ... | ... | ... | ... |
| 19 | 55F | ... | ... | ... | + | ... | ... | ... | ... | + | ... |
| 20 | 44F | + | + | ... | ... | ... | ... | ... | ... | ... | + |
| 21 | 45M | ... | ... | ... | + | ... | ... | + | ... | ... | ... |
| 22 | 61F | + | ... | + | + | ... | ... | ... | + | ... | ... |
| 23 | 53F | + | + | ... | ... | + | + | ... | ... | ... | ... |
| 24 | 50F | + | ... | + | ... | ... | ... | ... | ... | ... | ... |
| 25 | 48F | + | + | ... | ... | + | ... | ... | ... | ... | ... |
| **Atrial Flutter** | | | | | | | | | | | |
| 26 | 45M | + | ... | + | ... | ... | ... | ... | ... | ... | ... |
| 27 | 54M | + | ... | + | ... | ... | ... | ... | + | ... | ... |
| Total n | ... | 18 | 11 | 7 | 10 | 6 | 2 | 2 | 2 | 1 | 1 |
| % | ... | 67 | 41 | 26 | 37 | 22 | 7 | 7 | 7 | 4 | 4 |

* All patients had sinus rhythm at the time of electrocardiographic recording.
C = complete; EAP = ectopic atrial pacemaker; I = incomplete; LAE = left atrial enlargement; MI = myocardial infarction pattern (anterior wall); RAD = right axis deviation; RAE = right atrial enlargement; RBBB = right bundle branch block; RVH = right ventricular hypertrophy.

Preoperative resting electrocardiograms were available in all patients (Table I). All demonstrated sinus rhythm, except 1 patient with an ectopic atrial pacemaker. The electrocardiograms were reviewed with regard to intraventricular conduction delay, ventricular hypertrophy, axis, and the presence of atrial enlargement.[4] Eighteen patients had preoperative cardiac catheterization at the Mayo Clinic, and 3 had it performed elsewhere. Pulmonary arterial mean pressure ranged from 14 to 46 mm Hg (mean 24) (19 patients), whereas the right atrial mean pressure ranged from 4 to 20 mm Hg (mean 7) (18 patients). Left-to-right shunts varied from 40 to 76% (mean 60%) (21 patients).

The operations were performed between August 1955 and February 1980. The defects in 5 patients operated on between August 1955 and November 1958 were closed with Ivalon® sponge using the "atrial well technique,"[5] whereas defects in 22 repaired after 1958 used direct suture. Right atrial size was estimated at operation on a scale of 1 (mild) to 6 (severe) in 25 patients.

## Results

**Preoperative arrhythmias:** Before operation, 16 patients had paroxysmal atrial fibrillation, 9 had paroxysmal supraventricular tachycardia,[6] and 2 had paroxysmal atrial flutter. Among these 3 groups, there were no significant differences in age, sex, New York Heart Association class, length of symptoms preoperatively, number of tachycardia episodes, mean pulmonary arterial and right atrial pressures, shunt size, type of surgical closure, right atrial size, or follow-up period.

**Early postoperative arrhythmias:** All 16 patients with preoperative paroxysmal atrial fibrillation had atrial fibrillation during the immediate postoperative period. At discharge, 10 patients had returned to sinus rhythm, whereas 6 continued to have atrial fibrillation. Five of the 6 patients later had transient conversion to normal sinus rhythm, whereas 1 patient had persistent atrial fibrillation (Fig. 1). In contrast, 7 of 9 patients with preoperative paroxysmal supraventricular tachycardia had no early postoperative arrhythmia (Fig. 2). One patient had two 4-hour episodes of paroxysmal supraventricular tachycardia on the first and second postoperative days, and the other patient had a 1-hour episode of paroxysmal supraventricular tachycardia on the second day. All 9 patients were in sinus rhythm at discharge. In both patients with preoperative paroxysmal atrial flutter, atrial flutter developed during the postoperative period. In 1 patient, it persisted at discharge.

**Follow-up study:** All patients with paroxysmal atrial fibrillation were followed up 3 to 25 years (mean 12). Of 16 patients with preoperative paroxysmal atrial fibril-

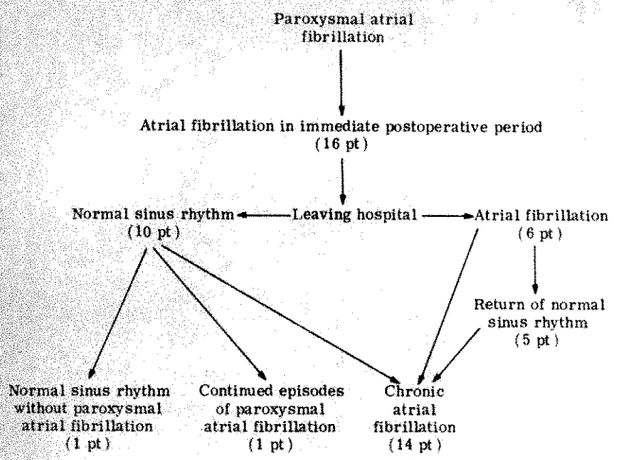



**FIGURE 1.** Course of patients (pt) with paroxysmal atrial fibrillation due to a secundum atrial septal defect.

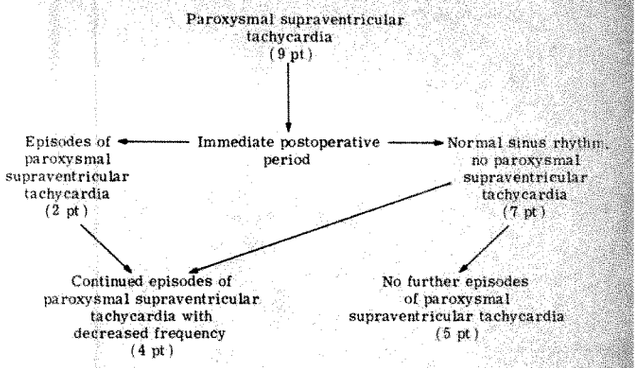



**FIGURE 2.** Course of patients (pt) with paroxysmal supraventricular tachycardia due to a secundum atrial septal defect.

lation, 14 continued to have increasingly frequent episodes postoperatively, finally culminating in chronic atrial fibrillation. Only 2 of the 16 patients are currently in sinus rhythm. One, a 51-year-old woman, now 13 years after operation, continues to have 1 or 2 episodes of atrial fibrillation per year and requires digitalis. Before operation, she had an 18-month history of paroxysmal atrial fibrillation. The other patient, a 51-year-old man with 7 episodes of atrial fibrillation before operation, has had no further episodes of tachycardia and requires no medication (Fig. 1).

The 9 patients with preoperative paroxysmal supraventricular tachycardia were followed from 1.5 to 23 years (mean 10). Five patients have had no further episodes of sustained paroxysmal supraventricular tachycardia postoperatively. As a group, the 5 patients before operation had from 7 to >100 episodes of tachycardia over 3 to 20 years (mean 9). Three of the 5 patients are currently taking no medication. Of the 9 patients having preoperative paroxysmal supraventricular tachycardia, 4 continued to have episodes of symptomatic tachycardia postoperatively, which gradually decreased in frequency. One patient, a 47-year-old woman, had 4 episodes during the first 5 postoperative years and has been asymptomatic for the past 6 years while on digitalis and propranolol therapy. This patient had had approximately 1 episode of tachycardia per month in the year before operation. A second patient, a 45-year-old man, had 1 episode 4 years after operation and then was asymptomatic for the next 7 years, after which he was lost to follow-up study. A third patient, a 53-year-old woman, has had approximately 10 episodes during the 7 years since operation, but none for the past year and is taking no medication. She had 6 episodes of paroxysmal supraventricular tachycardia during the 2 years before operation. The fourth patient, a 50-year-old woman, has also had approximately 10 episodes of paroxysmal supraventricular tachycardia while taking digitalis and propranolol during the 18 months since operation, but she felt that the frequency had greatly decreased compared with that before operation. Preoperatively, she had 1 to 2 episodes per week.

One of the 2 patients with preoperative atrial flutter had no further episodes for 12 years after operation. This 54-year-old man had a short history of arrhythmia preoperatively, with 2 disabling episodes of atrial flutter during 1 month. The other patient, a 45-year-old man, continued to have paroxysmal atrial flutter, which changed to chronic atrial fibrillation approximately 14 years after operation.

## Discussion

The favorable response to closure of an isolated ASD in older patients has been documented.[2–4,6–13] Many patients have a significant decrease in "palpitations" after operation.[12,13] However, no previous report has reviewed the patient's specific preoperative atrial tachyarrhythmia and follow-up clinical course after operation.

The supraventricular arrhythmias in these patients are not unexpected. Cardiovascular disorders with atrial enlargement, atrial distention, or increased atrial pressure are associated with an increased incidence of supraventricular arrhythmias, including paroxysmal atrial fibrillation, paroxysmal atrial flutter, and paroxysmal supraventricular tachycardia.[14–16]

The electrophysiologic mechanisms involved vary in terms of mechanisms of onset and perpetuation, depending on the particular rhythmic disturbance. In atrial fibrillation, multiple circus movements or wavelets of impulse transmission are probably involved.[15–18] The atrial fibrillation may be maintained, particularly in dilated atria, because the number of circuits is large, with less chance of spontaneous organization and termination.[15] Atrial dilatation is the common pathologic finding in patients who have atrial fibrillation of recent onset as compared with patients who have chronic atrial fibrillation in whom both atrial dilatation and atrial myocardial changes are found.[19] Atrial flutter is rare in the normal heart, usually being associated with atrial dilatation and conduction disturbances,[14,15] both of which are common in patients with ASD.

In contrast to the chaotic electrical activation in atrial fibrillation, paroxysmal supraventricular tachycardia

is more homogeneous. It is usually reentrant, although enhanced automatic mechanisms have been described.[20–24] The precise mechanism in our patients is unknown, as electrophysiologic studies were not performed. The increased incidence of atrial premature contractions associated with atrial dilatation could initiate reentrant tachycardia in the atrioventricular node or atrium and could account for the increased frequency of tachycardia.

The disparity in outcome between patients with preoperative paroxysmal atrial fibrillation and those with paroxysmal supraventricular tachycardia was striking. All but 2 patients who had atrial fibrillation eventually had sustained atrial fibrillation as compared with patients who had paroxysmal supraventricular tachycardia, whose rhythmic disturbance usually improved. There are several potential reasons for this difference. Although atrial size was similar in each group, the patients with atrial fibrillation may have had more extensive atrial disease, leading to continued lack of homogeneity with respect to conduction or refractoriness and resulting in sustained atrial fibrillation. Postoperative abolition of paroxysmal supraventricular tachycardia could be due to relief of atrial distention, thus reducing the tendency for atrial ectopy and thus decreasing the initiating mechanism for reentry. In addition, surgical incision might disrupt a portion of the reentrant circuit.

Irrespective of the anatomic and physiologic substrates involved, paroxysmal supraventricular tachyarrhythmia is relatively common in adults with ASD and may be the presenting symptom. The course of the arrhythmia postoperatively depends on its specific type. Paroxysmal atrial fibrillation tends to recur postoperatively, finally culminating in chronic atrial fibrillation. In contrast, paroxysmal supraventricular tachycardia can be expected to gradually improve or disappear after operation.

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## References

1. **Craig RJ, Selzer A.** Natural history and prognosis of atrial septal defect. Circulation 1968;37:805–815.
2. **Sommer LS, Voudoukis IJ.** Atrial septal defect in older age groups: with especial reference to atypical clinical and electrocardiographic manifestations. Am J Cardiol 1961;8:198–202.
3. **Kelly JJ Jr, Lyons HA.** Atrial septal defect in the aged. Ann Intern Med 1958;48:267–283.
4. **Chou T-C.** Electrocardiography in Clinical Practice. New York: Grune & Stratton, 1979:27–40.
5. **Gross RE, Watkins E Jr, Pomeranz AA, Goldsmith EI.** A method for surgical closure of interauricular septal defects. Surg Gynecol Obstet 1953;96: 1–23.
6. **Katz LN, Pick A.** Clinical Electrocardiography. Philadelphia: Lea & Febiger, 1956:275–287.
7. **Daicoff GR, Brandenburg RO, Kirklin JW.** Results of operation for atrial septal defect in patients forty-five years of age and older. Circulation 1967;35: Suppl I:I-143–I-147.
8. **Richmond DE, Lowe JB, Barratt-Boyes BG.** Results of surgical repair of atrial septal defects in the middle-aged and elderly. Thorax 1969;24; 536–542.
9. **St John Sutton MG, Tajik AJ, McGoon DC.** Atrial septal defect in patients ages 60 years or older: operative results and long-term postoperative follow-up. Circulation 1981;64:402–409.
10. **Wolf PS, Vogel JHK, Pryor R, Blount SG Jr.** Atrial septal defect in patients over 45 years of age: merits of surgical versus medical therapy. Br Heart J 1968;30:115–124.
11. **Cooley DA, Hallman GL, Hammam AS.** Congenital cardiovascular anomalies in adults: results of surgical treatment in 167 patients over age 35. Am J Cardiol 1966;17:303–309.
12. **Dave KS, Pakrashi BC, Wooler GH, Ionescu MI.** Atrial septal defect in adults: clinical and hemodynamic results of surgery. Am J Cardiol 1973; 31:7–13.
13. **Saksena FB, Aldridge HE.** Atrial septal defect in the older patient: a clinical and hemodynamic study in patients operated on after age 35. Circulation 1970;42:1009–1020.
14. **Leier CV, Meacham JA, Schaal SF.** Prolonged atrial conduction: a major predisposing factor for the development of atrial flutter. Circulation 1978;57:213–216.
15. **Allessie MA, Bonke FIM.** Atrial arrhythmias: basic concepts. In: Mandel WJ, ed. Cardiac Arrhythmias, Their Mechanisms, Diagnosis, and Management. Philadelphia: JB Lippincott, 1980:145–166.
16. **Curry PVL, Shenasa M.** Atrial arrhythmias: clinical concepts. In Ref 15: 167–192.
17. **Wells JL Jr, Karp RB, Kouchoukos NT, MacLean WAH, James TN, Waldo AL.** Characterization of atrial fibrillation in man: studies following open heart surgery. PACE 1978;1:426–438.
18. **Abildskov JA, Millar K, Burgess MJ.** Atrial fibrillation. Am J Cardiol 1971;28:263–267.
19. **Davies MJ, Pomerance A.** Pathology of atrial fibrillation in man. Br Heart J 1952;34:520–525.
20. **Josephson ME, Kastor JA.** Supraventricular tachycardia: mechanisms and management. Ann Intern Med 1977;87:346–358.
21. **Wu D, Denes P, Amat-y-Leon F, Dhingra R, Wyndham CRC, Bauernfeind R, Latif P, Rosen KM.** Clinical, electrocardiographic and electrophysiologic observations in patients with paroxysmal supraventricular tachycardia. Am J Cardiol 1978;41:1045–1051.
22. **Goldreyer BN, Gallagher JJ, Damato AN.** The electrophysiologic demonstration of atrial ectopic tachycardia in man. Am Heart J 1973;85:205–215.
23. **Gillette PC, Garson A Jr.** Electrophysiologic and pharmacologic characteristics of automatic ectopic atrial tachycardia. Circulation 1977;56: 571–575.
24. **Scheinman MM, Basu D, Hollenberg M.** Electrophysiologic studies in patients with persistent atrial tachycardia. Circulation 1974;50:266–273.

# Epicardial and Endocardial Activation in Patients With Endocardial Cushion Defect

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**Epicardial and left ventricular endocardial activation were assessed in 5 patients (aged 4 months to 9.5 years) with endocardial cushion defect (ECD) during surgical repair. Epicardial activation was recorded from 40 to 47 sites over the epicardium; left ventricular endocardial activation was measured at 3 sites immediately after institution of cardiopulmonary bypass. Compared with the reported activation sequence in normal hearts, the pattern of excitation in hearts of patients with ECD was abnormal; epicardial excitation began at the left ventricular diaphragmatic surface and spread laterally and anteriorly over the anterobasal left ventricle. It then merged with right ventricular wavefronts ending along the right ventricular anterior atrioventricular groove and outflow tract. Left ventricular endocardial activation also occurred earliest in the diaphragmatic segment of the left ventricle with later wavefronts recorded laterally and anteriorly.**

**This study demonstrates, for the first time in human subjects, correlation between left ventricular epicardial and endocardial activation in patients with ECD. The data indicate that earliest endocardial and epicardial activation occurs at the left ventricular diaphragmatic segments of the heart, and are consistent with the known posterior and inferior displacement of the specialized atrioventricular conduction system in patients with ECD.**

The electrocardiographic and vectorcardiographic pattern of a left superior frontal plane mean QRS electrical axis with a counterclockwise loop, commonly observed in patients with both partial and complete forms of ECD, has been attributed by anatomic and pathologic studies[1,2] to posterior and inferior displacement of the atrioventricular node and His bundle along with early take-off of the posterior fascicles of the left bundle. Although data from previous electrophysiologic studies[3–5] mapping ventricular activation in patients with ECD are consistent with these anatomic observations, these studies recorded activation from the epicardial surface, but not the endocardial surface. The present study was designed to examine the sequence of both endocardial and epicardial activation of the left ventricle in patients with ECD and to correlate left ventricular epicardial activation with endocardial activation.

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## Methods

Five children participated in this study (Table I), 3 females and 2 males aged 4 months to 9.5 years. Preoperative electrocardiograms were obtained in all 5 patients; vectorcardiograms were obtained in 2. Simultaneous electrocardiograms (using leads II, aVF, and $V_6$) and ventricular electrograms were recorded at surgery. All electrograms were recorded through bipolar electrodes (1 mm apart) connected to an Electronics for Medicine V1250A amplifier. The signal was filtered through a band width of 30 to 250 Hz, monitored on an Electronics for Medicine (VR12) switched-beam oscilloscope and recorded on photographic paper moving at 100 to 150 mm/s. Epicardial activation was recorded from 40 to 47 sites over the left and right ventricular epicardium, depending on individual heart size, before the initiation of cardiopulmonary bypass. After institution of cardiopulmonary bypass, the left ventricular endocardium was mapped through the atrial septal defect and the mitral valve from 3 sites: (1) the posterior paraseptal left ventricle, (2) the anterolateral left ventricular free wall, and (3) the anterior paraseptal left ventricle (Fig. 1). Esophageal temperature was maintained at 30 to 35°C during the study. The epicardial mapping procedure was completed within 15 minutes; left ventricular endocardial mapping was performed within 3 minutes after initiation of cardiopulmonary bypass. Activation times were measured from the onset of the QRS complex to the first fast action deflection to cross the isoelectric line in the electrogram; activation times in 5 to 15 consecutive sinus beats were measured and a mean activation time was computed. Values at

**TABLE I Clinical Data**

| Patient | Age & Sex | Diagnosis | Electrocardiogram | | Vectorcardiogram | |
|---|---|---|---|---|---|---|
| | | | QRS Duration (s) | Mean Frontal QRS Axis | Frontal Loop Rotation | Superior Frontal Plane (ms)* |
| 1 | 5 yr, F | ECD-P, cleft MV | 0.09 | 290° | CCW | 30 |
| 2 | 9 yr 6 mo, F | ECD-P, cleft MV | 0.10 | 250° | . . . | . . . |
| 3 | 4 yr, M | ECD-P, cleft MV | 0.08 | 320° | . . . | . . . |
| 4 | 1 yr 10 mo, M | ECD-P, cleft MV | 0.07 | 300° | . . . | . . . |
| 5 | 4 mo, F | ECD-C | 0.06 | 270° | CCW | 28 |

CCW = counterclockwise; ECD-C = endocardial cushion defect, complete; ECD-P = endocardial cushion defect, partial; MV = mitral valve.
* QRS axis within.

each mapping site in each patient were normalized by dividing the local activation time by the latest recorded ventricular activation time overall and then multiplied by 100. Due to elevation or retraction of the heart during intraoperative mapping, the QRS duration recorded on the surface electrocardiogram varied by approximately 15%; activation times were therefore corrected to baseline QRS duration.

**Definitions:** Epicardial breakthrough (EBT) is the site of emergence of a radially propagating wavefront at the epicardial surface, producing an island of early activation surrounded completely by points of later activation.[6] Latest epicardial activation (LEA) was defined as the latest recorded ventricular activation.[6]

## Results

The clinical, anatomic, and electrocardiographic data for each patient are summarized in Table I. The QRS duration ranged from 0.06 to 0.10 second (mean 0.08). The mean frontal plane QRS axis was superior in all cases, ranging from 320 to 250° (average 286). Vectorcardiograms were obtained in 2 patients (Cases 1 and 5). Both revealed counterclockwise frontal plane loops which became superior within 30 ms (30 and 28 ms, respectively). Analysis of scalar electrocardiograms on the remaining 3 patients indicated superior counterclockwise frontal plane loops.

**Epicardial map:** Epicardial maps were similar in all patients. No difference was observed in the map from the single patient (Case 5) with complete ECD. A typical example of local epicardial activation times (Patient 3) is depicted in Figure 2. The sequence of left ventricular activation was abnormal; the usual left ventricular EBT site in the basal area of the anterolateral left ventricle[6] was absent. In contrast, earliest left ventricular activation occurred at the diaphragmatic surface 15 ms after the onset of the electrocardiographic QRS complex. Subsequent left ventricular breakthrough was seen at 25 ms along the apical anterolateral left ventricular wall. Latest left ventricular activation was observed at the basal area of the anterolateral wall, 47 ms after the QRS onset; latest right ventricular activation, which represented the latest epicardial activation time recorded overall, was demonstrated in the anterior right atrioventricular groove at 61 ms.

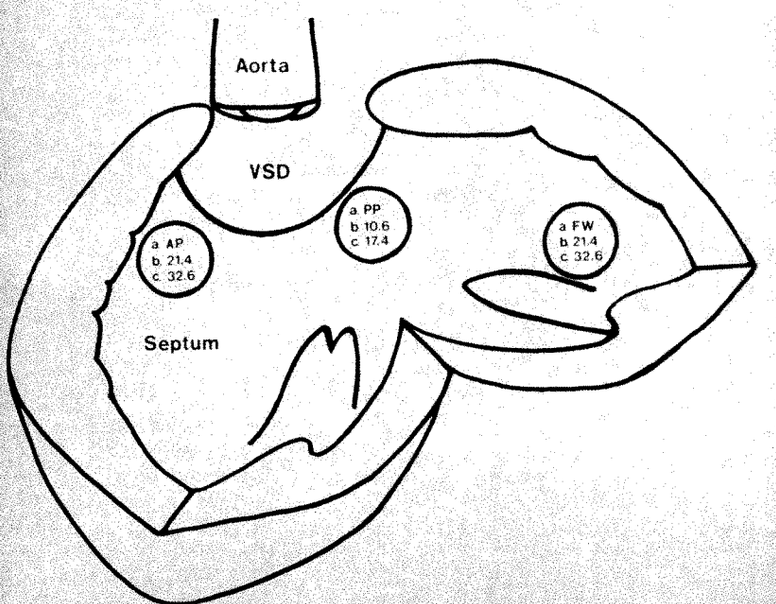



**FIGURE 1.** Composite map of left ventricular endocardial activation, with the left ventricle opened as a book. Mapping sites (a) are shown at PP (posterior paraseptal), AP (anterior paraseptal), and FW (free wall). Arrival of local activation at each site is recorded as mean milliseconds after QRS onset (b) and mean percent latest epicardial activation (c). Earliest left ventricular activation occurs posteriorly, with subsequent activation anteriorly and laterally. VSD = ventricular septal defect.

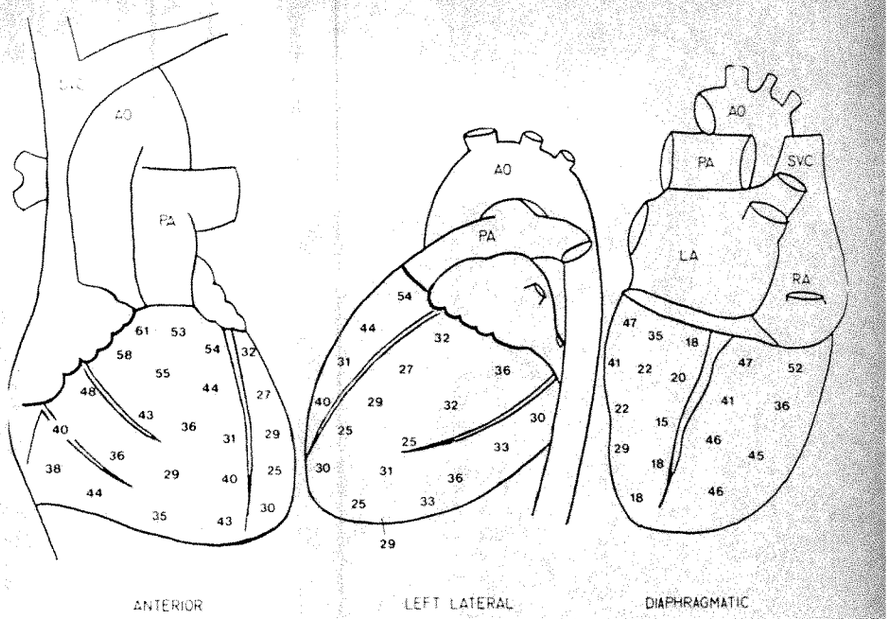



**FIGURE 2.** Epicardial maps from Patient 3. In this and Figure 3, the anterior, left lateral, and diaphragmatic views are shown. Each data point reflects arrival (in milliseconds) of local activation. Earliest epicardial activation occurs over the diaphragmatic left ventricle 15 ms after QRS onset. Activation then sweeps anteriorly and laterally to merge with an anterior right ventricular wavefront. Terminal left ventricular activation occurs over the anterobasal area. Terminal epicardial activation is recorded over the right ventricular inflow area. AO = aorta; LA = left atrium; PA = pulmonary artery; RA = right atrium; SVC = superior vena cava.

**Epicardial breakthrough:** EBT sites for both the left ventricle and the right ventricle are summarized in Table II. The distribution of left ventricular EBT sites was similar in all 5 patients. In each patient earliest left ventricular EBT (as well as earliest overall epicardial activation) was demonstrated over the diaphragmatic left ventricular surface, occurring 4 to 15 ms (mean 11.2) after the QRS onset. A subsequent left ventricular EBT site was observed along the anterolateral left ventricle in each patient (located toward the apical anterolateral left ventricle in Patients 3 and 4). The mean activation time at this left ventricular EBT site was 18.0 ms (range 14 to 15). The earliest right ventricular EBT site varied among the 5 patients; in Patients 1 and 3, the anterior paraseptal right ventricle was activated 22 and 29 ms, respectively, after QRS onset. The posterior right ventricle was activated in advance of the anterior paraseptal right ventricle in patients 2 and 5 (23 and 20 ms, respectively). The anterior paraseptal right ventricular and posterior right ventricular activations were virtually simultaneous (23 and 24 ms) in the remaining patient (Patient 4).

**Latest epicardial activation:** The site and timing of LEA are summarized in Table II. The latest left ventricular activation site was abnormally located in each of the 5 patients. In 4, the basal areas of the anterolateral left ventricle were activated last (34 to 50 ms after QRS onset, mean 45); in Patient 4, the anterior left ventricle and the basal segment of the anterolateral left ventricle were simultaneously activated (34 ms), forming the site of latest left ventricular activation. The diaphragmatic left ventricle was never the site of latest left ventricular activation. The site of latest right ventricular activation was in each patient the latest activated site on the ventricular epicardium, occurring 52 to 92 ms after onset of the QRS. In Patients 1 and 5, the inferior lateral inflow area of the right ventricle was the latest right ventricular site activated (63 and 52 ms,

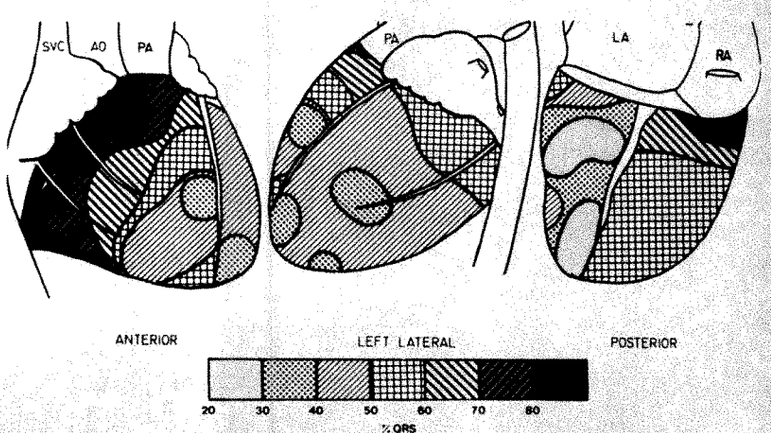



**FIGURE 3.** Composite epicardial map. Each point reflects mean percent latest epicardial activation at that point. Isochronic lines are drawn at 10 ms intervals. The pattern of epicardial activation corresponds to that described in Figure 2, and is discussed in the text. AO = aorta; LA = left atrium; PA = pulmonary artery; RA = right atrium; SVC = superior vena cava.

**TABLE II Epicardial and Endocardial Activation Data**

| Patient | EBT Site, Timing (ms) | | | | LEA Site, Timing (ms) | | Endocardial Activation Site Timing (ms) | | |
|---|---|---|---|---|---|---|---|---|---|
| | LV | | RV | | | | Posterior Paraseptal | Free Wall | Anterior Paraseptal |
| | EBT1 | EBT2 | EBT1 | EBT2 | LV | RV | | | |
| 1 | DLV, 4 | ALLV, 20 | ARV, 22 | PRV, 30 | BALV, 50 | RVI, 63 | 11 | 20 | 12 |
| 2 | DLV, 9 | ALLV, 14 | PRV, 23 | ARV, 36 | BALV, 47 | RVI, 92 | 0 | 11 | 19 |
| 3 | DLV, 15 | AALV, 25 | ARV, 29 | PRV, 36 | BALV, 47 | RVI, 61 | 8 | 35 | 39 |
| 4 | DLV, 14 | AALV, 16 | PRV, 23 | ARV, 24 | ALV, 34 BALV | RVI, 71 | 18 | 25 | 24 |
| 5 | DLV, 14 | ALLV, 15 | PRV, 20 | ARV, 26 | BALV, 37 | RVI, 52 | 16 | 17 | 13 |
| Mean (ms) | 11.2 | 18.0 | 23.4 | 30.4 | 43.0 | 69.6 | 10.6 | 21.6 | 21.4 |
| % LEA | 25 | 34 | 36 | ... | ... | ... | 17.4 | 33.8 | 32.6 |

AALV = apical anterolateral left ventricle; ALV = anterior left ventricle; ALLV = anterolateral left ventricle; ARV = anterior right ventricle; BALV = basal anterolateral left ventricle; DLV = diaphragmatic left ventricle; LV = left ventricle; PRV = posterior right ventricle; RV = right ventricle; RVI = right ventricular inflow area.

respectively); in the remaining 3 patients, activation terminated over the high anterior right ventricular inflow area near the proximal right coronary artery (61 to 92 ms, mean 75).

**Pattern of epicardial activation:** The pattern of epicardial activation—earliest to latest—was examined. Because the pattern of activation was similar in direction among the 5 patients, mean percent of LEA for each site among the patients was computed. A composite isochronic map for epicardial activation was constructed using these mean values (Fig. 3). Earliest EBT occurred at the diaphragmatic left ventricular surface at 25% LEA (mean 11.2 ms after QRS onset). A second left ventricular EBT site occurred at the left ventricular apical anterolateral surface at 34% LEA (mean 18 ms after QRS onset). Epicardial activation began over the diaphragmatic left ventricle and then fused with activation from the second left ventricular EBT site. Left ventricular activation advanced anterolaterally to the basal area of the anterolateral left ventricle. At 36% LEA (mean 23.4 ms) an anterior paraseptal right ventricular breakthrough site was observed. Activation from this epicardial site spread in a regular tangential manner over the anterior right ventricle to the atrioventricular groove and merged posteriorly with the advancing left ventricular wavefront. Latest right ventricular activation (and overall epicardial activation) was recorded over the anterior basal right ventricle.

**Endocardial activation:** Directed by the anatomic landmarks of the mitral valve commissures, we measured local excitation times at 3 widely separated left ventricular endocardial sites. The sequence of endocardial activation recorded from our patients with ECD is markedly different compared with that recorded from isolated adult human hearts by Durrer et al.[7] In 4 of our 5 patients, earliest left ventricular endocardial excitation was recorded from the posterior paraseptal segment (mean 9.3 ms after QRS onset, 14% LEA). In Patient 5 left ventricular endocardial activation at each of the 3 sites occurred within a 4 ms span (13 to 17 ms after QRS onset), virtually simultaneous with earliest recorded epicardial activity. In Patient 2, earliest left ventricular endocardial activity occurred simultaneously with the onset of the electrocardiographic QRS complex. Subsequent endocardial excitation, on the average, occurred at the left ventricular anterior paraseptal and anterolateral free wall at 33% and 34% LEA, respectively (Fig. 1). Thus, in 4 of our 5 patients, left ventricular activation sequence proceeded from the posterior segment anteriorly and laterally within the ventricle, an abnormal sequence.

## Discussion

In 1958, Lev[1] demonstrated anatomic posterior displacement of the left bundle by anatomic dissection of the conduction system in 4 hearts with ECD. Subsequent anatomic studies[2] confirmed posterior displacement of the atrioventricular node, common bundle, and short posteriorly directed left bundle fibers. In addition, anteriorly directed left bundle fascicles were decreased in number and increased in length; the right bundle branch fibers were also longer than normal. Durrer et al[3] demonstrated with epicardial mapping abnormally early activation of the posterior basal left ventricle, and Spach et al,[4] using isopotential body surface mapping, recorded an abnormal pattern of ventricular activation in ECD, best explained by earliest left ventricular diaphragmatic excitation with subsequent spread of the activation superiorly. The electrophysiologic study of Boineau et al[5] in 4 patients with ECD revealed earliest diaphragmatic left ventricular wall and later anterior left ventricular wall activation, with latest activation in the anterior right ventricular epicardium. In the same report, the sequence of endocardial Purkinje activation (recorded from a dog with congenital atrial septal defect, primum, by means of plunge electrodes) corresponds to the aforementioned anatomic developmental asymmetry of the ventricular conduction system. Our data confirm these studies and correlate for the first time in human subjects recordings from both the epicardial and left ventricular endocardial surfaces of the heart.

No published data of ventricular activation in human hearts from children of this age exist. Therefore, our data were compared to activation sequences obtained from studies in adults with normal QRS morphology and axis.[6,7] In our study, earliest epicardial activation of either ventricle occurred on the diaphragmatic sur-

face of the left ventricle between 4 and 15 ms (mean 11.2). Likewise, latest left ventricular epicardial activation was abnormal; in patients with a normal QRS, latest left ventricular epicardial activation occurred inferiorly 60 to 86 ms (mean 70) after QRS onset. In our patients, latest left ventricular activation never occurred inferiorly, but at the basal region of the anterolateral left ventricle between 34 and 50 ms (mean 43) after QRS onset.

The pattern of epicardial activation in our patients was likewise abnormal. In patients with a normal QRS morphology and axis, anterior right ventricular epicardial activation occurred before left ventricular epicardial activation.[6] In general, depolarization of the right ventricular outflow tract actually preceded posterobasal left ventricular activation. In contrast, the sequence of ventricular epicardial activation was altered in our patients with ECD; after early diaphragmatic left ventricular activation, the wavefront spread laterally and superiorly to the anterior left ventricle, with terminal anterior right ventricular activation. This abnormal early diaphragmatic left ventricular activation corresponds to the documented posterior displacement of the His bundle and shortened left bundle fascicles directed toward the posterior wall,[2] as well as a decreased number, increased length, or both, of anteriorly directed left bundle fascicles and right bundle branch fibers which has been observed in patients with ECD.

Our left ventricular endocardial data corresponded to the observed epicardial activation sequence; earliest left ventricular endocardial activation was recorded at the posterior segment with subsequent endocardial depolarization occurring along the anterolateral free wall and anterior paraseptal left ventricle. This endocardial activation sequence differs from previously described activation in isolated normal human hearts.[7] Four of our 5 patients with ECD revealed earliest posterior left ventricular endocardial activation, followed by free wall and anterior paraseptal areas. Patient 5 showed virtually simultaneous anterior, posterior, and free wall endocardial depolarization. The discrepancy in this patient may be explained by a lack of exact correspondence between the recorded and the actual sites of early left ventricular endocardial activation.

The clinical significance of this study is evident. Preliminary reports have suggested that both abnormal hemodynamic function and an imbalance between right and left ventricular mass may contribute to the superior meanrontal plane QRS axis in patients with ECD[8] and tricuspid atresia.[9] In view of the observation that the earliest points of endocardial and epicardial ventricular activation in our patients were displaced from the anterior left ventricle to the diaphragmatic left ventricle, our data reinforce the interpretation of others who have suggested that the major determinant of the superior mean frontal plane QRS axis in patients with ECD is due to the posterior and inferior displacement of the specialized atrioventricular conduction tissue,[1–5] rather than to either congenitally or hemodynamically induced ventricular hypertrophy. Ventricular epicardial and endocardial mapping would further clarify these and other variables (differential [right versus left] ventricular volume or pressure load), contributing to the superior QRS axis in patients with tricuspid atresia and other congenital cardiac defects (such as tetralogy of Fallot, double-outlet right ventricle, pulmonary stenosis, and ventricular septal defect) which can be associated with a superior mean frontal plane QRS axis.

## References


1. **Lev M.** The architecture of the conduction system in congenital heart disease. Arch Pathol 1958;65:174–191.
2. **Feldt RH, DuShane JW, Titus JL.** The atrioventricular conduction system in persistent common atrioventricular canal defect. Correlations with ECG. Circulation 1970;42:437–444.
3. **Durrer D, Roos JP, vanDam RTh.** The genesis of the ECG of patients with ostium primum defects (ventral atrial septal defects). Am Heart J 1966; 71:642–650.
4. **Spach MS, Boineau JP, Long EC, Gabor JB, Gallie ThM.** Genesis of the vectorcardiogram (electrocardiogram) in endocardial cushion defects. In: Hoffman I, Taymor RC, eds. Vectorcardiography, 1965. Amsterdam: North Holland, 1965:307–326.
5. **Boineau JP, Moore EN, Patterson DF.** Relationship between the ECG, ventricular activation and the ventricular conduction system in ostium primum ASD. Circulation 1973;48:556–564.
6. **Wyndham CR, Meeran MK, Smith T, Saxena A, Engleman RM, Levitsky S, Rosen KM.** Epicardial activation of the intact human heart without conduction defect. Circulation 1979;59:161–168.
7. **Durrer D, vanDam RTh, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC.** Total excitation of the isolated human heart. Circulation 1970;41:899–912.
8. **Borkon AM, Varghese PJ, Pieroni DR, Ho CS, Rowe RD.** An alternative explanation for superior axis in ostium primum ASD other than left anterior hemiblock (abstr). Pediatr Res 1974;8:347.
9. **Kulangara RJ, Boineau JP, Moore HV, Rao PS.** Ventricular activation and genesis of QRS in tricuspid atresia (abstr). Circulation 1981;64:Suppl IV: IV-225.

# Atypical Fallot's Tetralogy With Doubly Committed Subarterial Ventricular Septal Defect

## Diagnostic Value of 2-Dimensional Echocardiography

HORACIO CAPELLI, MD and JANE SOMERVILLE, MD, FRCP

**Five patients with clinical features of tetralogy of Fallot had subarterial doubly committed ventricular septal defect (VSD) with absence or deficiency of the infundibular septum. Two-dimensional (2-D) echocardiography differentiated this special group from those with the usual Fallot's anatomy. In addition to the long-axis view of the left ventricle which showed the subaortic VSD and the aortic and mitral fibrous continuity, the short-axis view at the cardiac base clearly demonstrated the subpulmonary extension of the VSD in the atypical group. Two-dimensional echocardiography was found superior to biplane angiography, which in 3 patients suggested the erroneous diagnosis of double-outlet right ventricle with pulmonic valve stenosis. This variant form of Fallot's tetralogy poses special surgical problems.**

The usual type of VSD found in patients with Fallot's tetralogy is large and subaortic: that is, it lies immediately beneath the aortic cusps which form the superior border.[1] The defect extends posteriorly to the tricuspid anulus. Thus, the posterosuperior border of the VSD is formed by the fibrous continuity between the aortic and tricuspid valves, and aortic and mitral continuity is also present.[2] A variant form has been recognized in patients with the clinical features of tetralogy of Fallot in which the VSD is below the aortic valve and extends up into the right ventricular outflow tract beneath the pulmonic valve because part or all of the infundibular septum is absent or deficient.[3,4] The posterosuperior border of this VSD is separated from the tricuspid anulus by muscle and the superior border is formed by the aortic valve and also part or all of the pulmonic valve. It is rightly described as subarterial[5] but it is also doubly committed to both aortic and pulmonic valves. In these patients the right ventricular obstruction is mainly due to pulmonic valve stenosis.[3,4] Although this variant form may appear as a case of mild Fallot's tetralogy, it requires an outflow patch enlargement across the pulmonic ring.[3]

Before operation, an erroneous diagnosis of double-outlet right ventricle is frequently made from angiographic appearances. The reliability of 2-D echocardiography in the recognition of Fallot's tetralogy with doubly committed subarterial VSD in 5 patients is reported herein.

### Methods

Five consecutive patients aged 4 months to 28 years with Fallot's tetralogy and doubly committed subarterial VSD were investigated between March 1981 and November 1981. They had full preoperative evaluation with 2-D echocardiography and biplane angiography using conventional anteroposterior and lateral views. Additional angiography using the elongated right anterior oblique projection with 30° craniocaudal tilt was used in 2. The anatomy of the VSD and the right ventricular outflow tract was demonstrated at open heart surgery in 4 and at necropsy in 1 patient who died from cerebral damage which occurred before an emergency Blalock shunt.

The 2-D echocardiograms were performed with an advanced laboratory mechanical sector scanner at 3.0 MHz (ATL-Mark 300). Patients were studied in the supine or left lateral 30° decubitus position. The transducer was placed to obtain the long- and short-axis views from the parasternal position, apical 4-chamber view, and the short-axis and 4-chamber views at the level of the great vessels from the subcostal position.[6] During the same period, 20 patients aged 6 months to 15 years with the classic form of Fallot's tetralogy and subsequent radical correction were studied; the 2-D echocardiographic findings were used for comparison.

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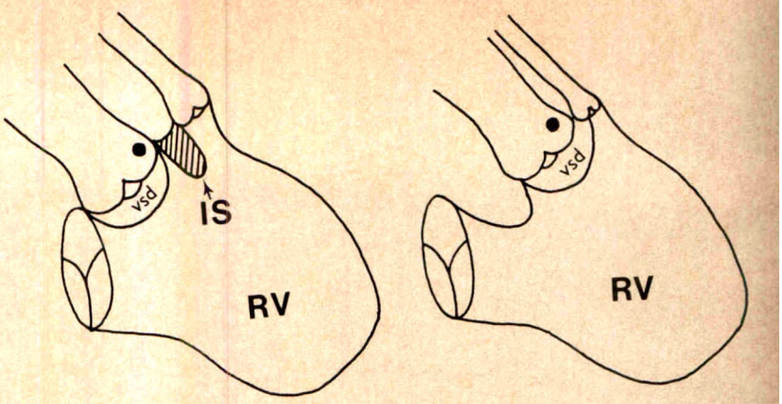



**FIGURE 1.** Anatomy of the ventricular septal defect (VSD) in patients with Fallot's tetralogy as viewed from the right ventricle (RV). **Left,** classic Fallot. Here, the ventricular septal defect lies beneath the aortic valve cusps (subaortic) and extends to the tricuspid anulus. It is separated from the pulmonic anulus by hypertrophied and displaced infundibular septum (IS). **Right,** Fallot tetralogy with doubly committed subarterial ventricular septal defect. The defect is still beneath the aortic cusps and does not extend posteriorly to the tricuspid anulus. It extends into the right ventricular outflow beneath the pulmonic anulus; the infundibular septum is absent.

## Results

**Pathologic anatomy:** The anatomy of the VSD in the 5 patients with the variant form was, at operation in 4 patients and at necropsy in 1, as described in Figure 1. In all instances the pulmonic valve was stenotic, bicuspid, and associated with a small ring. The right ventricular outflow tract appeared narrowed despite absence (4 patients) or hypoplasia (1 patient) of infundibular septum; no infundibular ostium was present. There was fibrous continuity between the anterior mitral valve and the aortic wall seen through the defect.

Two patients, aged 13 and 28 years, had associated aortic regurgitation due to prolapsing right coronary cusp, the aortic ring being completely calcified in the older patient.

**Two-dimensional echocardiographic findings:** *Classic Fallot's tetralogy:* The parasternal long-axis view of the left ventricle allowed clear visualization of the subaortic VSD, the malalignment of the ventricular septum, and the aortic-mitral fibrous continuity (Fig. 2). The relation of the VSD to the aortic valve cusps and to the infundibular septum and pulmonic valve was best seen in the short-axis view of the great vessels from the parasternal and subcostal positions. In these views, it was obvious that the large VSD was beneath the right coronary cusp and part of the noncoronary cusp extending to the tricuspid valve (Fig. 3). In both short-axis views the right ventricular outflow tract was obviously narrowed, and a conspicuous mass of tissue—hypertrophied infundibular septum—was identified between the aortic and pulmonic anuli. The pulmonic valve was in the usual position, that is, anterior to the right of the aortic valve in the echocardiographic image.

**Fallot's tetralogy with doubly committed subarterial ventricular septal defect:** The echocardiographic findings in the long-axis parasternal view were the same as in classic Fallot's tetralogy, which were described and shown previously (Fig. 2).

The position and anatomy of the VSD was also delineated in the short-axis view of the great vessels from

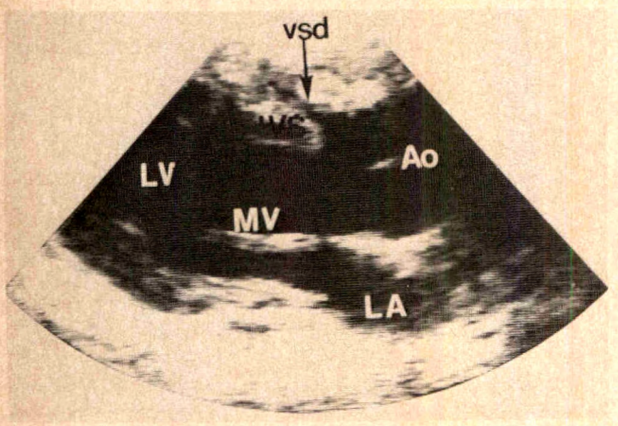



**FIGURE 2.** Two-dimensional echocardiographic long-axis view of the left ventricle (LV) in a patient aged 6 years with classic Fallot's tetralogy. It shows the large aorta overriding the subaortic ventricular septal defect (VSD) and the aortic-mitral fibrous continuity. Ao = aortic valve; IVS = intraventricular septum; LA = left atrium; MV = mitral valve.

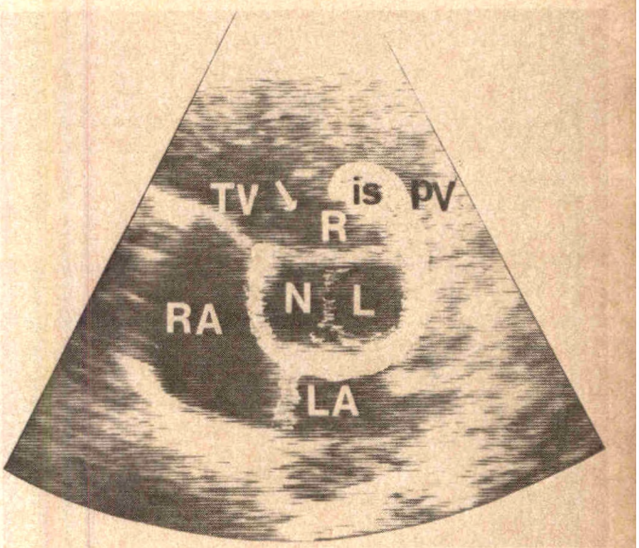



**FIGURE 3.** Two-dimensional echocardiographic parasternal short-axis view of the aorta from a patient aged 12 years with classic Fallot's tetralogy. It shows the ventricular septal defect lying beneath the right coronary cusp (R) extending to the noncoronary cusp (N). It reaches the tricuspid anulus by hypertrophied infundibular septum (IS). (This figure was retouched.) L = left coronary cusp; LA = left atrium; PV = pulmonic valve; RA = right atrium; TV = tricuspid valve.

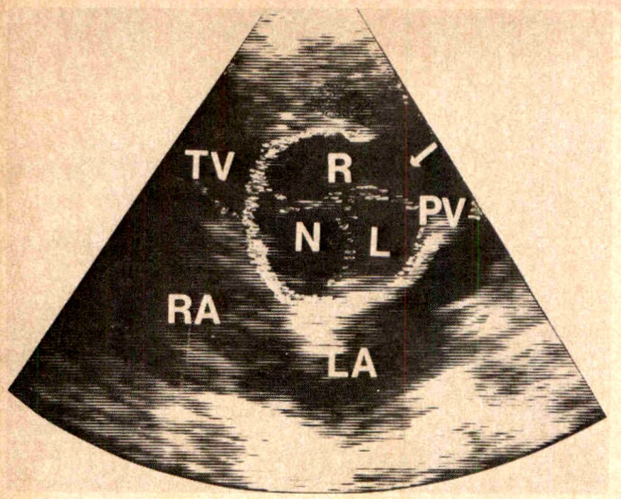



**FIGURE 4.** Two-dimensional echocardiographic parasternal short-axis view of the aorta in a patient aged 13 years with Fallot's tetralogy with doubly committed subarterial ventricular septal defect. Here, the ventricular septal defect lies beneath the right coronary cusp extending to the left coronary cusp. It is separated from the tricuspid anulus and extends into the outflow beneath the pulmonic valve. The infundibular septum is absent. (This figure was retouched.) Abbreviations as in Figure 3.

parasternal and subcostal positions. However, in this group the VSD was seen not only under the right coronary cusp, but also extended to the left commissure and below the pulmonic anulus, being clearly separated from the tricuspid valve (Fig. 4). The right ventricular outflow tract looked mildly narrowed, and there was no tissue separating the aortic and pulmonic valve rings. In these patients both arteries appeared adjacent to each other.

**Angiographic findings:** The right ventricular angiogram in the anteroposterior view showed the aortic and pulmonic rings side by side without the negative image of tissue separating the valves below (Fig. 5, top). In the lateral view the VSD looked classically subaortic and the aorta appeared much more anterior than in classic Fallot, suggesting that the aorta was coming directly off the right ventricle as in double-outlet right ventricle (Fig. 5, bottom), aortic-mitral continuity was difficult to identify. In 3, aged 4 months to 28 years, the appearances suggested discontinuity favoring the diagnosis of double-outlet right ventricle and pulmonic valve stenosis but 2-D echocardiography clearly demonstrated continuity.

## Discussion

Real-time 2-D echocardiography has been reported to be helpful in demonstrating the intracardiac anatomy in Fallot's tetralogy.[7–9] The standard parasternal long-axis view allows appreciation of the dilated aortic root overriding a large subaortic VSD and is reliable in demonstrating the aortic-mitral fibrous continuity. This was clearly seen in all of our patients irrespective of angiographic findings. However, in this view it was not possible to see the diagnostic subpulmonary extension of the VSD in the variant form with doubly committed subarterial VSD since it is observed from the left ventricle and thus appears to be only subaortic. The short-axis view at the cardiac base from parasternal position best demonstrated the position of the VSD in relation to the aortic, pulmonic, and tricuspid valves. The same view from subcostal position usually allows a better definition of certain anterior structures than can be obtained from the precordial position.[6] It was the best projection in assessing the morphology of the right ventricular outflow tract and specifically in detecting the absent infundibular septum in the 4-month-old patient. However, in the other 4 patients over age 12 years, it was not a good view because of the long distance between the subcostal area and the base of the heart which impaired definition.

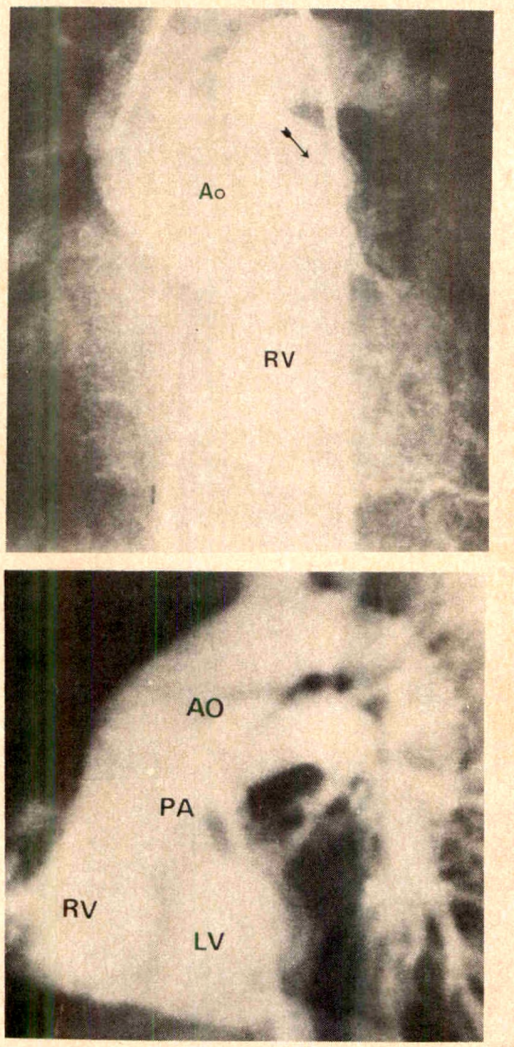



**FIGURE 5.** Right ventricular angiograms from patients with Fallot's tetralogy with doubly committed subarterial ventricular septal defect. Both have severe pulmonic valve stenosis. **Top,** anteroposterior view from a patient aged 16 years. It shows the aortic and pulmonic valves side by side without the negative image of tissue separating the valves below. **Arrow** indicates the pulmonic valve. **Bottom,** lateral view from a patient aged 4 months. The aorta (Ao) appears to be coming directly off the right ventricle as in double-outlet right ventricle. Aortic-mitral continuity is difficult to identify. LV = left ventricle; PA = pulmonary artery; RV = right ventricle.

Various descriptions have been used for this variant anatomic form of Fallot such as Fallot with subpulmonic,[3,4] subarterial,[5] or bulboventricular[10] VSD. We prefer simple descriptive terminology rather than nomenclature which involves imagination about cardiac embryology or development. Fallot's tetralogy with doubly committed subarterial VSD describes the defect simply. This entity is uncommon among series of Caucasian or European patients with tetralogy of Fallot. However, 4 of our 5 patients were Arabs from the Middle East. Our experience suggests that it occurs in at least 10% of patients with Fallot's tetralogy from the Arabian Gulf, an incidence similar to that in the Japanese.

A history of true cyanotic attacks was not present in any of our 5 patients. This is presumed to be related to the absence or deficiency of part of the anteriorly displaced infundibular septum which prevents development of a labile muscular and subsequently fixed obstruction in the right ventricular outflow tract. The severity of the right ventricular obstruction in these patients depends on the severity of the pulmonic valve stenosis and on the hypoplasia of the infundibulum or outflow tract of the right ventricle. After patching the VSD and opening the pulmonic valve once the ventriculotomy is closed, the surgeon may find important residual right outflow obstruction, irrespective of the resection of muscle. This results because the patch in the closed VSD extends up into the right ventricular outflow where previously a hole had been present, causing a narrowing beneath the pulmonic ring. Such cases require an outflow patch enlargement across the pulmonic ring, as did all 5 of our patients. Otherwise, right ventricular failure and unexpected death may complicate the postoperative course in what was thought to be a "good risk" patient.

Preoperative diagnosis may be difficult because in some patients the angiographic lateral view may suggest the diagnosis of double-outlet right ventricle with pulmonic valve stenosis. The absence of interposed muscle between aortic and pulmonic rings gives the erroneous impression of both vessels being committed to the right ventricle in a side-by-side position and appearing to be separated from the mitral valve. In the long-axis parasternal view of the left ventricle, 2-D echocardiography clearly delineates the aortic-mitral continuity and is therefore superior to angiography in ruling out double-outlet right ventricle.

Our patients were diagnosed as having Fallot's tetralogy with doubly committed subarterial VSD before surgery; however, angiography had been thought to show double-outlet right ventricle in 3. However, angiography was superior to echocardiography in assessing the size of the pulmonary arteries, particularly the left, which still remains as 1 of the unsolved challenges for echocardiography.

Two-dimensional echocardiography is a relevant noninvasive technique for diagnosing Fallot's tetralogy. However, it is important as part of a routine evaluation to delineate the VSD in both long- and short-axis parasternal views to see the boundaries of the defect in relation to the aortic cusps and pulmonic anulus. Without the short-axis parasternal view, the doubly committed subarterial VSD with absence or deficiency of the infundibular septum may be missed. The surgeon, particularly early in his experience, should be warned of the presence of this variant and the problems which may be encountered.

**Acknowledgment:** We thank Marc de Leval, MD, who operated on these patients and who carefully explained and described the intracardiac anatomy.

## References

1. **Goor DA, Lillehei CW, Edwards JE.** Ventricular septal defect and pulmonic stenosis with and without dextroposition. Anatomic features and embryologic implications. Chest 1971;60:117–128.
2. **Becker AE, Connor M, Anderson RH.** Tetralogy of Fallot: a morphometric and geometric study. Am J Cardiol 1975;35:402–412.
3. **Neirotti R, Galindez E, Kreutzer G, Rodriguez Coronel A, Pedrini M, Becu L.** Tetralogy of Fallot with subpulmonary ventricular septal defect. Ann Thorac Surg 1978;25:51–56.
4. **Ando M.** Subpulmonary ventricular septal defect with pulmonary stenosis. (letter). Circulation 1974;50:412.
5. **Soto B, Pacifico AD, Ceballos R, Bargeron L.** Tetralogy of Fallot: an angiographic-pathologic correlative study. Circulation 1981;64:558–566.
6. **Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT.** Two dimensional real-time ultrasonic imaging of the heart and great vessels. Technique, image orientation, structure, identification and validation. Mayo Clin Proc 1978; 53:271–303.
7. **Hagler DJ, Tajik AJ, Seward JB, Mair DD, Ritter DG.** Wide-angle two-dimensional echocardiographic profiles of conotruncal abnormalities. Mayo Clin Proc 1980;55:73–82.
8. **Sahn DJ, Terry R, O'Rourke R, Leopold G, Friedman WF.** Multiple crystal cross-sectional echocardiography in the diagnosis of cyanotic congenital heart disease. Circulation 1974;50:230–238.
9. **Henry WL, Maron BJ, Griffith JM.** Cross-sectional echocardiography in the diagnosis of congenital heart disease: identification of the relation of the ventricles and great arteries. Circulation 1977;56:267–273.
10. **Matsuda H, Ihara K, Mori T, Kitamura S, Hawashima Y.** Tetralogy of Fallot associated with aortic insufficiency. Ann Thorac Surg 1980;29:529–533.

# Supraventricular Tachycardia in Infants: Use of the "Diving Reflex"

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**The effectiveness of the "diving reflex" in treating paroxysmal supraventricular tachycardia (PSVT) in 10 infants aged under 6 months is demonstrated. No rhythm disturbances were encountered during the maneuver, even in patients receiving digitalis. The recommended water temperature is 5°C and the total time of facial immersion, between 6 and 7 seconds. The diving reflex might be considered the first therapeutic approach in infants under 6 months old with PSVT.**

PSVT is a commonly observed pediatric emergency[1] in infants, and rapid conversion to sinus mechanism is imperative. Many methods of treatment have been advocated, such as vagal maneuvers (stimulated by carotid sinus and unilateral eyeball pressure, induction of vomiting, breath-holding, or the Valsalva maneuver), which have rarely been successful in terminating tachycardia in infants. Other therapies such as intravenous digitalis, verapamil, and direct current countershock entail risks.

Immersion of the face in cold water, which stimulates the diving reflex, may stop attacks of PSVT in both adults and children,[2–4] but the procedure has not often been used in infants with PSVT.[5,6] We have used the diving reflex in the treatment of PSVT in 10 infants; our experience is reported herein.

## Methods

The patients ranged in age from 14 days to 5 months (average 55 days). Seven were boys and 3 were girls. Only 1 patient had associated congenital heart disease (moderate pulmonary valvular stenosis). Three patients were receiving digitalis therapy (15 μg/kg/day orally) when hospitalized but without beneficial effect.

All but 1 had features of congestive heart failure as judged by sweating, tachypnea, gallop rhythm, enlargement of liver, peripheral cyanosis, and restlessness. Five patients had type A and 1 had type B Wolff-Parkinson-White syndrome, 2 had normal electrocardiograms, and 1 had a short P-R interval with normal ventricular depolarization (Lown-Ganong-Levine pattern). The ventricular rate during PSVT varied from 270 to 320 beats/min (mean 295). The QRS configuration remained unchanged during the attacks in all patients. Carotid sinus massage, unilateral eyeball pressure, and induction of vomiting were unsuccessful in stopping the PSVT in all patients.

The diving maneuver was performed as follows: diving reflex was stimulated through immersion of the infant's face in a basin of ice water at 4 to 5°C for 6 to 7 seconds. Their nostrils were manually closed to prevent aspiration. A precordial lead (generally lead $V_1$) connected the patient to a continuous writing electrocardiograph before and during facial immersion. The sensitivity of the recorder was adjusted for optimal amplitude to keep note of a satisfactory P wave. A defibrillation machine was held in readiness throughout in case of serious ventricular tachyarrhythmias. A 24-hour Holter monitoring was performed on every patient the day after the conversion to sinus rhythm as a precaution and to confirm the results.

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## Results

In all patients in whom the diving reflex maneuver was applied, sinus rhythm was restored immediately (Fig. 1). The diving reflex was used 13 times in the 10 patients because in 1 patient PSVT recurred once, and in another, twice. Ventricular arrhythmias did not occur during the maneuver or during Holter monitoring, even in the 3 patients receiving digitalis. After conversion to sinus rhythm, all patients were treated with digitalis (digoxin orally 10 to 15 μg/kg/day) which was continued for 1 year. Five patients were followed for 1 year, and none had any clinical recurrence of PSVT.

## Discussion

The diving reflex is an oxygen-conserving reflex consisting of striking bradycardia and peripheral vasoconstriction which results in increased blood flow to the brain and heart. This reflex was first observed in diving vertebrates such as seals and ducks.[7] In aquatic vertebrates, the diving reflex is strongly developed and occurs during both activity and rest.

This reflex is initiated partly through the stimulation of afferent nerve endings in the area of the mouth and nose by the cold water. The efferent limb of the reflex is mediated by increased sympathetic stimulation to peripheral vessels (except to the brain and heart) and, simultaneously, by intense vagal stimulation to the heart.[8,9] The increased vagal tone to the heart seems to produce the bradycardia connected with facial immersion. Apnea alone causes similar but much less extreme cardiovascular response.

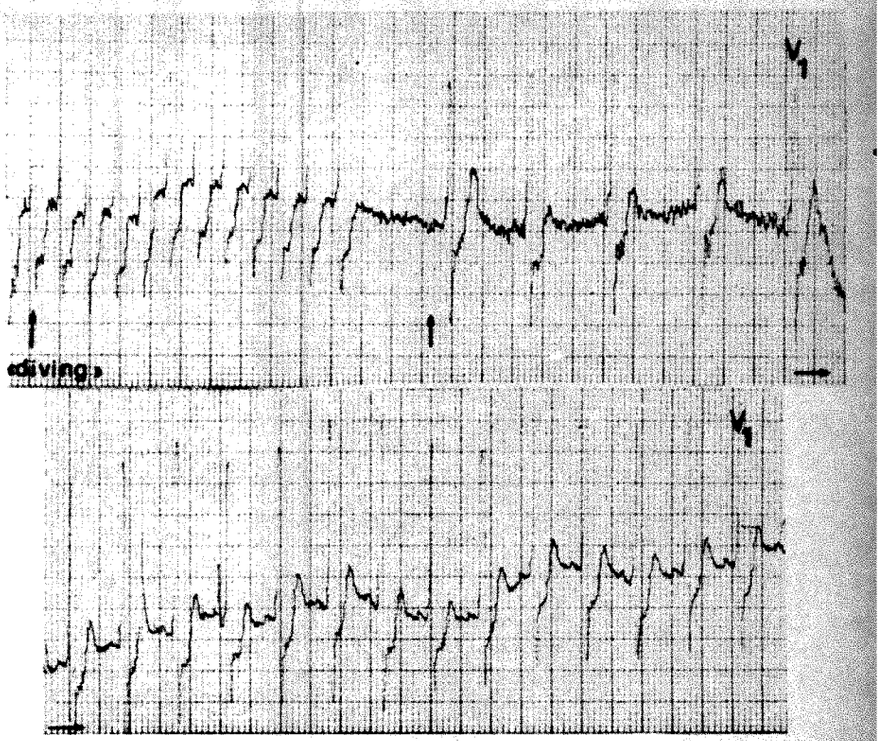



**FIGURE 1.** Continous tracing during immersion (**arrow**) that shows conversion of PSVT to normal sinus rhythm in approximately 3.5 seconds, by breaking the arrhythmias in the retrograde limb of the reentrant circuit through the atrioventricular node.

Investigations into the cardiovascular effects of facial immersion and into the factors affecting the diving reflex in man[10–16] have shown that the greatest decrease in the heart rate was during breath-holding in cold water immersion. Because the decrease in heart rate occurs rapidly and most prominently after facial immersion in cold water, diving bradycardia is believed to be a reflex mainly stimulated by facial immersion. Thus, asphyxia is not the main factor in evoking the diving reflex, but remains important in that it intensifies the bradycardia stimulated by facial immersion.

The first successful clinical applications of the diving reflex as a treatment for PSVT were recorded in adults.[2,3,17]

The temperature of the bath used for immersion has been noted to play an important role in decreasing the heart rate.

It was found that the vagal response becomes more intense when the temperature of the bath is <20°C, and it has been suggested that the diving bradycardia is most profound at about 18°C.[18,19]

Ventricular tachycardia has been observed in adults after facial immersion for 30 seconds in an ice-water bath at about 4°C.[20] Perhaps the severely cold temperature and the prolonged immersion resulted in a considerable catecholamine discharge which may have been responsible for ventricular dysrhythmias.

The diving reflex can be induced quite easily; it is a noninvasive, painless, and rapidly reversible procedure. This maneuver is also useful in patients who are receiving digitalis. This kind of treatment does not provide protection against future episodes of PSVT and, of course, it cannot replace conventional prophylactic therapy.

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## References

1. **Keith JD, Rowe RD, Vlad P.** Heart Disease in Infancy and Childhood. 2nd ed. New York: McMillan, 1978:1056–1062.
2. **Wildenthal K, Atkins J, Leshin S, Skelton CL.** The diving reflex used to treat paroxysmal atrial tachycardia. Lancet 1975;1:12–14.
3. **Wildenthal K, Atkins JM.** Use of the diving reflex for the treatment of paroxysmal supraventricular tachycardia. Am Heart J 1979;98:536–537.
4. **Whitman V, Zakeosian G.** The diving reflex in termination of supraventricular tachycardia in childhood. J Pediatr 1976;89:1032–1033.
5. **Whitman V, Friedman Z, Berman W, Maisels MJ.** Supraventricular tachycardia in newborn infants: an approach to therapy. J Pediatr 1977; 91:304–305.
6. **Hamilton J, Moodie D, Levy J.** The use of the diving reflex to terminate supraventricular tachycardia in a 2-week-old infant. Am Heart J 1979;97: 371–374.
7. **Yonce LR, Folkow B.** The integration of the cardiovascular response to diving. Am Heart J 1970;79:1–4.
8. **Andersen HT.** The reflex nature of the physiological adjustments to diving and their afferent pathway. Acta Physiol Scand 1963;58:263–273.
9. **Finley JP, Bonet JF, Waxman MB.** Autonomic pathways responsible for bradycardia on facial immersion. J Appl Physiol 1979;47:1218–1222.
10. **Brick I.** Circulatory response to immersing the face in water. J Appl Physiol 1966;21:33–36.
11. **Craig AB Jr.** Heart rate response to apneic underwater diving and to breath holding in man. J Appl Physiol 1963;18:854–862.
12. **Kawakami Y, Natelson B, DuBois AB.** Cardiovascular effects of a face immersion and factors affecting diving reflex in man. J Appl Physiol 1967;23:964–970.
13. **Kobayasi S, Ogawa T.** Effect of water temperature on bradycardia during nonapneic facial immersion in man. Jpn J Physiol 1973;23:613–624.
14. **Olsen CR, Fanestil DD, Scholander PF.** Some effects of breath holding and apneic underwater diving on cardiac rhythm in man. J Appl Physiol 1962; 17:461–466.
15. **Paulev PE.** Cardiac rhythm during breath holding and water immersion in man. Acta Physiol Scand 1968;73:139–150.
16. **Paulev PE, Hansen HG.** Cardiac response to apnea and water immersion during exercise in man. J Appl Physiol 1972;33:193–198.
17. **Whayne TF Jr, Killip T.** Simulated diving in man: comparison of facial stimuli and response in arrhythmia. J Appl Physiol 1967;22:800–807.
18. **Hunt NG, Whitaker DK, Willmott NJ.** Water temperature and the "diving reflex." Lancet 1975;1:572.
19. **Pickering R, Bolton-Maggs P.** Treatment of supraventricular tachycardia. Lancet 1975;1:340.
20. **Condry P, Jain A, Marshall R, Bowter A.** Ventricular tachycardia caused by the diving reflex. Lancet 1975;2:1263.

# Impact of 2-Dimensional Echocardiography on the Management of Distressed Newborns in Whom Cardiac Disease Is Suspected

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**The course and management of 40 consecutive newborns (aged <2 weeks) who presented with signs and symptoms of congenital heart disease were reviewed to determine the impact of 2-dimensional (2-D) echocardiography on their subsequent management. Of the 40 patients with congenital heart disease, 60% did not undergo cardiac catheterization. Forty-two percent of the patients who were treated surgically went directly to operation without preoperative cardiac catheterization. Only 40% of the patients with congenital heart disease required cardiac catheterization in the newborn period, and 43% of these procedures were primarily therapeutic (that is, balloon atrial septostomy). In each patient 2-D echocardiography correctly identified the major cardiac malformation and there was good agreement with angiographic, surgical, and autopsy findings. The most commonly overlooked defect was a patent ductus arteriosus. Thus, 2-D echocardiography not only allows diagnosis of congenital heart disease in the newborn but can expedite clinical management. No longer is cardiac catheterization necessarily the primary means for an anatomic diagnosis of congenital cardiac malformations in the newborn.**

Most noncardiac causes of cyanosis can be excluded by clinical or laboratory findings.[1,2] In addition to the physical examination, laboratory results, chest x-ray study,[3] and electrocardiogram, cardiac catheterization has to date played a central role in the anatomic and hemodynamic assessment of the distressed newborn in whom a cardiac malformation is suspected. In the last few years, 2-D echocardiography has also become established as a tool for the diagnosis of congenital heart disease.[4–15] In addition, contrast[16,17] and Doppler[18–20] echocardiography have enhanced the echocardiographic examination, and high-frequency transducers have increased the feasibility of accurately examining the small neonatal heart.

Because the 2-D echocardiographic examination may allow a definitive anatomic diagnosis in cases of congenital heart disease, it therefore also has potential use in directing medical or surgical management and in changing the indications for cardiac catheterization. Although 2-D echocardiography is now an accepted part of the diagnostic evaluation, its impact on the subsequent management of the newborn has not previously been emphasized. Perhaps a complete 2-D echocardiographic examination may replace cardiac catheterization as the "examination of choice" in selected newborns with congenital heart disease.

This report reviews the course and management of 40 consecutive newborns aged <2 weeks who presented with clinical features suggesting congenital heart disease and emphasizes the increasing importance of high-resolution 2-D echocardiography in the evaluation and management of distressed newborns.

## Methods

Forty consecutive distressed newborns aged <2 weeks (mean 3.5 days) were suspected of having a significant cardiac problem. Usually clinical examination had taken place and the potential of a serious cardiac malformation had been recognized before the 2-D examination. Appropriate labora-

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tory tests, chest x-ray examination, and electrocardiogram were not always available before the echocardiographic examination (12 of 40 patients, 30%) (Table I). In each case, the 2-D echocardiographic examination was performed early in the hospitalization before management decisions (medical treatment, cardiac catheterization, or surgery) were made (Table I).

To assess the role of echocardiography in the management of these newborns, we paid particular attention to our ability to establish complete and accurate anatomic diagnosis and determine appropriate further intervention on the basis of information obtained at echocardiography.

An Advanced Technology Laboratory (Mark V) 2-D mechanical sector scanner with a 5-MHz transducer and Doppler and M-mode capabilities was utilized. A detailed and complete 2-D echocardiographic examination of cardiac and extracardiac vascular structures was performed in each instance. The usual 2-D echocardiographic scanning techniques have been described,[13] including the use of contrast[16,17] and Doppler echocardiography.[18-20]

Echocardiographic findings were compared with angiographic and surgical findings when available (Table I). In patients who died and were autopsied, the pathologic anatomy of the cardiopulmonary specimen was studied in detail and

**TABLE I Clinical Data in 35 Patients**

| Case | Age (days) & Sex | Diagnosis* Clinical | Diagnosis* Echocardiography (Catheterization) | Procedure and Additional Findings (Surgery/Autopsy) |
|---|---|---|---|---|
| | | Managed Without Cardiac Catheterization (21 Patients) | | |
| 1 | 2/F | PA + VSD, ?PDA, UVH | PA, DORV, PDA | NS; died, no Au |
| 2 | 1/M | PS vs TGA vs EA | PA with IVS | PV, BT shunt; PDA† lig; died, no Au |
| 3 | 1/M | PA with PDA vs TA | PA, IVS, HRH, ASD, PDA | BT shunt; PDA† lig |
| 4 | 1/F | * | PA, IVS, HRH | PV, BT shunt; PDA† lig |
| 5 | 1/F | UVH, ?EA | PA, mild EA, ASD | Waterston shunt; died, no Au |
| 6 | 1/M | * | PS, TOF | . . . |
| 7 | 1/M | * | PA, dextrocardia, UVH, common AV valve | Waterston shunt; Au+, asplenia |
| 8 | 7/F | PDA vs VSD | PDA | . . . |
| 9 | 7/M | VSD, AS; R/O truncus | PDA | . . . |
| 10 | 3/F | PDA, HLH | PDA | PDA lig; Au |
| 11 | 14/F | PDA | PDA | . . . |
| 12 | 2/F | * | PDA | PDA lig; Au |
| 13 | 2/F | * | Paramembranous VSD | Closure VSD & ASD;† PDA† lig; Au+ (3 1-mm VSD) |
| 14 | 4/F | VSD; R/O PDA, ASD | TOF, ASD | . . . |
| 15 | 1/M | * | Complete AV canal, PDA | NS; died, no Au |
| 16 | 14/F | Complete AV canal | Complete AV canal | . . . |
| 17 | 2/M | TGA vs PA/TA vs HLH | HLH | NS; died, no Au |
| 18 | 3/M | L-TGA with VSD, PDA, UVH | HLH | NS; died no Au |
| 19 | 1/M | * | Severe AS | Aortic valvotomy; PDA† lig |
| 20 | 1/F | TI, PFC, PDA, PS | AS | . . . |
| 21 | 2/F | Interrupted arch; R/O TAPVC | Shone's syndrome | . . . |
| | | Required Therapeutic Cardiac Catheterization (Balloon Septostomy, 6 Patients) | | |
| 22 | 1/F | RVOT obstruct. | Severe EA, RVOT obstruct., ASD; PDA‡ | BT shunt, PDA lig; Au+, patent RVOT |
| 23 | 14/M | * | TA, ASD | PAB |
| 24 | 4/F | PS vs PA vs EA vs TGA; R/O TAPVC | TGA with IVS, PDA‡ | Septectomy |
| 25 | ½/M | * | TGA with IVS | BT shunt, PAB; died, no Au |
| 26 | 1/M | IDM; R/O TGA, PDA | TGA with IVS | Jatene procedure; PDA† lig; Au |
| 27 | 1/M | * | TGA with IVS, ASD, PDA | . . . |
| | | Required Diagnostic Cardiac Catheterization (8 Patients) | | |
| 28 | 3/M | CAVF vs AP window vs PDA; R/O AS, truncus | PS, ASD, ?interrupted arch; normal arch, PDA‡ | PV |
| 29 | 8/M | VSD, ?PS | PS, TGA, UVH | BT shunt |
| 30 | 2/F | PS vs TGA with IVS vs PA/TA | HOCM | RVOT myectomy; Au |
| 31 | 2/M | * | Hypoplastic tricuspid valve, PFO | . . . |
| 32 | 14/F | VSD | Paramembranous VSD | Closure VSD; PDA† lig |
| 33 | 1/F | PA with PDA | Complete AV canal, common atrium, small LV and MV; PDA‡ | NS; Au |
| 34 | 2/F | HLH | Interrupted arch, VSD, ASD, PDA; postductal coarc‡ | MPA-desc aorta graft, PDA lig, PAB; Au |
| 35 | 14/M | Coarc, VSD and PDA; R/O interrupted arch | Interrupted arch, PDA, VSD | Pulm art-desc aorta graft, PDA lig, PAB |

* Asterisks in this column indicate that no definite clinical diagnosis was made before 2-D echocardiography was performed. † Additional significant finding at surgery. ‡ Additional significant finding at catheterization.

AS = aortic stenosis; AP = aortopulmonary; ASD = atrial septal defect; Au = autopsy; Au+ = additional finding at autopsy; AV = atrioventricular; BT = Blalock-Taussig; CAVF = coronary arteriovenous fistula; Coarc = coarctation; DORV = double-outlet right ventricle; EA = Ebstein's anomaly; HLH = hypoplastic left heart; HRH = hypoplastic right heart; HOCM = hypertrophic obstructive cardiomyopathy; IDM = infant of a diabetic mother; IVS = intact ventricular septum; lig = ligation; LV = left ventricle; MPA-desc = main pulmonary artery-descending; MV = mitral valve; NS = surgery not performed; obstruct. = obstruction; PA = pulmonary atresia; PAB = pulmonary artery banding; PDA = patent ductus arteriosus; PFC = persistent fetal circulation; PFO = patent foramen ovale; Pulm art-desc = pulmonary artery-descending; PS = pulmonary stenosis; PV = pulmonary valvotomy; R/O = rule out; RVOT = right ventricular outflow tract; TA = tricuspid atresia; TAPVC = total anomalous pulmonary venous connection; TGA = transposition of the great arteries; TI = tricuspid insufficiency; TOF = tetralogy of Fallot; UVH = univentricular heart; VSD = ventricular septal defect.

correlated with echocardiographic findings. The patients have been categorized according to whether they (1) had a noncardiac disorder (5 patients), (2) were managed without cardiac catheterization (21 patients), or (3) required either therapeutic or diagnostic cardiac catheterization (14 patients).

## Results

### Part I

**Noncardiac disorders (5 patients):** No structural cardiac abnormalities were found with 2-D echocardiography in 5 cyanotic patients. Three patients had persistent fetal cardiopulmonary circulation, 1 had transient tachypnea of the newborn, and 1 had transient cyanosis. All were managed medically without further diagnostic cardiac studies. One patient with persistent fetal circulation died from progressive hypoxia at age 3 days.

**Congenital heart disease (35 patients):** The 35 newborns with cardiac defects were reviewed in detail to assess the influence of 2-D echocardiography on their management. Three basic groups were analyzed: (1) no additional diagnostic studies needed (21 of 35, 60%); (2) diagnostic or therapeutic catheterization needed (14 of 35, 40%); and (3) operation needed (19 of 35, 54%; 8 of these 19 patients (42%) had no preoperative cardiac catheterization).

*1. No additional diagnostic studies needed:* Twenty-one patients (60%) underwent no further diagnostic cardiac studies in the neonatal period; 13 were managed medically and 8 went directly to operation after echocardiography. Two patients (Cases 17 and 18) had currently uncorrectable cardiac anatomy (hypoplastic left heart); 1 (Case 1) had trisomy 18 in addition to double-outlet right ventricle with pulmonary atresia. Of the remaining 10 medically treated patients, 3 had a patent ductus arteriosus. Five patients (Cases 6 and 14, tetralogy of Fallot; Case 16, complete atrioventricular canal; Case 20, supravalvular and valvular aortic stenosis; and Case 21, Shone's syndrome) are currently being treated medically. One patient (Case 13 Down's syndrome) underwent closure of a ventricular septal defect at age 8 months, without preoperative cardiac catheterization, and died postoperatively from respiratory insufficiency. One patient (Case 15) with complete atrioventricular canal died from severe congestive heart failure at age 1 day.

Eight additional patients had no further diagnostic studies but proceeded directly to operation (see later).

*2. Need for catheterization:* Fourteen newborns (40%) with cardiac anomalies detected with echocardiography had cardiac catheterization in the newborn period. Six patients (43%) underwent catheterization primarily for balloon atrial septostomy (therapeutic catheterization). After septostomy, angiography confirmed the echocardiographic diagnosis without demonstrating any other significant malformation. Four (Cases 24 to 27) had transposition of the great arteries, 1 (Case 23) had tricuspid atresia, and 1 (Case 22) had severe Ebstein's anomaly and associated pulmonary atresia. In these 6 patients, the balloon atrial septostomy was partly directed and its adequacy was confirmed by 2-D echocardiography. One patient has been managed medically and 5 subsequently required surgery, 3 of whom died.

Eight (57%) of the 14 patients required diagnostic cardiac catheterization in the first 2 weeks of life. These catheterizations were done (in addition to 2-D echocardiography) either to permit further delineation of extracardiac anatomy (Cases 28, 34, and 35) or to assess hemodynamic function (Cases 29 through 33). Interrupted aortic arch was suspected echocardiographically in 3 patients, and cardiac catheterization confirmed this diagnosis in 2 (Cases 34 and 35) but not in the third (Case 28). Five patients underwent cardiac catheterization for hemodynamic data—2 patients to assess right ventricular outflow gradient (Cases 29 and 30), 1 to evaluate tricuspid stenosis as a therapeutic baseline (Case 31), 1 to determine the degree of atrioventricular valve regurgitation in the presence of complete atrioventricular canal (Case 33), and 1 with a membranous ventricular septal defect to rule out associated muscular ventricular septal defects (Case 32). Two patients were subsequently managed medically and 6 were managed surgically. Three patients died, 2 treated surgically and 1 treated medically.

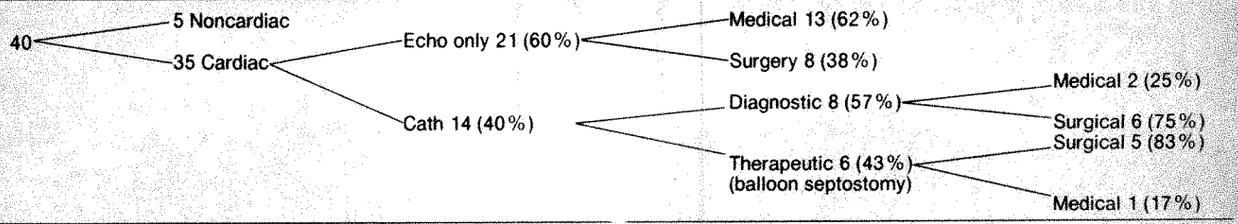
*3. Need for operation:* Nineteen newborns (54%) underwent surgery. Eight of the 19 surgical patients (42%) underwent an operation soon after 2-D echocardiographic evaluation without preoperative cardiac catheterization; 2 operations were for ligation of a patent ductus arteriosus. Most of the operations (5 patients) were emergency procedures and were confined to placement of a systemic-to-pulmonary artery shunt (Cases 2 to 5 and 7). One patient (Case 19) had an aortic valvotomy. In 5 of the remaining 11 patients who had preoperative cardiac catheterization, this examination was primarily therapeutic (balloon septostomy) and was not used as the primary diagnostic procedure.

For comparison with this recent experience, the preoperative management of 25 infants aged <2 weeks who underwent surgery from 1977 through 1980 was reviewed. Ten distressed newborns with an isolated patent ductus arteriosus went directly to surgery without cardiac catheterization. All of the remaining 15 patients had preoperative cardiac catheterization. In the present study, both patients with isolated patent ductus arteriosus went directly to surgery; however, 6 (35%) of the remaining 17 patients also went to surgery without catheterization. This later group consisted mainly of those who required an emergency shunt procedure and did not require further anatomic delineation other than that obtained with 2-D echocardiography (Table II).

### Part II

**Mortality:** Sixteen (46%) of the 35 newborns with a cardiac anomaly ultimately died. In addition, 1 patient with persistent fetal cardiopulmonary circulation died. Two patients (Cases 17 and 18) had a currently uncorrectable cardiac malformation and 1 (Case 1) had trisomy 18. All 3 died early in life. Seven patients (Cases

**TABLE II Management of 40 Newborns in Whom Congenital Heart Disease Was Suspected and Impact of 2-Dimensional Echocardiography**




| | No Catheterization | | Catheterization | | |
|---|---|---|---|---|---|
| | Noncardiac | Cardiac | Diagnostic | Therapeutic | Total |
| Surgical | 0 | 8 | 6 | 5 | 19 |
| Medical | 5 | 13 | 2 | 1 | 21 |
| | 5 | 21 | 8 | 6 | 40 |

Cath = catheterization; echo = echocardiography.

2, 5, 7, 25, 26, 30, and 34) died in the immediate postoperative period. Two patients died from unrelated medical problems—myotonic dystrophy (Case 10) and after colostomy for imperforate anus (Case 33). Three patients died late after operation: 1 (Case 13, with Down's syndrome) from respiratory insufficiency, 1 (Case 12) from septic shock, and 1 (Case 22) from arrhythmias. One critically ill newborn (Case 15) with complete atrioventricular canal died from congestive heart failure in the first 24 hours of life.

### Part III

**Angiographic-surgical-autopsy correlation (Table I):** In 24 (69%) of 35 patients evaluation of the cardiac defect with angiography, during surgery, or at autopsy (or more than 1 of these methods) was possible: 14 with angiography, 13 during surgery, and 10 at autopsy. In all 24 patients, the major anatomic cardiac malformation was correctly diagnosed with 2-D echocardiography. The following lesions were missed or mistakenly interpreted by the echocardiographer:

*Patent ductus arteriosus:* Eight patients had an associated patent ductus arteriosus which was not visualized with 2-D echocardiography but was found during catheterization (4 patients), surgery (6 patients), or autopsy (1 patient). Thus, in 8 (47%) of 17 patients with patent ductus arteriosus, the echocardiographer failed to recognize the lesion; however, in all 5 patients with an isolated patent ductus arteriosus, the echocardiographer did recognize the lesion. Patent ductus arteriosus was commonly missed when associated with other, more significant cardiac defects.

*Extracardiac anatomy:* In 2 patients, 2-D echocardiographic assessment of extracardiac anatomy was incomplete. In 1 (Case 34) with a correct diagnosis by 2-D echocardiography of interrupted aortic arch, an additional distal coarctation was not recognized but was found on angiography. In the other patient (Case 28), severe valvular pulmonary stenosis was correctly diagnosed; however, the echocardiographic examination also suggested interruption of the aortic arch, which was not found at catheterization.

*Intracardiac anatomy:* In 2 patients, 2-D echocardiographic assessment of intracardiac anatomy was incomplete. In Patient 13, in whom a correct diagnosis of a large paramembranous ventricular septal defect was made by 2-D echocardiography, 3 additional clinically insignificant (<1 mm) muscular ventricular septal defects were found at autopsy. The sizes of these ventricular septal defects were considered beyond the resolution of available echocardiographic instrumentation and of no hemodynamic significance. In this same patient a small secundum atrial septal defect was also found at surgery. In Patient 22, with a correct 2-D echocardiographic diagnosis of severe Ebstein's anomaly, right ventricular outflow obstruction was suggested by the large amount of tricuspid valve tissue in the outflow tract. A right ventricular angiogram also showed no blood exiting the right ventricle through the right ventricular outflow tract, and a diagnosis of pulmonary valve atresia was "confirmed." However, at autopsy the right ventricular outflow tract was patent, and the echocardiographic and angiographic findings were attributed to redundant tricuspid valve tissue in the right ventricular outflow tract and severe tricuspid regurgitation, both of which impeded forward blood flow.

## Discussion

Two-dimensional echocardiography has become established as an excellent noninvasive tool for the diagnosis of congenital heart disease. It is particularly useful in the recognition of altered ventricular anatomy, and it may be uniquely superior to angiography in visualizing altered anatomy about the internal "crux" of the heart (that is, the anatomic meeting point of the atrial and ventricular septa and the septal portion of the atrioventricular valves).[13] Two-dimensional echocardiography is less applicable for the complete assessment of extracardiac anatomy such as pulmonary artery distribution, coronary anatomy, mediastinal vascular anomalies, or atypical coarctation. To this end, Doppler[18–20] and contrast-assisted[16,17] echocardiography have played an important role in the assessment of certain extracardiac congenital cardiac anomalies.

Cardiac catheterization remains the standard means of diagnosing most congenital heart diseases. In addition to anatomic delineation, flow and pressure hemodynamics can be appreciated qualitatively and quantitatively. Over the past 10 years, M-mode and 2-D echocardiography have become accepted as excellent in diagnosing many structural (acquired or congenital) and hemodynamic cardiac abnormalities. It is logical that certain functions heretofore obtained invasively with angiography would be supplanted by a noninvasive echocardiographic technique. Because angiography entails the use of radiation[21] and contrast medium and is associated with morbidity and mortality, a technique that provides much of the same information with no ionizing radiation or contrast medium and little or no morbidity would be preferred. In our institution and others, there has been a shift toward the noninvasive technique either to supplement or to replace cardiac catheterization in selected situations. This has been particularly noticeable in critically ill infants. This shift in utilization appears to permit a more goal-oriented approach to both procedures. There is an impression that as fewer catheterizations are performed, there is more selective utilization of angiography and more dependence on echocardiography as the diagnostic procedure of choice from which clinical decisions regarding further management, medical or surgical, can be made. With the introduction of high-resolution, 2-D sector echocardiography, this impact has been very noticeable in infants, in whom altered hemodynamic function is often clinically predictable. Most sick newborns presenting with cyanosis or heart failure previously underwent diagnostic cardiac catheterization. The only common exception was in patients with patent ductus arteriosus, in which the clinical examination was often diagnostic. In a review of 15 newborns undergoing cardiac surgery (excluding patent ductus arteriosus) before sophisticated 2-D echocardiography was available, all had preoperative cardiac catheterization. In this study, 35% (6 of 17) of such patients went directly to surgery without cardiac catheterization. We attribute this change in great part to the introduction of high-resolution 2-D echocardiography.

In our 40 newborns, 5 were immediately recognized as having noncardiac problems on echocardiography, and they were managed accordingly. The most impressive feature is that in 27 (68%), the clinician used the echocardiogram and not cardiac catheterization as the primary imaging tool with which to direct further management. Nineteen (54%) of 35 patients with congenital heart disease required surgery in the neonatal period. Eight (42%) of these 19 patients went directly to surgery after 2-D echocardiographic examination and without preoperative cardiac catheterization. Fourteen (40%) of the 35 patients had cardiac catheterization in the neonatal period. These catheterizations were requested for 3 primary reasons: therapeutic balloon septostomy, anatomic assessment, and hemodynamic evaluation. To these ends, the echocardiographer must perform a complete examination of the intra- and extracardiac anatomy. In this series the most common request for cardiac catheterization was for further delineation of extracardiac anatomy (that is, pulmonary and aortic arch anatomy). Confident echocardiographic recognition of a transposition complex permits the clinician to proceed directly to atrial septostomy without previous angiography.

At our institution, both the clinicians and the surgeons have had confidence in the echocardiographic data obtained. The physician doing the echocardiographic examination must be expertly trained and knowledgeable. If this procedure is undertaken to replace portions of the cardiac catheterization, the echocardiographic examination must be performed with comparable expertise. There must be a strong working relation among clinician, echocardiographer, angiographer, and surgeon to bring about such a change in practice. When achieved, such use of the echocardiographic techniques appreciably expedites management of the critically ill newborn and reduces the need for cardiac catheterization.

## References


1. **Schaffer AJ, Avery ME.** Diseases of the Newborn. 4th ed. Philadelphia: WB Saunders, 1977:219–312.
2. **Fyler DC, Rosenthal A.** Neonatal heart disease. In: Avery GB, ed. Neonatology: Pathophysiology and Management of the Newborn. Philadelphia: JB Lippincott, 1975:295–334.
3. **Kelley MJ, Jaffe CC, Shoum SM, Kleinman CS.** A radiographic and echocardiographic approach to cyanotic congenital heart disease. Radiol Clin North Am 1980;18:411–440.
4. **Sahn DJ, Henry WL.** Clinical applications of real-time two-dimensional scanning in congenital heart disease. Cardiovasc Clin 1978;9:295–316.
5. **Lange LW, Sahn DJ, Allen HD, Goldberg SJ.** Subxiphoid cross-sectional echocardiography in infants and children with congenital heart disease. Circulation 1979;59:513–524.
6. **Martin RP, French JW.** The role of two-dimensional echocardiography in the evaluation of congenital heart disease. Adv Cardiol 1980;27:266–280.
7. **Kotler MN, Mintz GS, Parry WR, Segal BL.** Two dimensional echocardiography in congenital heart disease. Am J Cardiol 1980;46:1237–1246.
8. **Meyer RA.** Echocardiography in pediatric patients. Cardiovasc Clin 1981;11:187–225.
9. **Houston AB, Gregory NL, Coleman EN.** Two-dimensional sector scanner echocardiography in cyanotic congenital heart disease. Br Heart J 1977; 39:1076–1081.
10. **Bierman FZ, Williams RG.** Prospective diagnosis of d-transposition of the great arteries in neonates by subxiphoid, two-dimensional echocardiography. Circulation 1979;60:1496–1502.
11. **Snider AR, Silverman NH.** Suprasternal notch echocardiography: a two-dimensional technique for evaluating congenital heart disease. Circulation 1981;63:165–173.
12. **Rudolph AM, Silverman NH.** Echocardiography in the differential diagnosis of cardiopulmonary distress in the neonate. Contrib Gynecol Obstet 1979;6:102–108.
13. **Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT.** Two-dimensional real-time ultrasonic imaging of the heart and great vessels: technique, image orientation, structure identification, and validation. Mayo Clin Proc 1978;53: 271–303.
14. **Sahn DJ, Allen HD, Lange LW, Goldberg SJ.** Cross-sectional echocardiographic diagnosis of the sites of total anomalous pulmonary venous drainage. Circulation 1979;60:1317–1325.
15. **Hagler DJ, Tajik AJ, Seward JB, Mair DD, Ritter DG.** Real-time wide-angle sector echocardiography: atrioventricular canal defects. Circulation 1979;59:140–150.
16. **Seward JB, Tajik AJ, Hagler DJ.** Contrast echocardiography in the assessment of cyanotic and complex congenital heart disease: peripheral venous, invasive, and unique applications. In: Meltzer RS, Roelandt J, eds. Contrast Echocardiography. The Hague, The Netherlands: Martinus Nijhoff, 1982:235–277.
17. Meltzer RS, Roelandt J, eds. Contrast Echocardiography. The Hague, The Netherlands: Martinus Nijhoff, 1982.
18. **Stevenson JG, Kawabori I, Dooley T, Guntheroth WG.** Diagnosis of ventricular septal defect by pulsed Doppler echocardiography: sensitivity, specificity and limitations. Circulation 1978;58:322–326.
19. **Stevenson JG, Kawabori I, Guntheroth WG.** Pulsed Doppler echocardiographic evaluation of the cyanotic newborn: identification of the pulmonary artery in transposition of the great arteries. Am J Cardiol 1980;46:849–854.
20. **Stevenson JG, Kawabori I, Guntheroth WG.** Pulsed Doppler echocardiographic diagnosis of patent ductus arteriosus: sensitivity, specificity, limitations, and technical features. Cathet Cardiovasc Diagn 1980;6:255–263.
21. **Waldman JD, Rummerfield PS, Gilpin EA, Kirkpatrick SE.** Radiation exposure to the child during cardiac catheterization. Circulation 1981;64: 158–163.

# Rest and Exercise Ventricular Function in Adults With Congenital Ventricular Septal Defects

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**Rest and exercise right and left ventricular function were compared using equilibrium gated radionuclide angiography in 19 normal sedentary control subjects (mean age 28 years, range 22 to 34) and 34 patients with hemodynamically documented congenital ventricular septal defect (VSD) (mean age 27 years, range 20 to 40). The 34 patients with VSD were divided into 3 groups: those in Group 1 (17 patients) had pulmonary to systemic blood flow ratios of less than 2 to 1; those in Group 2 (12 patients) had prior surgical closure of VSD (mean interval from surgery 17 years, range 9 to 22), and those in Group 3 (5 patients) had Eisenmenger's complex. Gated radionuclide angiography was performed at rest and during each level of graded supine bicycle exercise to fatigue. Heart rate, blood pressure, maximal work load achieved, and right and left ventricular ejection fractions were assessed. The control subjects demonstrated an increase in both the left and right ventricular ejection fractions with exercise (0.70 ± 0.07 to 0.79 ± 0.05 and 0.46 ± 0.06 to 0.57 ± 0.04; $p < 0.001$ for left and right ventricles, respectively). All study groups failed to demonstrate an increase in ejection fraction in either ventricle with exercise. Furthermore, resting left ventricular ejection fraction in Groups 2 and 3 was lower than that in the control subjects (0.59 ± 0.09 and 0.54 ± 0.06 versus 0.70 ± 0.07; $p < 0.001$) and resting right ventricular ejection fraction was lower in Group 3 versus control subjects (0.30 ± 0.07 versus 0.46 ± 0.06; $p < 0.001$). Thus (1) left and right ventricular function on exercise were abnormal in patients with residual VSD as compared with control subjects; (2) rest and exercise left ventricular ejection fractions remained abnormal despite surgical closure of VSD in the remote past; (3) resting left and right ventricular function was abnormal in patients with Eisenmenger's complex; (4) lifelong volume overload may be detrimental to myocardial function.**

Few data are available on the effects of long-term volume overload on right and left ventricular function.[1] However, patients with patent congenital VSD reaching adulthood provide an ideal opportunity to assess this effect because of chronic biventricular volume overload. Rest and exercise gated equilibrium radionuclide angiography has become a widely accepted noninvasive technique for the evaluation of ventricular performance. Wackers et al[2] and Maddahi et al[3] validated the reliability and reproducibility of this technique for the left and right ventricles, respectively.

This study was undertaken to evaluate ventricular performance in adult patients with isolated VSD using gated radionuclide angiography. The result is then compared with (1) age-matched normal control subjects, (2) patients with VSD who had previously undergone surgical closure, and (3) patients with Eisenmenger's complex.

## Methods

**Patient population:** Thirty-four patients with previous angiographically proven isolated VSD were selected for study from our adult congenital heart clinic follow-up population. All patients were aged 20 to 40 years with no known history of coronary artery disease or other concurrent forms of heart disease. The patients were divided into 3 groups.

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**TABLE I Clinical Characteristics and Gated Nuclear Angiographic Results in Patients With Patent Small Shunts (Group I)**

| Patient | Age (yr) | Shunt Size at Last Cath | Functional Class | Level of Physical Conditioning | Ejection Fraction | | Peak Work Load (kpm/kg) | Peak HR × SBP ($\times 10^3$ mm Hg/min) |
|---|---|---|---|---|---|---|---|---|
| | | | | | LV (Rest/Ex) | RV (Rest/Ex) | | |
| 1 | 20 | 1.3:1 | I | Active | 81/79 | 47/50 | 12.6 | 36.0 |
| 2 | 20 | 1.4:1 | I | Active | 64/60 | 35/42 | 9.2 | 19.5 |
| 3 | 20 | 1.8:1 | I | Active | 68/69 | 40/41 | 15.7 | 27.0 |
| 4 | 21 | 1.3:1 | I | Active | 66/63 | 46/46 | 10.3 | 22.4 |
| 5 | 21 | 1.2:1 | I | Active | 70/68 | 51/55 | 8.1 | 21.6 |
| 6 | 21 | 1.5:1 | I | Sedentary | 76/70 | 44/44 | 8.1 | 18.0 |
| 7 | 22 | 1.5:1 | I | Active | 60/60 | 40/53 | 10.8 | 20.0 |
| 8 | 24 | 1.6:1 | I | Active | 58/58 | 53/45 | 11.9 | 34.2 |
| 9 | 25 | 1.1:1 | I | Active | 63/66 | 32/48 | 13.3 | 25.5 |
| 10 | 26 | 1.2:1 | I | Sedentary | 76/69 | 43/47 | 8.8 | 17.3 |
| 11 | 28 | 1.8:1 | I | Active | 70/65 | 28/30 | 9.0 | 15.0 |
| 12 | 28 | 1.4:1 | I | Sedentary | 71/72 | 46/42 | 7.5 | 18.0 |
| 13 | 29 | 1.3:1 | I | Sedentary | 65/72 | 48/53 | 3.7 | 22.4 |
| 14 | 29 | 1.2:1 | I | Active | 64/62 | 40/41 | 11.0 | 22.8 |
| 15 | 29 | 1.9:1 | I | Active | 81/79 | 55/57 | 6.3 | 18.4 |
| 16 | 31 | 1.1:1 | I | Active | 81/66 | 56/42 | 9.5 | 39.1 |
| 17 | 39 | 1.8:1 | I | Active | 76/63 | 52/41 | 9.3 | 25.0 |

Cath = catherization; Ex = exercise; LV = left ventricle; RV = right ventricle; SBP = systolic blood pressure.

*Group 1:* This group included 17 patients (9 male and 8 female) who had persistent small left to right shunts without the necessity of surgical correction (Table I). Their mean age was 25 years (range 20 to 39). All had undergone at least 1 cardiac catheterization. The mean time lapse from the last catheterization to the present was 12 years (range 0 to 18). The mean pulmonary to systemic blood flow ratio at the time of the last catheterization was 1.4 to 1. Mean pulmonary artery pressure was normal at 16.7 ± 3.5 mm Hg (mean ± standard deviation [SD]). All patients were in New York Heart Association (NYHA) functional class I. Thirteen of 17 patients were physically active in sports on a regular basis, whereas 4 were considered sedentary. None of the patients was participating in any physical fitness training program. On physical examination all patients had findings typical of VSD.

*Group 2:* This included 12 patients (5 male and 7 female) who had undergone surgical closure of VSD 9 to 22 years (mean 17 years) before the study (Table II). Their mean age was 26 years (range 20 to 33 years). The operation was performed before the advent of present-day techniques of cardioplegia and myocardial protection. All patients were also in NYHA class I. However, only 5 of 12 patients were active physically. The remainder led voluntarily sedentary lives without participation in regular sports activities.

*Group 3:* This included 5 patients (1 male and 4 female) with Eisenmenger's complex documented at previous cardiac catheterization. Their mean age was 33 years (range 24 to 40). All were variably symptomatic with dyspnea on exertion. Two patients were in NYHA class II, the remainder in class III.

*Control:* The control group consisted of 19 healthy volunteers (15 male and 4 female) with a mean age of 28 years (range 22 to 34). This was comparable to the mean age of 27 years (range 20 to 40) in our overall study group. All of the volunteers had a normal cardiac history and normal results on physical examination.

**Protocol:** All patients had a complete history, physical examination, standard 12-lead electrocardiogram, posteroanterior and lateral chest X-ray, and supine multiple-gated equilibrium cardiac blood pool scintigrams both at rest and with graded bicycle exercise to fatigue.

**Radionuclide angiograms:** Equilibrium gated radionuclide angiograms were obtained by imaging the cardiac blood pool in the 45° left anterior oblique position with a 10° cranial

**TABLE II Clinical Characteristics and Gated Nuclear Angiographic Results in Patients With Postoperative Ventricular Septal Defect (Group II)**

| Patient | Age (yr) | Date of Last Op | Age (yr) at Last Op | Cardiac Operations (n) | Shunt Size Before Operation | Level of Physical Conditioning | Ejection Fraction | | Peak Work Load (kpm/kg) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | LV (Rest/Ex) | RV (Rest/Ex) | |
| 1 | 20 | 1963 | 3 | 1 | 3.2:1 | Sedentary | 61/50 | 53/57 | 3.2 |
| 2 | 20 | 1961 | 1 | 1 | . . . | Sedentary | 67/83 | 36/39 | 7.3 |
| 3 | 21 | 1961 | 2 | 1 | . . . | Active | 66/68 | 43/55 | 7.9 |
| 4 | 24 | 1959 | 4 | 1 | 2.5:1 | Sedentary | 55/50 | 51/46 | 9.0 |
| 5 | 25 | 1960 | 5 | 1 | . . . | Sedentary | 67/66 | 51/42 | 3.5 |
| 6 | 26 | 1961 | 9 | 1 | . . . | Sedentary | 66/67 | 38/35 | 15.0 |
| 7 | 26 | 1960 | 6 | 1 | 3.0:1 | Sedentary | 61/59 | 45/47 | 7.3 |
| 8 | 27 | 1965 | 13 | 1 | 3.0:1 | Active | 61/65 | 47/51 | 11.3 |
| 9 | 29 | 1965 | 6 | 1 | . . . | Active | 61/62 | 38/38 | 10.3 |
| 10 | 29 | 1965 | 15 | 2 | 1.4:1 | Sedentary | 41/28 | 40/34 | 4.2 |
| 11 | 32 | 1959 | 12 | 3 | 2.3:1 | Active | 61/52 | 40/37 | 9.2 |
| 12 | 33 | 1970 | 24 | 1 | 2.5:1 | Active | 43/44 | 34/36 | 14.7 |

Ex = exercise; LV = left ventricle; Op = operation; RV = right ventricle.

**TABLE III Heart Rate Response (± Standard Deviation, beats/min)**

| | Control Subjects | Group 1 | Group 2 | Group 3 |
|---|---|---|---|---|
| Rest | 72 ± 14 | 81 ± 15 | 76 ± 15 | 96 ± 5* |
| Peak exercise | 159 ± 17† | 146 ± 27† | 142 ± 20† | 121 ± 9†,‡ |

* $p < 0.05$ control subjects, Groups 1 and 2 versus Group 3 at rest. † $p < 0.001$ rest → peak exercise; all groups. ‡ $p < 0.001$ control subjects, Group 1 versus Group 3 at peak exercise.

**TABLE IV Systolic Blood Pressure Response (± Standard Deviation, mm Hg)**

| | Control Subjects | Group 1 | Group 2 | Group 3 |
|---|---|---|---|---|
| Rest | 122 ± 15 | 119 ± 16.5 | 115 ± 13 | 120 ± 22* |
| Peak exercise | 197 ± 32† | 158 ± 27† | 158 ± 25† | 146 ± 23†,‡ |

* p = NS all groups at rest. † $p < 0.001$ rest → peak exercise; all groups. ‡ $p < 0.001$ control subjects versus Groups 1, 2, and 3 at peak exercise.

tilt, after in vivo labelling of red blood cells with 25 mCi of technetium-99m.

Patients were imaged in the supine position using a portable gamma camera (Ohio Nuclear, Series Sigma 420) equipped with a general purpose parallel-hole collimator. The camera and an electrocardiographic gate (Ohio Nuclear) were interfaced to a dedicated computer (Digital Equipment Corporation 11/40 or 11/60).

Rest studies were acquired for 200 cardiac cycles. Graded exercise studies were performed using a Quinton supine bicycle ergometer as previously described from our laboratory.[4,5] Exercise was started at a work load of 200 kpm and increased in 200 to 300 kpm increments every 3 minutes to patient exhaustion. At each level of exercise, a stable heart rate was attained before a 2-minute acquisition period. Heart rate, blood pressure, and a single lead electrocardiogram (lead II) were monitored throughout the study. All control subjects and patients were encouraged to achieve peak exertion to the limit of symptoms in the supine posture.

**Data analysis:** All radionuclide angiographic analysis was performed on an 11/40 or 11/60 computer (Digital Equipment Corporation) using Gamma II software. Data were initially viewed in an endless loop format to visually define the borders of both the right and the left ventricles throughout the cardiac cycle. The right and left ventricular end-diastolic and end-systolic frames were determined from time-activity curves generated from regions of interest surrounding both ventricles. Four regions of interest were assigned to both end-systolic and end-diastolic frames; the 2 ventricles and a left and right paraventricular background region as previously described.[4,5]

Two experienced observers independently analyzed the studies, and the reproducibility of the data analysis was assessed by comparing their results. Interobserver correlation for both left and right ventricular ejection fractions in VSD patients as well as control subjects was excellent ($r = 0.88$).[4,5]

Ejection fractions (EF) were calculated by the following equation: $EF = EDC_{bc} - ESC_{bc}/EDC_{bc}$, where $EDC_{bc}$ = background corrected end-diastolic counts and $ESC_{bc}$ = background corrected end-systolic counts.

Statistical analysis of the change from rest to exercise in each group was carried out with the 2-tailed paired $t$ test. Comparisons among the 4 groups were carried out with the 2-tailed unpaired Student's $t$ test.

## Results

**Heart rate and systolic blood pressure response (Table III):** The resting heart rates (mean ± SD) were similar in Groups 1 and 2 compared with control subjects (81 ± 15 and 76 ± 15 versus 72 ± 14; p = not significant [NS]). However, Group 3 patients had a slightly higher resting heart rate (96 ± 5; $p < 0.05$ compared with control subjects, Groups 1 and 2).

All study groups demonstrated an increase in heart rate with exercise. However, Group 3 patients had the lowest peak exercise heart rate (121 ± 9; $p < 0.001$ compared with control subjects and Group 1).

Resting systolic blood pressure was similar in the 4 study groups (Table IV). Peak exercise systolic blood pressure (systolic BP ± SD) was again similar in Groups 1, 2, and 3 but was significantly higher in the control subjects (158 ± 27; 158 ± 25; 146 ± 23 versus 197 ± 32; $p < 0.001$).

**Work load:** The mean maximal work load achieved by control subjects (14 kpm/kg) was much higher than that in any of the groups with VSD. The mean maximal work loads in Groups 1 and 2 were moderately reduced at 9.3 and 8.6 ($p < 0.001$ versus control subjects) and markedly depressed in Group 3 at 4.1 kpm/kg ($p < 0.001$ compared with control subjects; $p < 0.05$ compared with Groups 1 and 2). As may be expected, patients who were active were able to reach significantly higher peak work loads than sedentary patients ($p < 0.01$ in Group 1 and $p < 0.003$ in Group 2).

**Ejection fractions (Table V):** *Normal subjects:* The mean left ventricular ejection fraction at rest (mean ejection fraction ± SD) was 0.70 ± 0.07 and increased to 0.79 ± 0.05 at peak exercise ($p < 0.001$). The mean

**TABLE V Mean Ejection Fractions (± Standard Deviation)**

| | Control Subjects | | Group 1 | | Group 2 | | Group 3 | |
|---|---|---|---|---|---|---|---|---|
| | Rest | Exercise | Rest | Exercise | Rest | Exercise | Rest | Exercise |
| LV | 70 ± 7 | 79 ± 5* | 70 ± 7 | 67 ± 6 | 59 ± 9† | 58 ± 14 | 54 ± 6† | 49 ± 2 |
| RV | 46 ± 6 | 57 ± 4* | 44 ± 8 | 46 ± 7 | 43 ± 6 | 43 ± 8 | 30 ± 7† | 34 ± 9 |

* $p < 0.001$ change in ejection fraction rest → peak exercise. † $p < 0.001$ ejection fraction rest versus control rest. LV = left ventricle; RV = right ventricle.

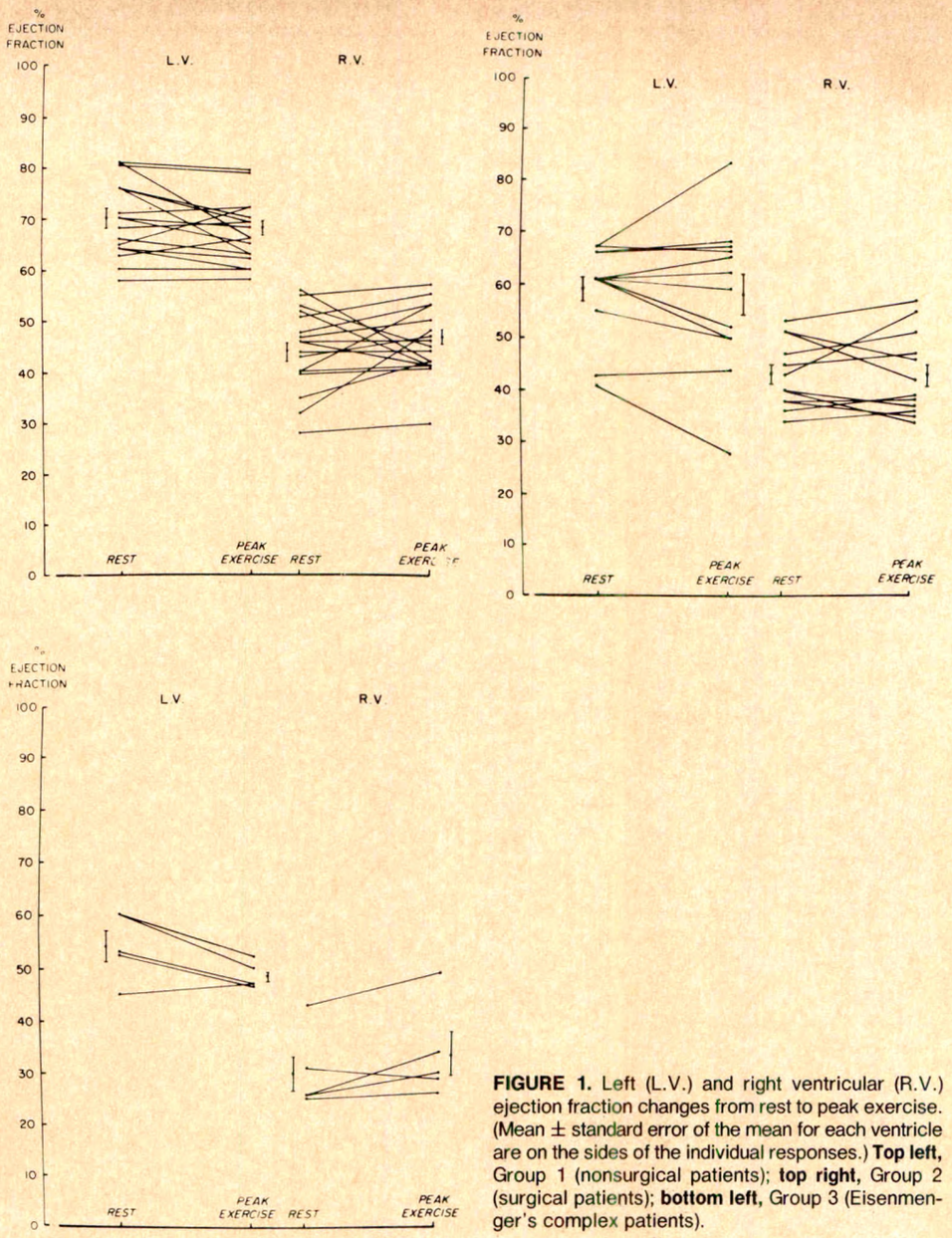



**FIGURE 1.** Left (L.V.) and right ventricular (R.V.) ejection fraction changes from rest to peak exercise. (Mean ± standard error of the mean for each ventricle are on the sides of the individual responses.) **Top left,** Group 1 (nonsurgical patients); **top right,** Group 2 (surgical patients); **bottom left,** Group 3 (Eisenmenger's complex patients).

right ventricular ejection fraction at rest was 0.46 ± 0.06 and increased to 0.57 ± 0.04 at peak exercise ($p < 0.001$).

*Group 1 (Fig. 1, top left):* Both left and right ventricular ejection fractions were similar to those in the control subjects at rest; however, both ventricles demonstrated a flat response to exercise, with a mean left ventricular ejection fraction of 0.70 ± 0.07 at rest and 0.67 ± 0.06 at peak exercise, and a mean right ventricular ejection fraction of 0.44 ± 0.08 at rest and 0.46 ± 0.07 at peak exercise ($p < 0.001$ versus control subjects at peak exercise for both left and right ventricles).

When physical conditioning was taken into account, this trend was still found to exist (Table I). The left ventricular ejection fraction at rest was 0.72 ± 0.05 for sedentary and 0.70 ± 0.08 for active individuals. On exercise, both decreased to 0.71 ± 0.02 for sedentary and 0.66 ± 0.07 for active patients ($p$ = NS between sedentary and active patients). Physical conditioning also did not account for an abnormal right ventricular ejection fraction response to exercise.

*Group 2 (Fig. 1, top right):* The resting left ventricular ejection fraction was lower than that for control subjects (0.59 ± 0.09 versus 0.70 ± 0.07; $p < 0.001$), whereas the right ventricular ejection fraction was similar to that of control subjects (0.43 ± 0.06 versus 0.46 ± 0.06; $p$ = NS). There was again a flat response to exercise for both ventricles, with a left ventricular ejection fraction at peak exercise of 0.58 ± 0.14 and a right ventricular ejection fraction at peak exercise of

0.43 ± 0.08 ($p < 0.001$ for both ventricles compared with the control subjects). Physical conditioning again did not account for the marked deviation from the normal exercise response (Table II).

*Group 3 (Fig. 1, bottom left):* Patients with Eisenmenger's complex had lower resting values for both left and right ventricles compared with control subjects (left ventricular ejection fraction 0.54 ± 0.06 versus 0.70 ± 0.07 and right ventricular ejection fraction 0.30 ± 0.07 versus 0.46 ± 0.06; $p < 0.001$). The ejection fraction response to exercise for both ventricles was similarly flat or decreased (left ventricular ejection fraction 0.49 ± 0.02 and right ventricular ejection fraction 0.34 ± 0.09 at peak exercise; $p < 0.001$ compared with control subjects). The mean ejection fraction response for both ventricles in all groups is displayed in Figure 2.

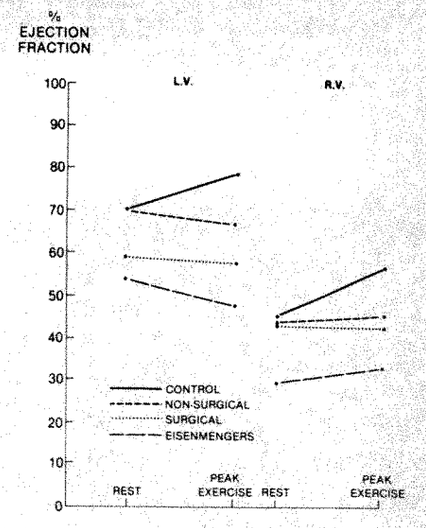



**FIGURE 2.** Mean left (L.V.) and right ventricular (R.V.) ejection fraction changes from rest to peak exercise in all groups compared with the control subjects. All study groups demonstrated a flat exercise response for both ventricles, whereas the ejection fraction increased with exercise in both ventricles in the control subjects. Control group, **unbroken line;** Group 1, **short dashes;** Group 2, **dotted line;** Group 3, **long dashes.**

## Discussion

**Group 1:** Patients with a small VSD (less than 2 to 1 pulmonary:systemic blood flow ratio with normal pulmonary vascular resistance) are believed to have a good overall prognosis with a functional status comparable to that of the general population.[6,7] In fact, a significant proportion may undergo spontaneous closure, and so far there is no evidence to suggest that an increase in shunt size can occur in these patients.[6–11]

Our results show that patients with small shunts had normal resting values for left and right ventricular ejection fraction, but they significantly failed to increase with exercise. The exercise response could not be predicted on the basis of history, physical examination, electrocardiogram, or chest roentgenogram, as all patients were in NYHA class I and had essentially normal electrocardiograms and chest X-rays.

The mean maximal work load attained was significantly lower than that of the control group; however, systolic blood pressure and heart rate response were normal in these patients. This finding could not be explained by a sedentary level of physical conditioning, which was present in only a small number of patients (4 of 17). This decrease in ejection fraction also did not correlate with age of patients, size of shunt, physical conditioning, or peak work load.

Several explanations for these findings are possible. The ventricles may respond to exercise by dilating and increasing their end-diastolic volumes during exercise with a constant ejection fraction. The stroke volume would increase during exercise as the end-diastolic volume increased; however, this increase could indeed represent previously unsuspected myocardial dysfunction secondary to chronic volume overload.

**Group 2:** All operated patients in our study had surgery through a right ventricular approach. All operations were performed before the advent of cardioplegia and modern myocardial protection, which may well be a significant factor influencing postoperative myocardial function. Furthermore, 10 of 12 patients had surgery after the age of 2 years, and the duration of uncorrected hemodynamic insult in patients with VSD may also be an important factor in predicting outcome.[12,13] The level of physical conditioning again did not appear to explain the abnormalities in exercise ejection fraction (Table V).

Several investigators have previously commented on impaired ventricular function after surgical repair of a congenital VSD. Jarmakani et al[14] looked at the velocity-pressure relation as a measure of left ventricular contractility in postoperative patients an average of 1.3 years after successful surgical closure. The ejection fraction was slightly depressed at rest in all patients studied. The same investigators looked at pre- and postoperative catheterization data in 23 patients to study the effect of VSD closure on left heart volume, mass, and contractility.[15] The postoperative catheterizations were performed 1 to 5 years after surgery, with a mean time lapse of 2 years. They found that although there had been significant regression in left ventricular volume and mass postoperatively, the results were still significantly higher than the normal values. Furthermore, postoperative resting left ventricular ejection fraction was lower than both the preoperative left ventricular ejection fraction and that of their normal control subjects (0.54 versus 0.60 and 0.63, respectively). They speculated that partially irreversible changes may be present in the myocardium associated with the hemodynamic effects of VSD.

Maron et al[16] studied the cardiac output and pulmonary arterial pressure response to upright exercise in 11 asymptomatic postoperative patients. Exercise studies were carried out 3 to 15 years (mean 9.5) after operative closure of isolated VSD. Ten of the 11 patients had had routine postoperative catheterizations within the first years after surgery and none had had evidence of residual shunt. Postoperative mean pulmonary arterial pressure was normal or mildly elevated at rest in

10 patients. During upright exercise sufficient to lower pulmonary arterial oxygen saturation to 30%, cardiac output was below the normal range in 5 patients, each of whom had been operated on after the age of 10 years. The investigators suggested that late cardiovascular function may be abnormal after repair of VSD and that the abnormalities may be related to age at operation.

Ahmad and Hallidie-Smith[17] found no abnormality of ejection fraction at rest in the early postoperative period in their study patients, and they speculated that abnormalities of postoperative myocardial function suggested by earlier studies may be related to the unavailability of currently used intraoperative myocardial preservation techniques. Further follow-up data on this group of patients will be necessary before this controversy can be settled. However, this finding is still clinically important, as a large number of these patients are being followed up by cardiologists. Therefore, baseline myocardial function determinations are important for future comparison if any change in clinical status occurs.

**Group 3:** At one extreme of the spectrum of population with chronic ventricular volume overload is the patient with Eisenmenger's complex. These patients had an extremely poor resting and exercise response as measured by all variables including heart rate and blood pressure response, maximal work load attained, and ejection fractions of both ventricles. These patients represent the end-stage of biventricular volume overload and pressure overload on the right ventricle as well as the added detrimental effect of right to left shunting of desaturated blood supplying hypertrophied viable myocardium.

In summary, with the aid of nuclear angiography, these data suggest the following: (1) The response of blood pressure, work load, and ejection fraction of both left and right ventricles to exercise in all patients with residual persistent VSD is abnormal compared with that of control subjects. (2) Rest and exercise left ventricular ejection fractions may be impaired postoperatively, and surgical closure does not appear to normalize ventricular function in patients operated on in the remote past or after the age of 2 years, or both. (3) Resting left and right ventricular function are abnormal in patients with Eisenmenger's complex. (4) Lifelong chronic volume overload, even to a small degree, may be detrimental to myocardial function.

## References


1. **Bruce RA, John GG.** Effects of upright posture and exercise on pulmonary hemodynamics in patients with central cardiovascular shunts. Circulation 1957;16:776–783.
2. **Wackers FJT, Berger HJ, Johnstone DE, Goldman L, Reduto LA, Langon RA, Gottschalk A, Zaret BL.** Multiple gated cardiac blood pool imaging for left ventricular ejection fraction: validation of the technique and assessment of variability. Am J Cardiol 1979;43:1159–1166.
3. **Maddahi J, Berman DS, Matsuoka DT, Waxman AD, Stankus KE, Forrester JS, Swan HJC.** A new technique for assessing right ventricular ejection fraction using rapid multiple-gated equilibrium cardiac blood pool scintigraphy. Circulation 1979;60:581–589.
4. **Bar-Shlomo BZ, Druck MN, Morch JE, Jablonsky G, Hilton JD, Feiglin DHI, McLaughlin PR.** Exercise left ventricular function in trained and untrained healthy subjects. Circulation 1982;65:484–488.
5. **Benson LN, Bonet J, McLaughlin PR, Olley PM, Feiglin DHI, Druck MN, Trusler G, Rowe R, Morch JE.** Assessment of right ventricular function during supine bicycle exercise after Mustard's operation. Circulation 1982;65:1052–1059.
6. **Bloomfield DK.** The natural history of ventricular septal defect in patients surviving infancy. Circulation 1964;29:914–955.
7. **Corone P, Doyon F, Gaudeau S, Guerin F, Vernant P, Duncan H, Rumeau-Rouquette C, Gaudeul P.** Natural history of ventricular septal defect: a study involving 790 cases. Circulation 1977;55:908–915.
8. **Campbell M.** Natural history of ventricular septal defect. Br Heart J 1971;33:246–257.
9. **Keith JD, Rose V, Collins G, Kidd BSL.** Ventricular septal defect: incidence, morbidity and mortality in various age groups. Br Heart J 1971;33:81–83.
10. **Walker WJ, Garcia-Gonzalez E, Hall RJ, Czarnecki SW, Franklin RB, Das SK, Cheitlin MD.** Interventricular septal defect: analysis of 415 catheterized cases, ninety with serial hemodynamic studies. Circulation 1965;31:54–65.
11. **Arcilla RA, Agustsson MH, Bicoff JP, Lynfield J, Weinberg M Jr, Fell EH, Gasul BM.** Further observations on the natural history of isolated ventricular septal defects in infancy and childhood: serial cardiac catheterization studies in 75 patients. Circulation 1963;28:560–571.
12. **Hallidie-Smith KA, Wilson RSE, Hart A, Zeidifard E.** Functional status of patients with large ventricular septal defect and pulmonary vascular disease 6 to 10 years after surgical closure of their defects in childhood. Br Heart J 1977;39:1093–1101.
13. **Sigmann JM, Perry BL, Behrendt DM, Stern AM, Kirsh MM, Sloan HE.** Ventricular septal defect: results after repair in infancy. Am J Cardiol 1977;39:66–71.
14. **Jarmakani JM, Graham TP Jr, Conent RV Jr.** Left ventricular contractile state in children with successfully corrected ventricular septal defect. Circulation 1972;65,66:Suppl 1:102–110.
15. **Jarmakani JM, Graham TP Jr, Canent RV Jr, Capp MP.** The effect of corrective surgery on left heart volume and mass in children with ventricular septal defect. Am J Cardiol 1971;27:254–263.
16. **Maron BJ, Redwood DR, Hirchfeld JW Jr, Goldstein RE, Morrow AG, Epstein SE.** Postoperative assessment of patients with ventricular septal defect and pulmonary hypertension: response to intense upright exercise. Circulation 1973;48:864–874.
17. **Ahmad M, Hallidie-Smith KA.** Assessment of left-to-right shunt and left ventricular function in isolated ventricular septal defect. Br Heart J 1979;41:147–158.

# Prognosis of Symptomatic Coarctation of the Aorta in Infancy

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**Medical and surgical advances have improved the outlook for infants with symptomatic coarctation of the aorta. To help predict the clinical course of individual patients and to aid in individualizing their treatment, a 10-year experience with this condition was reviewed. Of 97 infants with symptomatic coarctation, 10 had isolated defects. In these patients, medical treatment was successful and surgical intervention could be postponed to allow for growth. The 87 other patients with associated cardiac defects were generally sicker at presentation and required earlier operation. Eleven of these died before surgical correction, 10 died at the time of repair, and 13 died later. The overall survival rate after 8 years was 62%, with most deaths occurring in the first 6 months of life. Late surgical results are flawed by a 32% rate of residual coarctation. Late postoperative hypertension is uncommon, and is usually attributable to a residual coarctation.**

The natural history of coarctation of the aorta in children and adults has been well described in clinical[1] and autopsy studies.[2,3] Early studies specifically excluded infants. Surgical techniques to repair coarctation have so improved the course of this disease in older children and adults that the natural course can no longer be determined for this age group. In contrast, the management of symptomatic infants with coarctation remains problematic, despite substantial medical and surgical advances during the last decade. The report of the 11-center New England Regional Infant Cardiac Program (NERICP)[4] has provided some useful information on the mortality of this lesion in infancy. In the present study we have reviewed our own recent experience with coarctation in infants, placing emphasis on the role of associated intracardiac anomalies in determining mortality and morbidity.

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## Methods

We examined the records of 97 infants with aortic coarctation and congestive heart failure who presented to Texas Children's Hospital between January 1, 1970 and January 1, 1980. The criterion for entry into this series was that coarctation be documented at cardiac catheterization during the first 6 months of life. All patients received initial intensive medical therapy consisting of digoxin and furosemide, and 75 patients subsequently underwent surgical repair of coarctation. Eleven infants with complicated defects died before repair was attempted, and 11 others were awaiting repair at the time of this survey. Surgical treatment consisted of Dacron® patch aortoplasty as described by Reul et al[5] in 34 patients, classic primary resection with end-to-end anastomosis in 38 children, and repair employing the left subclavian artery (Blalock-Park[6] or Waldhausen-Nahrwold[7] technique) in 3 children.

To ascertain the prognosis of coarctation in this group of patients, we performed a clinical follow-up with emphasis on mortality, continued symptoms, the need for other surgical intervention, and the occurrence of unrelieved coarctation or systemic hypertension after initial repair. The mean duration of follow-up, excluding the patients who died, is now 62.6 months (5.2 years).

Because these patients manifest a broad range and combination of associated cardiac defects, they were classified into 4 subgroups. Group I consisted of 10 patients with isolated coarctation of the aorta. The mean follow-up for this group was 73.8 months. Group II included 43 patients with coarc-

**TABLE I Associated Cardiovascular Defects**

| | Group II (n = 43) | Group III (n = 15) | Group IV (n = 29) | Total (Groups I to IV) (n = 97) |
|---|---|---|---|---|
| Left-to-right shunts | | | | |
| PDA | 33 | . . . | 25 | 58 |
| VSD | 33 | . . . | 20 | 53 |
| ASD or PFO* | 19 | . . . | 11 | 30 |
| PAPVD | 1 | . . . | 1 | 2 |
| Left heart obstructive lesions | | | | |
| AS or subAS | . . . | 11 | 20 | 31 |
| MS or MR | . . . | 8 | 16 | 24 |
| Parachute MV | . . . | 7 | 11 | 18 |
| Small LV | . . . | 2 | 6 | 8 |
| Other lesions | | | | |
| TGA | 2 | . . . | . . . | 2 |
| ECD† | 2 | . . . | 1 | 3 |
| DORV | 2‡ | . . . | 1 | 3 |
| EFE | 2 | 2 | . . . | 4 |

* Excludes 8 patients in Groups III and IV with PFO but no shunt. † All 3 had complete atrioventricular canals, and are also listed above among ASD, VSD, and, in 1 case, MR. ‡ Both patients had Taussig-Bing malformation, and are also listed above among TGA and VSD.

AS = aortic stenosis; ASD = atrial septal defect; DORV = double outlet right ventricle; ECD = endocardial cushion defect; EFE = endocardial fibroelastosis; LV = left ventricular; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve; PAPVD = partial anomalous pulmonary venous drainage; PDA = patent ductus arteriosus; PFO = patent foramen ovale; TGA = transposition of the great arteries; VSD = ventricular septal defect.

tation and a left-to-right shunt lesion. The mean follow-up for Group II patients (excluding deaths) was 57.9 months. Group III consisted of 15 patients with associated left heart obstructive lesions (but no intracardiac shunts) who were followed up for an average of 81.3 months. Group IV included 29 patients with coarctation associated with both obstructive and shunt lesions. The mean follow-up for Group IV survivors was 56.0 months. Table I lists the specific associated lesions for each group. Bicuspid aortic valve without obstruction was not included in this tabulation.

The surgical and follow-up data were analyzed for each subgroup as well as for the entire group, using actuarial and chi-square or Student's $t$ test statistical methods whenever appropriate.

**Presentation:** Table II summarizes the presentation and clinical course in infancy of our patients. Because inclusion in the study required that the infants have signs and symptoms of congestive heart failure and have undergone cardiac catheterization in the first 6 months of life, they were all by definition sick infants. However, the patients with associated left-to-right shunt lesions (Groups II and IV) tended to have more florid symptoms of pulmonary congestion than those with single or multiple left heart obstructions alone (Groups I and III), and they were therefore studied and repaired at an earlier age.

For 76 patients, repair of the coarctation was the first (and sometimes only) surgical procedure performed. In the patients with associated left-to-right shunts (Groups II and IV), incidental ligation and division of the ductus arteriosus were performed during 43 (75%) of 57 repairs of coarctation, whereas pulmonary artery banding was carried out during 24 (42%) of 57 operations. Twenty-three of these infants had both

**TABLE II Presentation and Mortality of Coarctation**

| | Group I (n = 10) | Group II (n = 43) | Group III (n = 15) | Group IV (n = 29) | Total (n = 97) |
|---|---|---|---|---|---|
| Median age at catheterization (days) | 66 | 15 | 60 | 18 | 30 |
| Preoperative deaths | | | | | |
| Number | 0 | 4 | 3 | 4 | 11 |
| Percent of group | 0 | 9.3 | 20.0 | 13.8 | 11.3 |
| Median age (mo) | . . . | 1.0 | 2.0 | 1.0 | 1.0 |
| Initial coarctation repair | | | | | |
| Number | 10 | 37 | 9 | 20 | 75 |
| Percent of group | 100.0 | 86.0 | 60.0 | 69.0 | 77.3 |
| Median age (mo) | 10.5 | 1.0 | 2.0 | 1.5 | 2.0 |
| Simultaneous procedures (n)* | 0 | 28 | 0 | 16 | 44 |
| Surgical deaths | | | | | |
| Number | 0 | 9 | 0 | 1 | 10 |
| Percent of operations | 0 | 24.3 | 0 | 5.0 | 13.3 |
| Median age (mo) | . . . | 1.0 | . . . | 1.0 | 1.0 |
| Late deaths | | | | | |
| Subsequent surgery | 0 | 1 | 0 | 4 | 5 |
| Medical | 0 | 3 | 2 | 3 | 8 |
| Percent of surgical survivors | 0 | 14.3 | 22.2 | 36.8 | 23.2 |
| Cumulative deaths | | | | | |
| Number | 0 | 17 | 5 | 12 | 34 |
| Percent of group | 0 | 39.5 | 33.3 | 41.4 | 35.1 |
| Median age (mo) | . . . | 1.0 | 3.0 | 3.0 | 2.0 |

* Simultaneous procedures, in every case, were ductal ligation or pulmonary banding, or both.

**TABLE III Deaths Without Surgical Treatment**

| Case | Age at Death | Associated Lesions | Circumstances of Death |
|---|---|---|---|
| | | Group II | |
| 1 | 10 days | VSD, PDA, PFO | Refractory SVT, shock |
| 2 | 2 years | VSD; neurologic deficiency and dysmorphism | Sepsis |
| 3 | 5 days | Multiple VSD | Shock (postcath) |
| 4 | 7 days | ECD; Down's Syndrome | Congestive heart failure |
| | | Group III | |
| 5 | 40 days | EFE, small LV | Shock and DIC (1 day postcath) |
| 6 | 64 days | AS, parachute MV, MS | Shock and bradycardia |
| 7 | 120 days | AS, parachute MV, MS, Turner's Syndrome | Unknown |
| | | Group IV | |
| 8 | 3 days | PDA, small LV, hypoplastic aortic isthmus, ASD, VSD, parachute MV | Shock (postcath) |
| 9 | 2 days | AS, parachute MV, poor LV function, PDA, VSD; anisosplenia | Shock (postcath) |
| 10 | 84 days | AS, MS, PDA, VSD, small LV | Unknown |
| 11 | 12 days | ASD, PDA, hypoplastic aortic isthmus, small LV | Shock (1 day postcath) |

DIC = disseminated intravascular coagulation syndrome; postcath = postcatheterization; SVT = supraventricular tachycardia. Other abbreviations as in Table I.

pulmonary banding and ductal division concurrent to the repair of coarctation.

Later operations were often required, most commonly closure of the ventricular septal defect and debanding of the pulmonary artery. To date 11 ventricular septal defects have been surgically closed, and 12 of 24 pulmonary bands have been removed. Four patients underwent aortic valvotomy, 2 had subaortic resection, and 1 each had a mitral commissurotomy, subpulmonary resection, atrial septal defect closure, repair of the atrioventricular canal, and Blalock-Hanlon atrial septectomy. Three patients required revision of the original repair of coarctation.

**Mortality:** Cumulative mortality is expressed in tabular form (Table II) and as an actuarial survival curve (Fig. 1). Uncomplicated coarctation carried no mortality over the mean follow-up period of 73.8 months (median 72). Eleven children with complicated defects died before any surgery was attempted. Their course is summarized in Table III. All but 1 of these children are believed to have died in a low-output state and congestive heart failure as a direct result of their cardiac disease; the remaining patient (Case 2) died from overwhelming infection. Five of these patients (Cases 2, 4, 6, 7, and 10) were not offered surgery because of the severity of associated cardiac and extracardiac defects. Three other infants died in the catheterization laboratory, and 2 more died within 1 day of cardiac catheterization. One child with coarctation and multiple sites of left-to-right shunting died as a result of refractory supraventricular tachycardia.

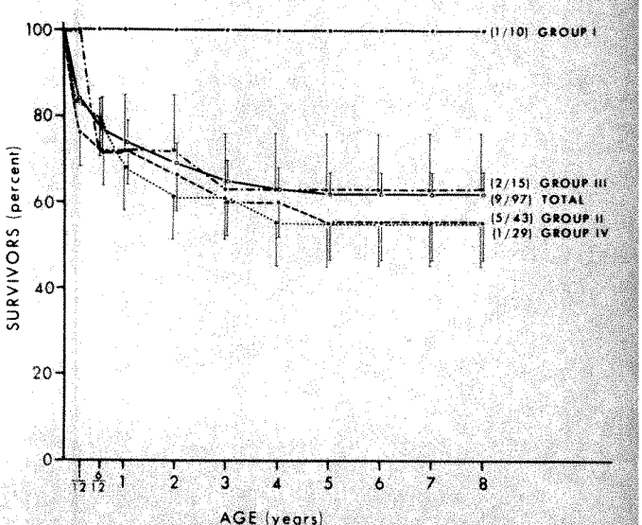



**FIGURE 1.** Survival of infants with symptomatic coarctation of the aorta. Data points represent mean actuarial survival, ±1 standard error of the mean. There were no deaths in Group I. The other 3 groups had similar survival curves, although the circumstances of death varied. The overall 8-year survival rate was 62%. Numbers in parentheses refer to the patient population in each group at the beginning and end of the actuarial survival curves. See text for more detailed explanation.

**TABLE IV Late Postoperative Morbidity**

| Group | Persistent CHF | Residual Coarctation (Gradient 10 torr) | Systemic Hypertension |
|---|---|---|---|
| I (n = 10) | 0 | 3 | 1 |
| II (n = 26) | 0 | 9 | 1 |
| III (n = 6) | 1 | 3 | 1 |
| IV (n = 14) | 5 | 3 | 0 |
| Total (n = 55) | 6 | 18 | 3 |

CHF = congestive heart failure.

There were 13 late deaths after surgical repair of coarctation, 5 of which were related to subsequent surgical intervention for associated lesions. Of the 8 late nonsurgical deaths, 3 occurred for reasons clearly related to associated cardiac anomalies, 2 were the result of overwhelming infection, and in 3 patients (1 each from Groups II, III, and IV) the cause of death is unknown.

Although there was some variability in the mode and timing of deaths among the postoperative groups with complicated lesions, the cumulative mortality for each of these groups was statistically comparable with the others. In actuarial terms, this translates to an overall 38% mortality rate over 8 years, with 42% of deaths occurring in the first month and 82% within 2 years.

**Postoperative morbidity:** Follow-up data at least 1 year after repair is available for 56 (75%) of 75 patients (Table IV). No patient in Group I or II had refractory congestive heart failure after repair, and more than three fourths of patients with other left-sided obstructions were relieved of symptoms after repair. Eighteen patients (32%) had continued evidence of coarctation after repair, defined as a gradient between arm and leg cuff pressures, or between proximal and distal intraaortic pressures, >10 torr. To date, 3 patients required revision of the coarctation repair, and these were all successful.

We evaluated for the presence of systemic hypertension, defined as a systolic blood pressure obtained in the right arm with an appropriate-sized cuff, which exceeded the normal mean for age and sex by >2 standard deviations.[8] Three patients (5%) met this criterion, 2 of whom also had evidence of a residual coarctation. The presence or type of associated cardiac defects did not appear to influence the occurrence of late postoperative hypertension.

## Discussion

The management of symptomatic infants with coarctation of the aorta remains problematic because of the high rate of mortality and morbidity in both surgically and medically treated patients. An update of the natural and unnatural course of these infants can be helpful in predicting the clinical course for individual patients and individualizing their treatment.

Patients with uncomplicated coarctation and congestive heart failure have recently become a subject of controversy. This combination is uncommon, comprising only 10% of the present series. In our experience and in that of others,[9–11] congestive symptoms could be controlled medically without incident until elective repair later in infancy or beyond. All 10 of our patients in this category were successfully treated medically without congestive failure. Five had later repair in the first year of life: 3 for systolic hypertension >200 mm Hg, and 2 because of social considerations. Overall, our 10 patients with uncomplicated coarctation underwent repair at a median age of 10.5 months (mean 20.2). However, Waldhausen et al[12] cited 2 cases of acute medical decompensation (including 1 death) as justification for their recommendation of immediate surgical repair in infancy. Although repair of uncomplicated coarctation carries a low risk at any age, we are concerned that early repair will increase the likelihood of a suboptimal result in terms of residual gradient. In our own experience, both the end-to-end anastomosis technique and the Dacron patch aortoplasty procedure have a significantly greater risk of a poor result if performed in infancy.[13] Several studies have been cited[14–17] as evidence that the subclavian flap technique effectively eliminates the effect of young age on surgical outcome. However, the follow-up period of these studies is brief, and data concerning the occurrence of residual gradient are scant or absent. At least 1 recent study, although not intended to be a comparative evaluation of surgical techniques, reported a higher rate of residual coarctation after subclavian flap repair than for either primary anastomosis or patch aortoplasty.[18] Until the effect of age is conclusively shown to be minimized by the subclavian flap technique, we continue to recommend medical management and elective surgical repair during childhood for most patients with isolated coarctation.

Complicated defects including coarctation present a different problem, where symptoms can be intractable and death a very real possibility. Although recent improvements in medical and surgical care have resulted in a reduced mortality compared with older series,[10] the 26% infant mortality reported in this series remains formidable. The fact that 10 infants died a cardiac death before operative treatment not only underscores the serious nature of this disease complex, but also suggests that we have relied too much on medical treatment alone in the past. However, the equal number of surgical deaths serves as a reminder that, for some infants, no currently available treatment may be sufficient. The cumulative mortality and morbidity figures for the 3 groups with complex defects are nearly identical, regardless of whether the associated defects consist primarily of a shunt, additional obstruction, or both. There is a difference between groups, however, in the circumstances of death: 9 of 10 surgical deaths occurred in Group II, whereas 9 of 13 late deaths occurred in Groups III and IV. When we compared our series with the earlier multicenter NERICP[4] group there was a striking similarity in the proportion and type of associated cardiac and extracardiac anomalies, as well as in the mortality risk of cardiac catheterization. Our more favorable early mortality experience probably reflects improvements in medical therapy as well as a trend toward earlier and more effective surgical intervention. In any event, coarctation in the form of a complex remains a dangerous condition requiring vigorous medical stabilization followed shortly thereafter by surgical repair. The specific technique of repair should depend on the preference and proficiency of the surgeon. Although some reports claim a superiority of patch aor-

toplasty to primary anastomosis,[19,20] we have found no significant difference in the effectiveness of these 2 procedures.[13] Many centers now prefer the subclavian flap technique for repair of infant coarctation, but our limited experience does not allow us to judge this technique. Simultaneous pulmonary artery banding for patients with ventricular septal defect should be considered on an individual, patient-by-patient basis, recognizing that isolated ventricular septal defect is often amenable to medical management and has the potential to close spontaneously. Pulmonary artery banding, on the other hand, commits the patient to a second surgical procedure. We therefore recommend that the size of the ventricular septal defect be assessed, either angiographically or echographically, as an aid in deciding whether or not a pulmonary band is needed. In this series, 24 patients received a pulmonary artery band out of 53 with associated ventricular septal defect. Six children had ventricular septal defects that closed spontaneously, and 5 of these 6 avoided a second thoracotomy because they had not received a pulmonary band. The 6th child required repeat operation to remove the pulmonary band and to resect a subaortic obstruction.

*Conclusion:* For infants with isolated coarctation of the aorta, the prognosis is excellent. For those with coarctation and associated cardiac anomalies, mortality remains high despite improved medical and surgical treatment. Early surgical intervention is both lifesaving and effective in reducing the symptoms of congestive heart failure, but surgical mortality is high and postoperative results remain flawed by a high rate of residual coarctation. Late systemic arterial hypertension occurs infrequently and is usually related to a residual coarctation. If an infant with complex coarctation receives early and vigorous management, the long-term prognosis depends primarily on the specific associated defects.

## References


1. **Campbell M.** Natural history of coarctation of the aorta. Br Heart J 1970; 32:633–640.
2. **Abbott ME.** Statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of the descending arch. Am Heart J 1928;3:381–421.
3. **Reifenstein GH, Levine SA, Gross RE.** Coarctation of the aorta. A review of 104 autopsied cases of the "adult type." Am Heart J 1947;33:146–168.
4. **Fyler DC, Buckley LP, Hellenbrand WE, Cohen HE, Kirklin JW, Nadas AS, Cartier JM, Breibart MH.** Report of the New England Regional Infant Cardiac Program. Pediatrics 1980;65(Suppl):375–461.
5. **Reul GJ, Kabbani SS, Sandiford FM, Wukasch DC, Cooley DA.** Repair of coarctation of the thoracic aorta by patch graft aortoplasty. J Thorac Cardiovasc Surg 1974;68:696–704.
6. **Blalock A, Park EA.** The surgical treatment of experimental coarctation (atresia) of the aorta. Ann Surg 1944;119:445–456.
7. **Waldhausen JA, Nahrwold DL.** Repair of coarctation of the aorta with a subclavian flap. J Thorac Cardiovasc Surg 1966;51:532–533.
8. **Blumenthal S, Epps RP, Heavenrich R, Lauer RM, Lieberman E, Mirkin B, Mitchell SC, Naito VB, O'Hare D, Smith WM, Tarazi RC, Upson D.** Report of the task force on blood pressure control in children. Prepared by the NHLBI Task Force on Blood Pressure Control in Children. Pediatrics 1977;50 (Suppl):797–820.
9. **Hesslein PS, McNamara DG.** Surgical intervention in infants with isolated coarctation of the aorta. J Thorac Cardiovasc Surg 1981;82:640.
10. **Hartman AF Jr, Goldring D, Strauss AW, Hernandez A, McKnight RC, Weldon CS.** Coarctation of the aorta. In: Moss AJ, Adams FH, Emmanoulides GC, eds. Heart Disease in Infants, Children, and Adolescents. 2nd ed. Baltimore: Williams & Wilkins, 1977:199–209.
11. **Chen S, Fagan LF, Mudd GJF, Willman VL.** Prognosis of infants with coarctation of the aorta. Am Heart J 1977;94:557–561.
12. **Waldhausen JA, Whitman V, Werner JC, Pierce WS.** Surgical intervention in infants with coarctation of the aorta. J Thorac Cardiovasc Surg 1981; 81:323–325.
13. **Hesslein PS, McNamara DG, Morriss MJH, Hallman GL, Cooley DA.** Comparison of resection versus patch aortoplasty for repair of coarctation in infants and children. Circulation 1981;64:164–168.
14. **Hamilton DI, DiEusanio G, Sandrasagra FA, Donnelly RJ.** Early and late results of aortoplasty with a left subclavian flap for coarctation of the aorta in infancy. J Thorac Cardiovasc Surg 1978;75:699–704.
15. **Thibault WN, Sperling DR, Gazzaniga AB.** Subclavian artery patch angioplasty. Arch Surg 1975;110:1095–1098.
16. **Midgley FM, Scott LP, Perry LW, Shapiro SR, McClenathan JE.** Subclavian flap aortoplasty for treatment of coarctation in early infancy. J Pediatr Surg 1978;13:265–268.
17. **Pierce WS, Waldhausen JA, Berman W Jr, Whitman V.** Late results of the subclavian flap procedure in infants with coarctation of the thoracic aorta. Circulation 1978;58:Suppl I:I-178–III-182.
18. **Kamau P, Miles V, Toews W, Kelminson L, Friesen R, Lockhart C, Butterfield J, Hernandez J, Hawes CR, Pappas G.** Surgical repair of coarctation of the aorta in infants less than six months of age. J Thorac Cardiovasc Surg 1981;81:171–179.
19. **Sade RM, Taylor AB, Chariker EP.** Aortoplasty compared with resection for coarctation of the aorta in young children. Ann Thorac Surg 1979;28: 346–353.
20. **Olson TH, Kugler JD, Clark EB, Mooring PK, Fleming WH, Hofschire PJ.** Coarctation of the aorta. A comparison of end-to-end anastomosis and patch angioplasty techniques (abstr). Pediatr Cardiol 1980;1:324.

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**Journal:** Vismara LA, Vera Z, Miller RR, Mason DT. Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. Am J Cardiol 1977; 39:1027–1034.

**Chapter in Book:** Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. Heart Disease in Infants, Children and Adolescents. Baltimore: Williams & Wilkins, 1968: 134–139.

**Book:** Berne E. Principles of Group Treatment. New York: Oxford University Press, 1966:26.

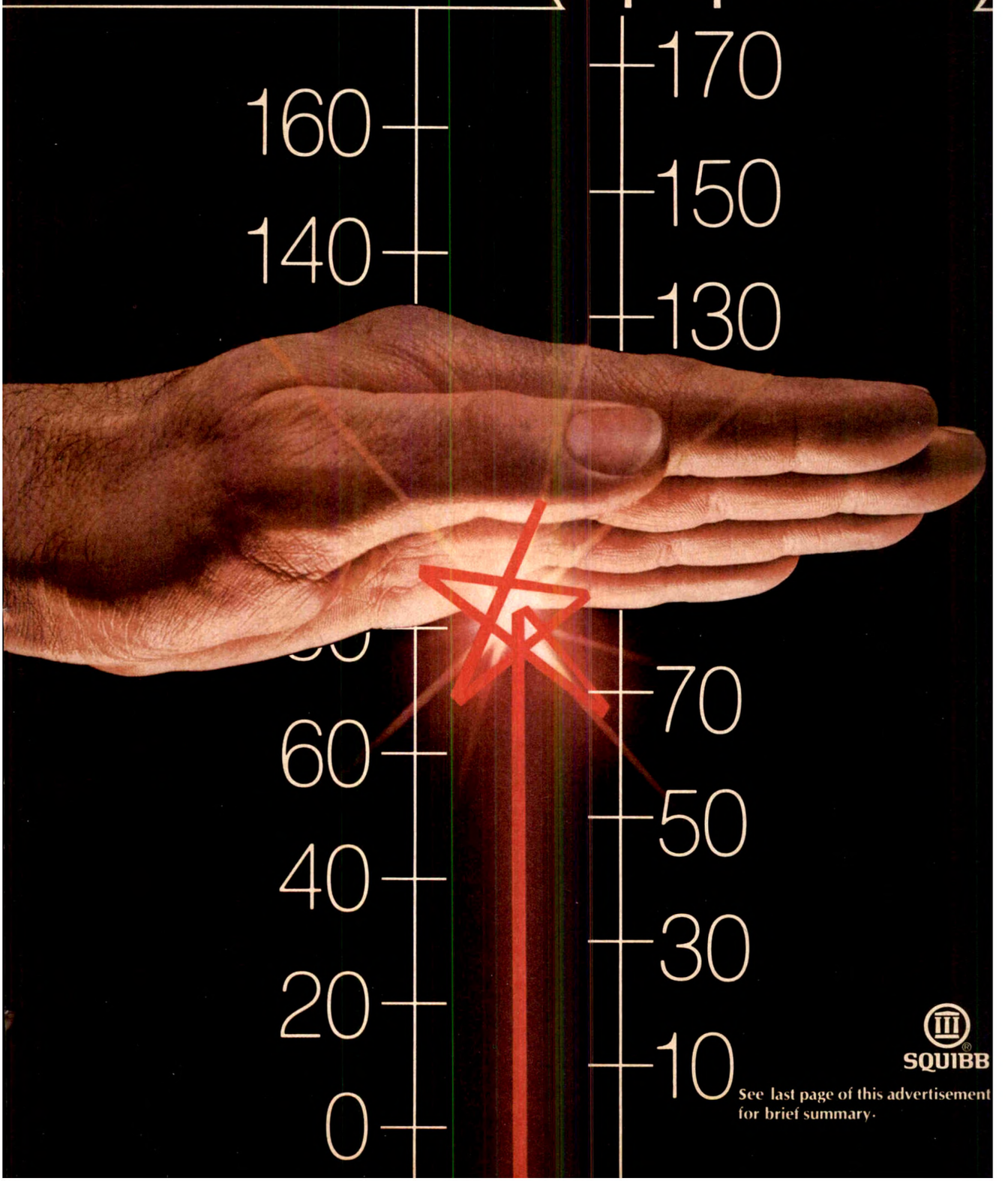
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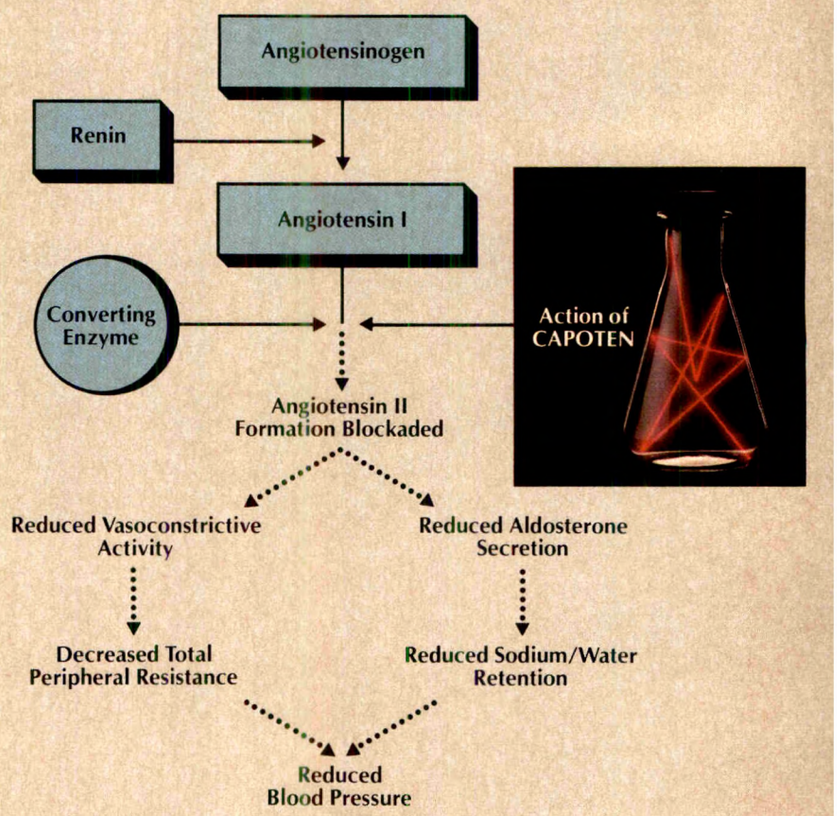

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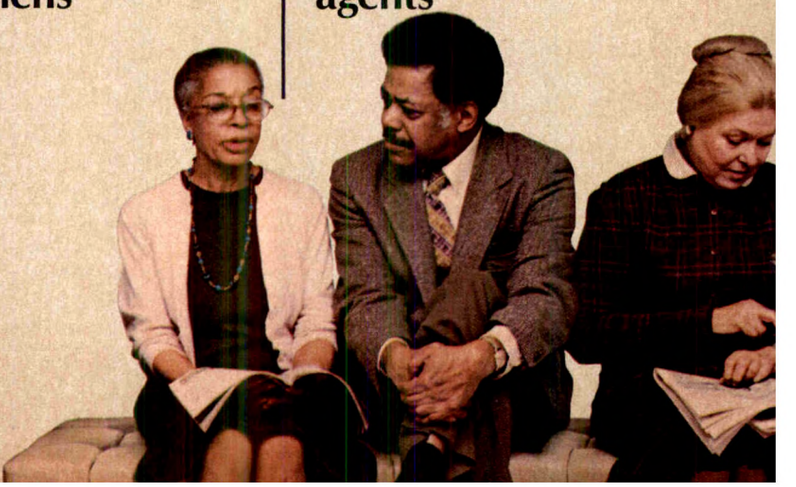



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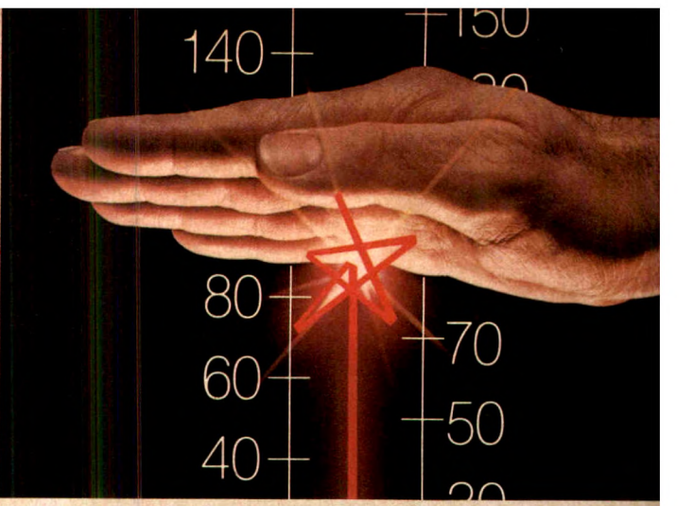
**whose blood pressure is uncontrolled by standard multidrug regimens**

**who have concomitant conditions contraindicating use of other antihypertensive agents**



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- ▶ No cardiac depression
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ACE INHIBITOR

## CAPOTEN®
## (captopril tablets)

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ACE* INHIBITOR

# CAPOTEN® (captopril tablets)

## Designed to control blood pressure even when coexisting disorders complicate hypertension management

Unlike some other antihypertensive agents, CAPOTEN is appropriate for use in the presence of a wide range of cardiovascular and metabolic disorders that often coexist with hypertension.

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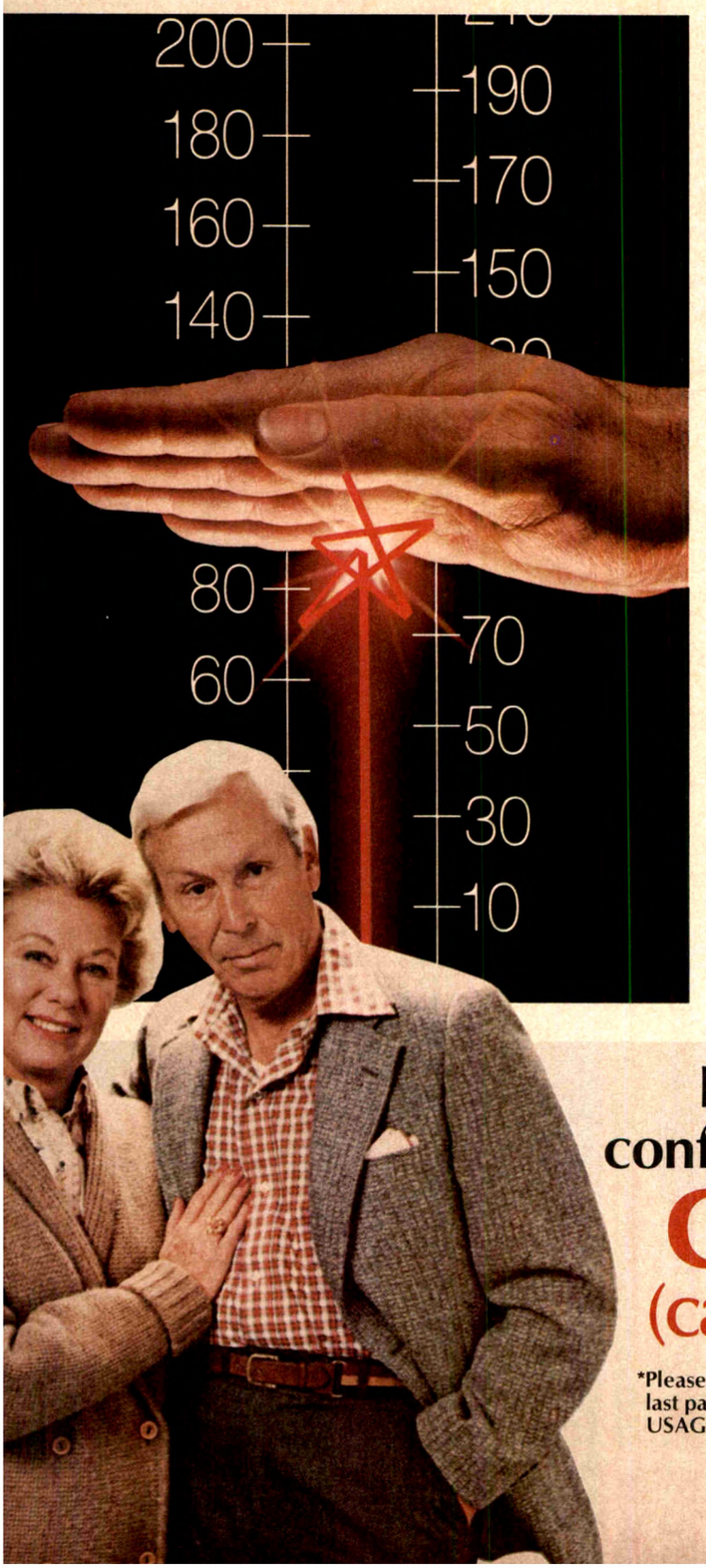
In scores of clinical studies, the effectiveness of CAPOTEN in lowering elevated blood pressure has been proven in many kinds of hypertension—even in those types that are most difficult to treat.

- ▶ **Essential hypertension**
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- ▶ **Hypertension associated with low, normal, and high plasma renin levels**
- ▶ **Renovascular hypertension**

*Angiotensin Converting Enzyme

# Designed to achieve your therapeutic goals in hypertension

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## Effective blood pressure control

▶ Routine monitoring procedures are recommended because serious side effects (neutropenia/agranulocytosis, proteinuria) have been associated with CAPOTEN.*

▶ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

▶ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

▶ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

▶ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

## In hypertension... confidence comes with

# CAPOTEN®

## (captopril tablets)

*Please see brief summary of prescribing information on the last page of this advertisement for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

**Captopril Tablets**

**DESCRIPTION:** Capoten (captopril) is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for converting angiotensin I to angiotensin II.

**INDICATIONS:** Because serious adverse effects have been reported (see WARNINGS), Capoten is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects. Usually, multidrug regimens include combinations of a diuretic, a sympathetic nervous system-active agent (such as a beta-blocker) and a vasodilator.

Capoten (captopril) is effective alone, but in the population described above, it should usually be used in combination with a thiazide-type diuretic. The blood pressure lowering effects of captopril and thiazides appear to be additive.

**WARNINGS: Proteinuria**—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. Existence of prior renal disease increased the likelihood of development of proteinuria. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued, but some patients had persistent proteinuria. The BUN and creatinine were seldom altered in the proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related; this is uncertain since patients were not biopsied prior to treatment and membranous glomerulopathy may be associated with hypertension in absence of captopril therapy. Since most cases of proteinuria occurred by the 8th month of captopril therapy, patients on captopril should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

**Neutropenia/Agranulocytosis**—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

**Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.**

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller, and it is sufficient in these patients to have white blood cell counts every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

**Hypotension**—Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in severely salt/volume depleted persons such as those treated vigorously with diuretics, e.g., patients with severe congestive heart failure (see PRECAUTIONS [Drug Interactions]).

**PRECAUTIONS: General:** *Impaired Renal Function*—Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible (see DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]). *Surgery/Anesthesia*—During major surgery or anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release; if hypotension occurs and is considered due to this mechanism, it is correctable by volume expansion.

**Drug Interactions:** *Hypotension: Patients on Diuretic Therapy*—A precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretic therapy and those on severe dietary salt restriction or dialysis. The possibility of hypotensive effects can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose. If hypotension occurs, place the patient in a supine position and, if necessary, administer an I.V. infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

*Agents Causing Renin Release*—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

*Agents Affecting Sympathetic Activity*—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

*Agents Increasing Serum Potassium*—Since captopril decreases aldosterone production, elevation of serum potassium may occur. Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. If the patient has received spironolactone at any time up to several months prior to captopril therapy, determine the serum potassium frequently since the effect of spironolactone persists.

**Drug/Laboratory Test Interaction:** Captopril may cause a false-positive urine test for acetone.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.

**Animal Toxicology:** Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels. Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD. The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacri-

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[illegible] 30 times MRHD, bone marrow suppression was found to be reversible upon continue drug administration. Captopril caused hyperplasia of the juxtaglomerular apparatus of th kidneys at doses 7 to 200 times the MRHD in rats and mice, at 20 to 60 times MRH in monkeys, and at 30 times the MRHD in dogs. Gastric erosions/ulcerations were i creased in incidence at 20 and 200 times MRHD in male rats and at 30 and 65 times MRH in dogs and monkeys, respectively. Rabbits developed gastric and intestinal ulcers whe given oral doses about 30 times MRHD for only 5 to 7 days. In the two-year rat study, irr versible and progressive variations in the caliber of retinal vessels (focal sacculatior and constrictions) occurred at all dose levels (7 to 200 times MRHD) in a dose-relate fashion. The effect was first observed in the 88th week of dosing, with a progressive increased incidence thereafter, even after cessation of dosing.

**Pregnancy: Category C**—Captopril was embryocidal in rabbits when given in doses 2 to 7 times (on a mg/kg basis) the maximum recommended human dose. The marked em bryocidal effect in rabbits was most probably due to the particularly marked decreas in blood pressure caused by the drug in this species. Captopril given to pregnant rats 400 times the recommended human dose continuously during gestation and lactatio reduced neonatal survival. No teratogenic effects (malformations) have been seen afte large doses of captopril in hamsters, rats, and rabbits.

There are no adequate and well-controlled studies in pregnant women. Captopr should be used during pregnancy only if the potential benefit justifies the potential ris to the fetus.

**Nursing Mothers:** Concentrations of captopril in human milk are about 1% of those maternal blood. The effect of low levels of captopril on the nursing infant has not bee determined. Exercise caution when administering captopril to a nursing woman, and, general, nursing should be interrupted.

**Pediatric Use:** Safety and effectiveness in children have not been established althoug there is limited experience with use of captopril in children from 2 months to 15 year of age with secondary hypertension and varying degrees of renal insufficiency. Dosage on a weight basis, was comparable to that used in adults. Captopril should be used i children only if other measures for controlling blood pressure have not been effective.

**ADVERSE REACTIONS:** Reported incidences are based on clinical trials involving abou 4000 patients.

*Renal*—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal in sufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patient but relationship to drug use is uncertain.

*Hematologic*—Neutropenia/agranulocytosis (probably drug related) occurred in abou 0.3% of captopril treated patients (see WARNINGS). Two of these patients develope sepsis and died.

*Dermatologic*—Rash (usually maculopapular, rarely urticarial), often with pruritus an sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1s 4 weeks of therapy. The rash is usually mild and disappears within a few days of dosag reduction, short-term treatment with an antihistaminic agent, and/or discontinuing the apy; remission may occur even if captopril is continued. Pruritus, without rash, in abou 2 of 100 patients. Between 7 and 10% of patients with skin rash have shown an eosino philia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, an photosensitivity have also been reported. Angioedema of the face, mucous membrane of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinu ance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor i 2 to 5 of 1000 patients.

*Cardiovascular*—Hypotension in about 2 of 100 patients. See PRECAUTIONS (Dru Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardia infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 100 patients.

*Dysgeusia*—About 7 of 100 patients developed a diminution or loss of taste percep tion; taste impairment is reversible and usually self-limited even with continued drug us (2 to 3 months). Weight loss may be associated with the loss of taste. Gastric irritation abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, an paresthesias reported in about 0.5 to 2% of patients but did not appear at increase frequency compared to placebo or other treatments used in controlled trials.

**Altered Laboratory Findings:** Elevations of liver enzymes in a few patients although n causal relationship has been established. A single case of hepatocellular injury wit secondary cholestasis has been reported in association with captopril use. A transien elevation of BUN and serum creatinine may occur, especially in volume-depleted or renc vascular hypertensive patients. In instances of rapid reduction of longstanding or severel elevated blood pressure, the glomerular filtration rate may decrease transiently, als resulting in transient rises in serum creatinine and BUN. Small increases in serum potas sium concentration frequently occur, especially in patients with renal impairment (se PRECAUTIONS).

**OVERDOSAGE:** Primary concern is correction of hypotension. Volume expansion with a I.V. infusion of normal saline is the treatment of choice for restoration of blood pres sure. Captopril may be removed from the general circulation by hemodialysis.

**DOSAGE AND ADMINISTRATION:** CAPOTEN (captopril) should be taken one hour befor meals. Dosage must be individualized.

Give consideration to recent antihypertensive drug therapy, extent of blood pressur elevation, salt restriction, and other circumstances before initiating therapy. If possible discontinue the patient's previous antihypertensive drug regimen for one week befor starting captopril. Initial dose of CAPOTEN (captopril) is 25 mg t.i.d. If satisfactory bloo pressure reduction is not achieved after 1 or 2 weeks, dose may be increased to 50 m t.i.d. If the blood pressure has not been satisfactorily controlled after another 1 to 2 weeks add a modest dose of a thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg daily) The diuretic dose may be increased at 1- to 2-week intervals until its highest usual anti hypertensive dose is reached. If further blood pressure reduction is required, CAPOTE (captopril) may be increased to 100 mg t.i.d. and then, if necessary, to 150 mg t.i.d (while continuing the diuretic). The usual dose range is 25 to 150 mg t.i.d. A maximum daily dose of 450 mg CAPOTEN (captopril) should not be exceeded.

For patients with accelerated or malignant hypertension, when temporary discontinua tion of current antihypertensive therapy is not practical, or when prompt titration to mor normotensive blood pressure levels is indicated, current antihypertensive medication ma be stopped and CAPOTEN (captopril) dosage promptly initiated at 25 mg t.i.d., under clos medical supervision. The daily dose of CAPOTEN (captopril) may be increased every 2 hours until a satisfactory blood pressure response is obtained or the maximum captopri dose is reached. In this regimen, addition of a more potent diuretic, e.g., furosemide may also be indicated. Beta-blockers may also be used in conjunction with captopri therapy (see PRECAUTIONS [Drug Interactions]), but the effects of the 2 drugs are less than additive.

**Dosage Adjustment in Renal Impairment**—Because CAPOTEN (captopril) is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal func tion. These patients will take longer to reach steady-state captopril levels and will reac higher steady-state captopril levels for a given daily dose than patients with normal rena function. Therefore, these patients may respond to smaller or less frequent doses. Ac cordingly, for patients with significant renal impairment, initial daily dosage of CAPOTE (captopril) should be reduced, and smaller increments utilized for titration, which should be quite slow (1- to 2-week intervals). After desired therapeutic effect has been achieved dose should be slowly back-titrated to determine minimal effective dose. When con comitant diuretic therapy is required, a loop diuretic (e.g., furosemide), rather than thiazide diuretic, is preferred in patients with severe renal impairment.

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# Equilibrium Radionuclide Gated Angiography in Patients With Tricuspid Regurgitation

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**Equilibrium gated radionuclide angiography was performed in 2 control groups (15 patients with no organic heart disease and 24 patients with organic heart disease but without right- or left-sided valvular regurgitation) and in 9 patients with clinical tricuspid regurgitation. The regurgitant index, or ratio of left to right ventricular stroke counts, was significantly lower in patients with tricuspid regurgitation than in either control group (range and mean ± standard error of the mean 0.4 to 1.0, 0.7 ± 0.1 versus 1.0 to 1.5, 1.3 ± 0.1 and 1.0 to 2.9, 1.5 ± 0.1, respectively, $p < 0.001$). Time-activity variation over the liver was used to compute a hepatic expansion fraction which was significantly higher in patients with tricuspid regurgitation than in either control group (1.4 to 11.4, 5.8 ± 1.0% versus 0.6 to 3.4, 1.9 ± 0.3% and 1.0 to 5.1, 2.3 ± 0.2%, respectively, $p < 0.001$). Fourier analysis of time-activity variation in each pixel was used to generate amplitude and phase images. Only pixels with values for amplitude at least 7% of the maximum in the image were retained in the final display. All patients with tricuspid regurgitation had >100 pixels over the liver automatically retained by the computer. These pixels were of phase comparable to that of the right atrium and approximately 180° out of phase with the right ventricle. In contrast, no patient with no organic heart disease and only 1 of 24 patients with organic heart disease had any pixels retained by the computer.**

**In conclusion, patients with tricuspid regurgitation were characterized on equilibrium gated angiography by an abnormally low regurgitant index (7 of 9 patients) reflecting increased right ventricular stroke volume, increased hepatic expansion fraction (7 of 9 patients), and increased amplitude of count variation over the liver in phase with the right atrium (9 of 9 patients).**

Tricuspid regurgitation can present a difficult clinical diagnosis, particularly when other cardiac lesions are present. Although first-pass radionuclide angiography was used to support the diagnosis in 1 case of traumatic tricuspid regurgitation,[1] equilibrium radionuclide gated angiography has not previously been employed to establish a diagnosis of tricuspid regurgitation. In this study, computer-processed results of equilibrium radionuclide angiography including Fourier analysis of time-activity variation in patients with clinically manifest tricuspid regurgitation were compared with results in 2 control groups, 1 consisting of patients with no organic heart disease and 1 consisting of patients with organic heart disease but no clinical evidence of right- or left-sided valvular regurgitation. Measurements of cardiac regurgitant index, hepatic expansion fraction, and amplitude and phase over the liver were abnormal in patients with tricuspid regurgitation.

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## Methods

**Patient selection:** Three groups of patients were studied: those with no organic heart disease, those with organic heart disease but without right- or left-sided valvular regurgitation, and those with tricuspid regurgitation. Criteria for inclusion of patients with no organic heart disease were normal results on cardiovascular examination, normal heart size on chest X-ray, and normal left ventricular ejection fraction and wall motion on equilibrium gated angiography. Absence of demonstrable organic heart disease was supported by M-mode echocardiography and cardiac catheterization with angiography in some patients.

Criteria for inclusion of patients with organic heart disease were the presence of diagnosed heart disease without clinical evidence of right- or left-sided valvular regurgitation on history, physical examination, and noninvasive studies. All patients in the group had cardiac catheterization to confirm the diagnosis and all had equilibrium gated angiographic study.

Criteria for inclusion of patients with tricuspid regurgitation were the presence of at least 2 of the following 3 findings on physical examination: abnormal CV wave in the internal jugular venous pulse, a systolic murmur at the left lower sternal border that increased in intensity on inspiration, and a palpable expansile liver. An equilibrium radionuclide angiographic study was performed in each patient. Other independent data for the presence of tricuspid regurgitation were elevated right atrial pressures and large right atrial CV waves at cardiac catheterization, saline microbubbles visualized for at least 4 beats at the right atrial inferior vena caval junction on 2-dimensional echocardiography,[2,3] visible systolic bulging (of an enlarged right atrium and a palpable thrill over the right atrial wall) during cardiac surgery, regurgitation of contrast material into the right atrium during right ventricular angiography, surgical tricuspid valvectomy, and autopsy evidence of a grossly dilated right atrium, ventricle, and tricuspid valve anulus.

**Equilibrium gated radionuclide angiography:** Each study was performed with the patient in the supine position using in vivo red blood cell labeling with technetium-99m.[4] A large field of view camera (Siemens) was positioned to obtain the best septal left anterior oblique view of the heart with a 10 to 15° caudal tilt. Data were acquired (Informatek Simis 3 computer) using 64 frames per cardiac cycle with 250,000 to 300,000 counts per frame and stored on tape for processing.

Computer processing for calculation of left ventricular ejection fraction and assessment of left ventricular regional wall motion employed methods previously described.[5–8] The left ventricular regurgitant index was calculated as the ratio of left ventricular stroke counts to right ventricular stroke counts.[9] The stroke counts were obtained from left and right ventricular time-activity curves of the respective regions of interest by subtraction of the respective ventricular end-systolic from the end-diastolic counts for each patient studied. This allowed for right ventricular end-systole to occur during a different frame from left ventricular end-systole.

**Hepatic expansion fraction:** In each patient the entire field-of-view image at end-diastole was used to manually outline for computer processing a region of high activity below and to the right of the heart thought to correspond to the liver. The upper border of this region of interest was determined by following a trough of activity between the heart and the liver. This border was drawn tightly to avoid including the heart itself. Hepatic counts for each time frame were determined by the computer. A time-activity curve for the liver was then generated. A hepatic expansion fraction was calculated using the following formula: hepatic expansion fraction = (maximal counts − minimal counts)/minimal counts. Maximal and minimal counts were chosen by numerical value regardless of the frame in which they occurred during the cardiac cycle (see section on Fourier analysis). Interobserver variability in the measurement of hepatic expansion fraction was evaluated in 4 study patients. Independently calculated values by 2 of us differed by 0.1, 0.1, 0.2, and 0.3 percentage points, respectively.

**Fourier analysis:** Amplitude and phase analysis was performed using the first Fourier harmonic of time-activity variation in each pixel to generate amplitude and phase images. Each displayed pixel was color coded according to its value for amplitude and phase, respectively.[10–12]

**TABLE I Results of Equilibrium Gated Angiography**

| | No OHD | OHD, No TI | TI | p Value |
|---|---|---|---|---|
| LVEF (%) | 68 ± 2 | 48 ± 6 | 53 ± 5 | NS |
| RI | 1.3 ± 0.1 | 1.5 ± 0.1 | 0.7 ± 0.1 | <0.001 |
| HEF (%) | 1.9 ± 0.3 | 2.3 ± 0.2 | 5.8 ± 1.0 | <0.001 |
| Hepatic amplitude present/ total patients | 0/15 | 1/24 | 9/9 | . . . |

Values are the mean ± standard error of the mean. HEF = hepatic expansion fraction; LVEF = left ventricular ejection fraction; OHD = organic heart disease; RI = regurgitant index; TI = tricuspid insufficiency.

Organs that have large changes in blood volume during the cardiac cycle, such as the heart, have high amplitude and well defined areas of coherent phase. However, organs not exhibiting ordered variation of blood volume during the cardiac cycle, even though they may contain a large volume of blood, such as the spleen, have low amplitude values and random phase. The former accentuates the statistical uncertainty in the calculation of phase values in such organs. Therefore, to eliminate areas of low amplitude and uncertain phase, 2 steps were taken. An amplitude threshold of 7% (of the maximal amplitude value of the entire image) was used to eliminate all pixels of low amplitude. The specific value of 7% was chosen empirically to best separate the control and study groups. Isolated clusters of 4 or fewer pixels, which also may represent statistical uncertainty, were automatically eliminated from the final amplitude image. The final phase image was derived from the final amplitude image. Thus, pixels eliminated from the amplitude image were also eliminated from the final phase image.

The phase image depicts pixels according to their respective phase relative to a 0° phase reference[10,11] (with the entire cardiac cycle representing 360°) and represents the relative timing of count variation. Structures that fill and empty synchronously, such as the right and left ventricles, have similar phase. Structures that fill and empty in opposition, such as the left atrium and left ventricle, have a phase difference in the vicinity of 180°.

**Statistical analysis:** The left ventricular ejection fraction, regurgitant index, hepatic expansion fraction, and amplitude and phase images for the 3 groups of patients were compared. Statistical analysis was carried out using Scheffe's method for analysis of variance.

## Results

**Clinical characteristics:** Fifteen patients with no organic heart disease comprised the first control group. They were aged 15 to 58 years (mean ± standard deviation 31 ± 12). Six patients were women and 9 were men. The clinical diagnosis was supraventricular tachycardia in 6 patients, noncardiac chest pain in 3, primary conduction disease in 2, and pancreatitis, pneumonia, gastroenteritis, and vasovagal syncope in 1 patient each. By study design, each patient had essentially normal findings on cardiovascular examination and normal cardiac size on chest X-ray. Additional independent data for the absence of heart disease included no significant abnormalities on M-mode echocardiography (11 of 11 patients) and normal cardiac catheterization with angiography (8 of 8 patients).

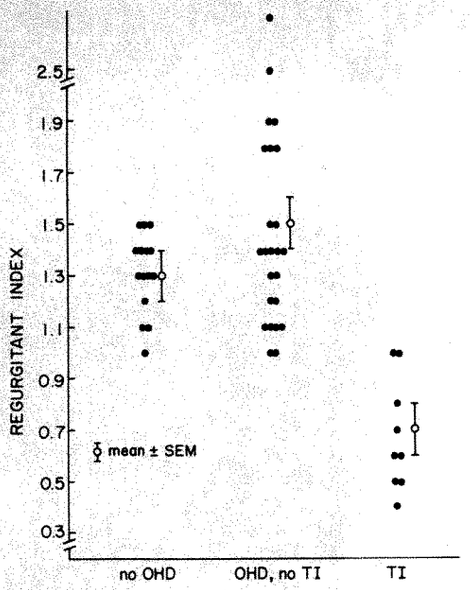



**FIGURE 1.** Regurgitant index is plotted on the ordinate. Each point represents 1 patient. **Left column,** values for patients with no organic heart disease (no OHD); **middle column,** values for patients with organic heart disease but without valvular insufficiency (OHD, no TI); **right column,** values for patients with tricuspid insufficiency (TI). Mean value for control patients is significantly higher than that of patients with tricuspid insufficiency ($p < 0.001$). SEM = standard error of the mean.

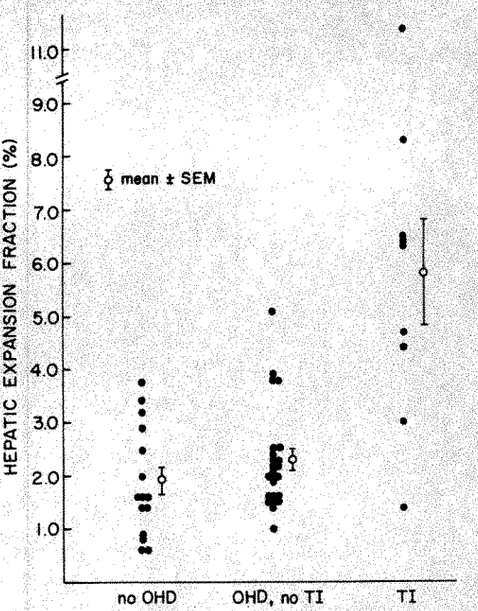



**FIGURE 2.** Hepatic expansion fraction in percentage is plotted on the ordinate. Each point represents 1 patient. **Left column,** values for patients with no organic heart disease (no OHD); **middle column,** values for patients with organic heart disease but without valvular insufficiency (OHD, no TI); **right column,** values for patients with tricuspid insufficiency (TI). Mean value for control patients is significantly lower than that of patients with tricuspid insufficiency ($p < 0.001$).

Twenty-four patients, aged 50 ± 14 years (range 14 to 69), with organic heart disease but without right- or left-sided valvular regurgitation comprised the second control group. There were 8 women and 16 men. The clinical diagnosis was atherosclerotic heart disease in 10 patients, cardiomyopathy in 8, mitral stenosis in 1, and miscellaneous cardiovascular diagnoses in the remaining 5. In each patient, the cardiovascular examination was appropriate for the clinical diagnosis and did not specifically suggest any right- or left-sided valvular regurgitation. The clinical diagnosis in each patient was confirmed by cardiac catheterization and angiography.

Nine patients, aged 41 ± 8 years (range 20 to 45), with tricuspid regurgitation comprised the study group. Five patients were women and 4 men. The clinical diagnosis was rheumatic heart disease in 5 patients, tricuspid valvectomy for bacterial endocarditis in 2, congenital heart disease in 1, and mixed-connective tissue disease with secondary pulmonary hypertension in 1. On physical examination, 7 patients had abnormal jugular venous CV waves, a positive Carvallo's sign, and an expansile liver. The remaining 2 patients had abnormal jugular venous CV waves and an expansile liver without documented Carvallo's sign to establish the presence of tricuspid regurgitation on clinical grounds. Independent data for the presence of tricuspid regurgitation were cardiac catheterization with elevated mean right atrial pressure and an increased right atrial CV wave (6 of 6 patients), positive contrast echocardiography (4 of 4 patients), positive findings at cardiac surgery (2 of 2 patients), positive contrast right ventricular angiography (1 of 1 patient), surgical tricuspid valvectomy in 2 patients, and postmortem evidence of a grossly dilated right atrium, ventricle, and tricuspid valve anulus in 1 patient.

**Equilibrium radionuclide angiography (Table I):** For patients with no organic heart disease, left ventricular ejection fraction ranged from 60 to 75% (mean ± standard error of the mean 68 ± 2%). For patients with organic heart disease without valvular regurgitation, left ventricular ejection fraction ranged from 19 to 82% (mean 48 ± 6%). For patients with tricuspid regurgitation, the left ventricular ejection fraction ranged from 22 to 74% (mean 53 ± 7%). Differences between each control group and the study group were not statistically significant.

For patients with no organic heart disease, the regurgitant index ranged from 1.0 to 1.5 (mean 1.3 ± 0.1). Normal in our laboratory is 0.9 to 1.7.[9] For patients with organic heart disease but without valvular insufficiency, the regurgitant index ranged from 1.0 to 2.9 (mean 1.5 ± 0.1). There was no significant difference in regurgitant index between these 2 control groups. In contrast, in patients with tricuspid regurgitation, the regurgitant index ranged from 0.4 to 1.0 (mean 0.7 ± 0.1), which was significantly lower than that in each control group ($p < 0.001$) (Fig. 1). Two patients with tricuspid regurgitation had a regurgitant index within the normal range. One of these patients had concomitant severe periprosthetic aortic regurgitation demonstrated by aortic root angiography. The other patient

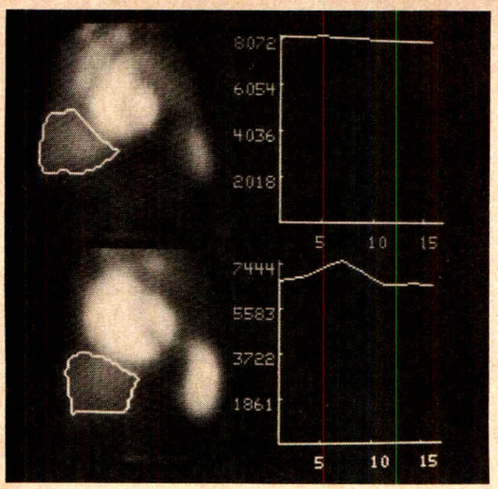



**FIGURE 3.** Hepatic expansion fraction. **Left,** end-diastolic image and outlined hepatic region of interest in a control patient (**above**) and a patient with tricuspid insufficiency (**below**). **Right,** corresponding time-activity curves for the hepatic regions of interest. Counts are represented on the ordinate and frame number on the **abscissa.** Note the ordered variation of hepatic activity during the cardiac cycle in the patient with tricuspid insufficiency.

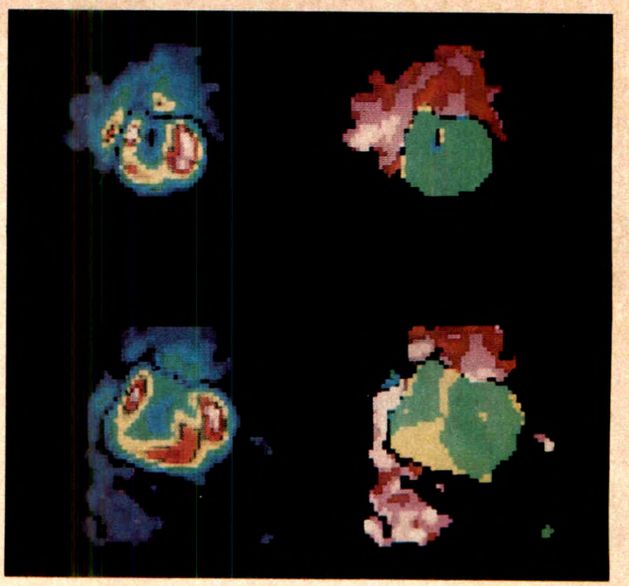


**FIGURE 4.** Final amplitude and phase images. **Left,** amplitude images in a control patient (**above**) and a patient with tricuspid insufficiency (**below**). **Right,** corresponding phase images. Note that in the control patient all pixels over the liver have been eliminated automatically (<7% maximal amplitude). In the patient with tricuspid insufficiency, pixels representing the liver have been retained (>7% maximal amplitude). The liver is of similar phase to the right atrium and of opposite phase to the right ventricle.

had concomitant severe mitral regurgitation demonstrated on left ventriculography.

**Hepatic expansion fraction (Table I):** For patients with no organic heart disease, the hepatic expansion fraction ranged from 0.6 to 3.4% (mean 1.9 ± 0.3%), reflecting the absence of substantial count variation over the liver during the cardiac cycle. For patients with organic heart disease without valvular regurgitation, the hepatic expansion fraction ranged from 1.0 to 5.1% (mean 2.3 ± 0.2%). There was no significant difference in the hepatic expansion fraction between these 2 control groups.

Four of 24 patients (17%) with organic heart disease without valvular regurgitation had values for hepatic expansion fraction that were above the range of those in patients with no organic heart disease. However, in none of these patients did the peak of hepatic activity occur simultaneously with or within 1 frame of the nadir of right ventricular activity (see later).

For patients with tricuspid regurgitation, the hepatic expansion fraction ranged from 1.4 to 11.4% (mean 5.8 ± 1.0%), which was significantly higher than that in each control group ($p < 0.001$) (Fig. 2). Two patients with tricuspid regurgitation had values for hepatic expansion fraction that were within the range of those in patients with no organic heart disease. Except in 1 of these patients, peak hepatic activity occurred simultaneously with or within 1 frame of the nadir of right ventricular activity in patients with tricuspid regurgitation. The outlined hepatic regions of interest and time-activity curves from representative patients with no organic heart disease versus those in the study group are illustrated in Figure 3.

**Amplitude and phase images (Fig. 4):** All patients with no organic heart disease and 23 of 24 patients with organic heart disease without valvular insufficiency had amplitude values for all pixels over the liver of <7% of the maximal amplitude in the image. Therefore, these pixels were automatically eliminated from the amplitude and phase images. In contrast, all patients with tricuspid regurgitation had at least 100 pixels over the liver with an amplitude >7% of the maximal amplitude in the image. Therefore, these pixels were automatically retained in the amplitude and phase images. Thus, substantial amplitude of hepatic blood volume variation with the cardiac cycle was present in all 9 patients with tricuspid regurgitation. On the phase images there is uniform phase for the atria and uniform (but 180° opposite) phase for the ventricles in all 3 groups of patients, reflecting that the atria fill when the ventricles empty (Fig. 4). Pixels over the liver in all patients with tricuspid regurgitation were in phase with the right atrium.

**Summary of data:** In summary, 3 variables were examined in each patient: regurgitant index, hepatic expansion fraction, and amplitude over the liver. All patients with no organic heart disease had a normal regurgitant index, low hepatic expansion fraction, and absence of significant amplitude over the liver. Of patients with organic heart without valvular regurgitation, all had a normal (17 patients) or increased (7 patients) regurgitant index. Twenty of 24 patients (83%) had low hepatic expansion fractions. Twenty-three of 24 (96%) had absence of significant amplitude over the liver.

In contrast, 7 of 9 patients (78%) with tricuspid regurgitation had a below-normal regurgitant index. Seven of 9 patients (78%) with tricuspid regurgitation had an above-normal hepatic expansion fraction. All 9

patients (100%) with tricuspid regurgitation had substantial amplitude over the liver. Looked at another way, in 5 of 9 patients with tricuspid regurgitation, all 3 measures gave abnormal values; 4 of 9 patients had abnormal values in only 2 measures.

## Discussion

Currently, the diagnosis of tricuspid regurgitation is established on the basis of physical findings. However, these findings may be obscured by multivalvular disease or after valve replacement for left-sided lesions. Right ventricular angiography and direct surgical evaluation are invasive and have been criticized as unreliable.[13] Contrast M-mode and 2-dimensional echocardiography,[2,3] sometimes with pulsed Doppler echocardiography,[14] has recently been useful in establishing the presence of tricuspid regurgitation. Intracardiac phonocardiography has also been useful when combined with right ventricular angiography.[15]

Equilibrium radionuclide gated angiography provides a noninvasive method for evaluating aortic or mitral insufficiency, or both.[9,16–19] However, there are no reports of a series of patients with right-sided valvular regurgitation. Patients with left-sided regurgitation have an increased left ventricular stroke volume and therefore an elevated regurgitant index. Patients with right-sided regurgitation would logically be expected to have an increased right ventricular stroke volume and consequently a decreased regurgitant index.

In the present study, 7 of 9 patients with tricuspid regurgitation had a low regurgitant index compared with that of patients without evidence of tricuspid regurgitation (Fig. 1). However, a low regurgitant index might be expected in many situations characterized by right ventricular volume overload. The physical findings of pulmonary regurgitation producing right ventricular volume overload are distinctive and usually not confused with those of tricuspid regurgitation. Intracardiac left to right shunting in atrial septal defect results in an increased Qp/Qs ratio because of right-sided volume overload.[20] However, concomitant left-sided regurgitation with increased left-sided stroke volume, depending on the degree, tends to normalize the ratio of left to right ventricular stroke counts. This was the case in 2 patients in the present series with tricuspid regurgitation whose values for regurgitant index were within the normal range.

To our knowledge, no reports have appeared analyzing the results of time-activity variation over noncardiac structures during equilibrium gated angiography. Eight of 9 patients with tricuspid regurgitation demonstrated ordered time-activity variation over the liver during the cardiac cycle (Fig. 2 and 3). Comparing the time-activity curves over the liver and the right ventricle, the peak of hepatic activity occurred within 1 frame or simultaneously with the nadir of right ventricular activity for 8 of 9 patients with tricuspid regurgitation. It seems doubtful that transmitted right ventricular, diaphragmatic, or abdominal aortic pulsations could result in an increased hepatic expansion fraction to the degree seen in patients with tricuspid regurgitation. A left ventricular to right atrial shunt as might occur in some patients with atrioventricular canal defects or ruptured sinus of Valsalva into the right atrium or right ventricle might mimic similar hemodynamic results and consequently an expansile liver. However, the clinical history and physical findings should allow differentiation of these patients.

At present, manual determination of a hepatic region of interest is somewhat subjective, depending as it does on outlining an area of high activity where the liver is located. The critical boundary of this region is found between the liver and the heart, especially in patients with right heart enlargement. Therefore, we made this border tight on the liver side. The finding that the apex of the hepatic time-activity curve corresponded to the nadir of the right ventricular time-activity curve (opposition of phase) is reassuring, because inclusion of a large area of right ventricle in the hepatic region of interest should obliterate this. Inclusion of the inferior vena cava within the hepatic region of interest seems probable, and this structure may also contribute to some of our findings.

Our group and others previously reported results of Fourier analysis in left ventricular regional wall motion abnormalities and in abnormal electrical activation including left bundle branch block and ventricular tachycardia.[10,12,21] In the present study, Fourier analysis was applied to each pixel from a large field-of-view image. The resulting amplitude image in all control patients had no pixels with substantial (>7% of maximum) amplitude over the liver. All patients with tricuspid regurgitation had ≥100 pixels with substantial amplitude over the liver. The maximal amplitude in the image should usually occur over the left ventricle. When a patient with tricuspid regurgitation has a low left ventricular ejection fraction, pixels over the liver may be included as having ≥7% of a low maximal amplitude and might not have substantial amplitude in an absolute sense. That the mean value of left ventricular ejection fraction in patients with organic heart disease without valvular regurgitation was lower than that in patients with tricuspid regurgitation argues against errors in resulting amplitude images.

Pixels corresponding to the right atrial and hepatic regions of interest were of similar phase to each other and of opposite phase to pixels corresponding to the right ventricular region of interest. Thus, pixels over the hepatic region of interest with substantial amplitude correspond to the physical finding of an expansile liver.

**Clinical significance:** We did not explore this technique in patients with severe right heart failure and hepatic congestion but without tricuspid regurgitation, although they would be an important control group. It would be very difficult to know conclusively that such patients did not have small degrees of tricuspid regurgitation. Because no strong standard is available for determining tricuspid regurgitation, no statement can be made about sensitivity or specificity of this method in such patients.

*In summary*, equilibrium gated angiography and Fourier analysis were used to distinguish patients with from those without clinical tricuspid regurgitation.

Characteristic findings of patients with tricuspid regurgitation included an abnormally low regurgitant index in 7 of 9 patients, an increased hepatic expansion fraction in 7 of 9 patients, and increased amplitude over the liver with pixels in phase with the right atrium in all 9 patients. These results imply that gated angiography can be used to confirm the presence of tricuspid regurgitation or to detect unsuspected tricuspid regurgitation. It is not known whether this method will allow quantification of the severity of this lesion.

## References


1. **Bardy BH, Talano JV, Meyers S, Lesh M.** Acquired cyanotic heart disease secondary to traumatic tricuspid regurgitation. Case report with review of the literature. Am J Cardiol 1979;44:1401–1406.
2. **Chen CC, Morganroth J, Mardelli TJ, Naito M.** Tricuspid regurgitation in tricuspid valve prolapse demonstrated with contrast cross-sectional echocardiography. Am J Cardiol 1981;46:983–987.
3. **Meltzer RS, Van Hoagenhuyze D, Serruys PW, Haalebos MM, Hugenholtz PG, Roelandt J.** Diagnosis of tricuspid regurgitation by contrast echocardiography. Circulation 1981;63:1093–1099.
4. **Pavel DG, Zimmer AM, Patterson VN.** In vivo labeling of red blood cells with 99mTc: a new approach to blood pool visualization. J Nucl Med 1978;18:305–308.
5. **Zaret BL, Strauss HW, Harley PJ, Natarajon TK, Pitt B.** Non-invasive scintiphotographic method for detecting regional ventricular dysfunction in man. N Engl J Med 1971;284:1165–1170.
6. **Federman J, Brown ML, Tancredie RG, Smith HC, Wilson DB, Becker GP.** Multiple-gated acquisition cardiac blood pool imaging; evaluation of left ventricular function correlated with contrast angiography. Mayo Clin Proc 1978;53:625–633.
7. **Pavel DG, Byrom E, Ayres B, Pietras R, Bianco J, Kanakis C.** Multifaceted evaluation of left ventricular function by the first transit technique using Anger type cameras and an optimized protocol: correlation with biplane roentgen angiography. In: Nuclear Cardiology: Selected Computer Aspects. New York: Society of Nuclear Medicine, 1978:129–138.
8. **Swiryn S, Pavel D, Byrom E, Wyndham C, Pietras R, Bauernfeind R, Rosen KM.** Assessment of left ventricular function by radionuclide angiography during induced supraventricular tachycardia. Am J Cardiol 1981;47:555–561.
9. **Lam W, Pavel DG, Byrom E, Sheik A, Best D, Rosen K.** Radionuclide regurgitant index-value and limitations. Am J Cardiol 1981;47:292–298.
10. **Adam WE, Tarkowska A, Bitter F, Stauch M, Geffers H.** Equilibrium radionuclide ventriculography. Cardiovasc Radiol 1979;2:161–173.
11. **Byrom E, Pavel DG, Swiryn S, Meyer-Pavel C.** Phase images of gated studies: a standard evaluation procedure. In: Esser P, ed. Functional Mapping of Organ Systems and Other Computer Topics. New York: Society of Nuclear Medicine, 1981:129–138.
12. **Swiryn S, Pavel DG, Byrom E, Witham D, Meyer-Pavel C, Wyndham CRC, Handler B, Rosen K.** Sequential regional phase mapping of radionuclide gated biventriculograms in patients with left bundle branch block. Am Heart J 1981;102:1000–1010.
13. **Lingamneni R, Cha SD, Maranhao V, Gooch AS, Goldberg H.** Tricuspid regurgitation: clinical and angiographic assessment. Cathet Cardiovasc Diagn 1979;5:7–17.
14. **Waggoner AD, Quinones MA, Young JB, Brando TA, Shah AA, Verani MS, Miller RR.** Pulsed Doppler echocardiographic detection of right-sided valve regurgitation. Experimental results and clinical significance. Am J Cardiol 1981;47:279–886.
15. **Cha SD, Gooch AS, Maranhao V, Koehler E.** Intracardiac phonocardiography in tricuspid regurgitation: relation to clinical and angiographic findings. Am J Cardiol 1981;48:578–583.
16. **Rigo P, Alderson PO, Robertson RM, Becker LC, Wayner HN.** Measurement of aortic and mitral regurgitation by gated cardiac blood pool scans. Circulation 1979;60:306–312.
17. **Sorenson SG, O'Rourke RA, Chadhuri TK.** Non-invasive quantitation of valvular regurgitation by gated equilibrium radionuclide angiography. Circulation 1980;62:1089–1098.
18. **Bough EW, Gansman E, North D, Shulsman RS.** Gated radionuclide angiographic evaluation of valve regurgitation. Am J Cardiol 1980;46:423–428.
19. **Boucher CA, Orada RD, Pohost GM.** Current status of radionuclide imaging in valvular heart disease. Am J Cardiol 1981;46:1153–1163.
20. **Bough EW, Gandsman EJ, Benham ID, Boden WE, North DL, Shulman RS.** Detection and quantification of atrial shunts in adults by gated radionuclide angiography (abstr). Am J Cardiol 1980;45:409.
21. **Swiryn S, Pavel DG, Byrom E, Bauernfeind RA, Strasberg B, Palileo E, Lam W, Wyndham CRC, Rosen KM.** Sequential regional phase mapping of radionuclide gated biventriculograms in patients with sustained ventricular tachycardia: close correlation with electrophysiologic characteristics. Am Heart J 1982;103:319–332.

# The Apex Impulse in Mitral Stenosis: Graphic Explanation Of the Palpable Movements at the Cardiac Apex

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**Simultaneously recorded phonocardiograms and apexcardiograms of 39 patients with mitral stenosis (MS) were retrospectively analyzed. A notch on the upstroke of the apexcardiogram coincidental with the first heart sound ($S_1$) occurred in 18 (47%) of the patients. The notch ratio or vertical distance from the onset of the apical impulse to the notch ratio or vertical distance from the onset of the apical impulse to the notch as a percentage of the total upstroke was measured and compared with the mean mitral diastolic gradient obtained at cardiac catheterization. Statistical analysis showed a significant relation ($r = 0.61$; $p < 0.01$) between notch ratio and the mean mitral diastolic gradient. This study reaffirms that the complex palpable movements at the cardiac apex, consisting of a "tap" representing $S_1$ occurring perceptibly after the onset of the apex impulse itself, are a useful diagnostic sign of MS. Furthermore, a graphic measurement of the extent of delay of $S_1$ with respect to the onset of the apical thrust can provide a rough measure of the severity of the valvular obstruction.**

For almost 2 centuries, physicians have been interested in palpation of the chest wall movements of cardiac origin as an aid to cardiac diagnosis. Several palpable phenomena have been described in association with MS, such as the precordial heave of right ventricular hypertrophy and the accentuated pulmonary component of the second heart sound. The events at the cardiac apex are usually referred to as a tapping impulse—an empirical description which is not particularly helpful in physical diagnosis. Almost 40 years ago, however, Cossio[1] analyzed palpable phenomena at the cardiac apex in MS and found that these consist of a complex sequence of a thrust resulting from ventricular systole on which a shock representing the delayed and accentuated first heart sound is surmounted. Our studies seek to confirm the validity of Cossio's observations and to determine whether the extent of the delay of the palpable shock of $S_1$ with respect to the onset of the ventricular thrust might have utility in predicting the severity of MS.

## Methods

Phonocardiographic and apexcardiographic records from 39 patients with predominant MS and 4 normal subjects were analyzed. The patients were identified from the computerized files of the Cardiac Graphics Laboratory at North Carolina Memorial Hospital, and all patients had complete hemodynamic data obtained at cardiac catheterization close in time to the noninvasive studies. In some patients with MS minor degrees of mitral or aortic regurgitation, or both, were also present, but those with severe regurgitant conditions were excluded. The normal subjects were studied for chest pain but proved to have normal coronary arteries and normal ventricular function.

Phonocardiograms were recorded from Leatham-type suction microphones at the upper right sternal border and the lower left sternal edge. Simultaneous apexcardiograms were recorded from a hand-held piezoelectric transducer with the patient lying in the left lateral decubitus position. The phonocardiograms and apex pulse were recorded on an Irex Continutrace 101 or 102 Recorder (Irex, Ramsey, New Jersey) at 100 mm/s paper speed.

From the combined electrocardiogram and phonocardiogram, the Q-$S_1$ interval was measured to document the delay in $S_1$ known to occur in MS.[2–4] The graphic equivalent of the palpable shock resulting from $S_1$ was perceptible as a notch on the upstroke of the apexcardiogram.[5,6] The "notch ratio" was calculated as the vertical distance from the onset of the apical upstroke to the level of the notch, divided by the entire height of the apexcardiogram (Fig. 1). In cases of atrial fibrillation, where the diastolic filling time varied on a beat-to-beat basis resulting in a fluctuating Q-$S_1$ time, 5 successive cycles were measured and the average was taken. In a few instances, a distinct notch could not be appreciated on the upstroke of the apexcardiogram and a change in slope coincidental with the mitral component of $S_1$ was substituted. In the normal controls where no notch was present, a vertical line was drawn through the onset of the high frequency vibrations representing the mitral contribution to $S_1$ and the point of intersection of this line with the apexcardiogram was taken as the notch position (Fig. 2).

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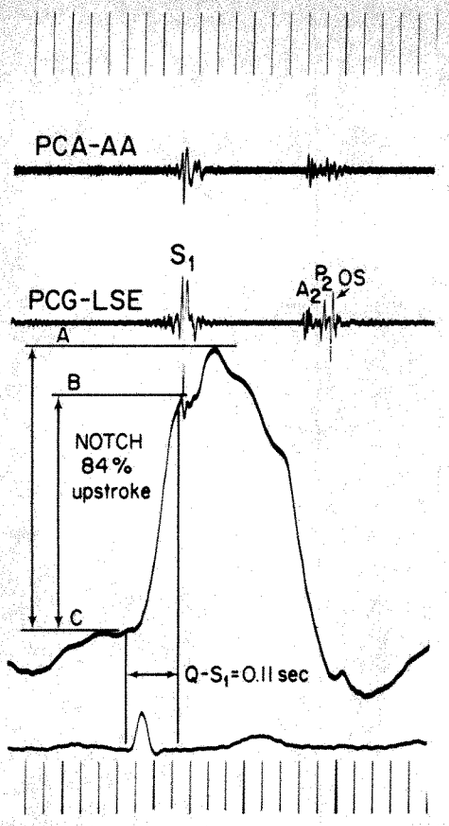



**FIGURE 1.** Apexcardiogram of a 36-year-old woman with severe mitral stenosis. The Q-$S_1$ interval is 0.11 second. The notch on the upstroke of the apexcardiogram (B-C) is measured at 84% of the total height (A-C). $A_2P_2$ = components of the second heart sound; OS = opening snap of the mitral valve; PCG-AA = phonocardiogram at aortic area; PCG-LSE = phonocardiogram at left sternal edge.

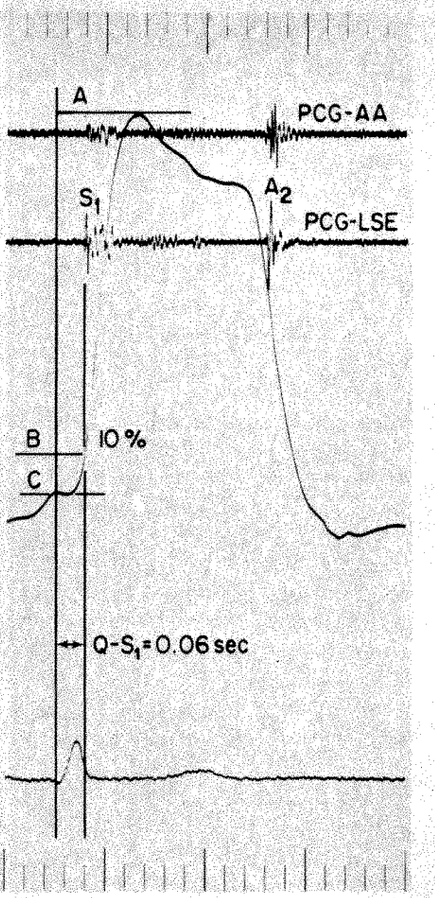



**FIGURE 2.** A normal subject. There is no notch on the upstroke of the apexcardiogram. The ratio BC/AC is therefore obtained from the time of the first high frequency vibrations of $S_1$ which occur 0.06 second from Q and almost immediately after the onset of the apical upstroke. PCG-AA = phonocardiogram at aortic area; PCG-LSE = phonocardiogram at left sternal edge.

**TABLE I Mean Mitral Diastolic Gradient and Notch Ratio Measurements***

| Notch Ratio or Position of Notch on Upstroke of Apexcardiogram (% of Rise) | Mean Mitral Diastolic Gradient (mm Hg) |
|---|---|
| 51 | 8.5 |
| 56 | 9.5 |
| 57 | 5.0 |
| 58 | 6.7 |
| 62 | 8.4 |
| 65 | 11.6 |
| 68 | 13.0 |
| 69 | 8.6 |
| 72 | 18.8 |
| 72 | 13.0 |
| 77 | 9.0 |
| 79 | 13.0 |
| 81 | 17.0 |
| 81 | 13.0 |
| 84 | 14.0 |
| 87 | 7.0 |
| 93 | 13.6 |
| 94 | 23.0 |
| 0 | 0 |
| 6 | 0 |
| 11 | 0 |
| 15 | 0 |

* Measurements collected from 18 patients with MS; data from normal subjects are included for comparison.

Hemodynamic studies were performed in the Cardiac Catheterization Laboratory, using standard methods in order to provide confirmation of the diagnosis as well as evidence of its severity. The mean mitral diastolic gradient was determined by planimetry of the area between the pulmonary capillary wedge pressure curve and the left ventricle.[7]

The mean mitral diastolic gradient was taken as the invasively obtained index of severity of stenosis. Care was taken to insure that heart rate and blood pressure were comparable, while both invasive and noninvasive records were obtained because of the profound effect of diastolic filling time on the Q-$S_1$ interval. To determine the relation between the mean mitral diastolic gradient and the notch ratio, univariant regression analysis was carried out.

## Results

A notch was present on the upstroke of the apexcardiogram in 18 of 39 patients, or 46%, of those with MS. The notch ratio and values for mean mitral diastolic gradient are listed in Table I. The notch ratios in the patients with MS ranged from 51 to 93%, reflecting the delay in mitral valve closure with respect to the onset of ventricular contraction. Regression analysis of the data from the patients listed in Table I indicated a sig-

nificant correlation ($r = 0.61$, $p < 0.01$) of notch ratio with the mean mitral diastolic gradient.

The 4 normal subjects are listed at the bottom of Table I. They had no mitral diastolic gradient and their notch ratios were low (0 to 15.3%).

## Discussion

Palpable events over the precordium in patients with MS have been appreciated since the early 19th century. In 1806, Corvisart[8] noted the thrust at the lower end of the sternum which we recognize as indicative of right ventricular hypertrophy. The accentuated and palpable first heart sound was described by Duroziez[9] in 1862, and the shock associated with an exaggerated second sound by Friedreich[10] in 1867. In 1898, Bard[11] studied the apex impulse in MS and concluded that it was made up of 2 almost simultaneous phenomena—the apical thrust resulting from ventricular systole on which is superimposed a palpable first heart sound. A detailed analysis of these palpable events at the cardiac apex in mitral stenosis was undertaken by Cossio[1] in Argentina. He recognized a relatively slow-rising impulse due to ventricular systole followed by a quick vibratory shock of $S_1$. Delay of the latter produced a complicated but informative palpatory sequence which he felt was almost pathognomonic of MS. Although Cossio's observations were made 40 years ago and are generally appreciated in Latin America,[12,13] there is only limited discussion of this physical sign in English textbooks,[14–17] and some authors do not mention it at all.[18,19]

The delay in the mitral component of the first heart sound in MS is due to the time required in early systole for left ventricular pressure to exceed that of the left atrium and to close the mitral valve. A measure of this delay ($Q\text{-}S_1$ time) has been used as an index of severity of stenosis.[2–4] This measurement requires a combination of phonocardiogram and electrocardiogram. The $Q\text{-}S_1$ time is affected by the duration of the electromechanical interval, the height of the ventricular pressure at the onset of systole, and the rate of rise of pressure. It is therefore only a crude index of severity and has been superseded by more accurate noninvasive methods. To exclude the effect of the electromechanical delay, Oreshkov[20] measured from the onset of the systolic wave in the apexcardiogram to the onset of the high frequency vibrations of $S_1$, termed the C-1 interval. He showed that duration of the C-1 interval correlated better with the diameter of the mitral orifice than did the $Q\text{-}S_1$ time. Similarly, the electromechanical interval does not interfere with our measurements which begin at the onset of the apical thrust, known to be synchronous with the beginning of the rise in pressure in the left ventricle.[21]

Although a significant correlation is demonstrated between the notch ratio (a measure of the delay of $S_1$ with respect to the onset of ventricular systole) and severity of stenosis, the relation is not linear. There are several possible reasons for this: the rate of rise of ventricular pressure is not uniform among the patients studied, the height of ventricular pressure at the onset

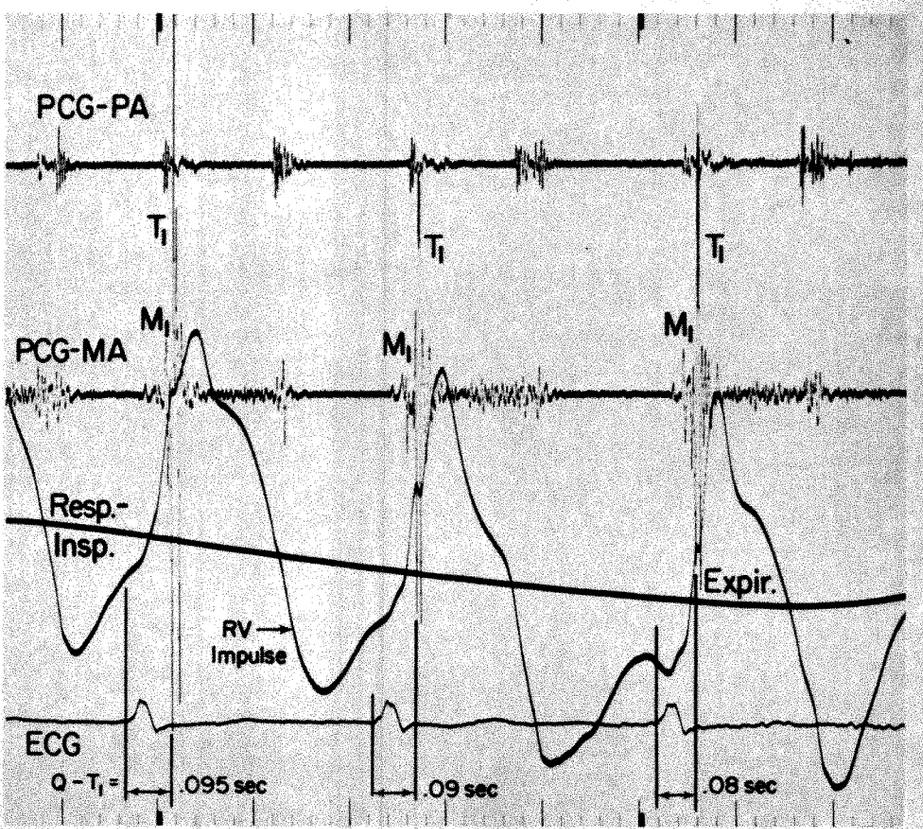



**FIGURE 3.** Simultaneous right ventricular (RV) impulse and phonocardiograms at pulmonary (PCG-PA) and mitral (PCG-MA) areas, with respiration (Resp.), from a 72-year-old woman who had an atrial septal defect and mild mitral regurgitation. The delayed, loud tricuspid valve closure ($T_1$) was palpable as a notch on the right ventricular impulse (see text). Expir. = expiration; ECG = electrocardiogram; Insp. = inspiration.

of systole varies, and there is known to be a variation in the rate of closure of the mitral valve after the left ventricle-left artery pressure crossover. In patients with atrial fibrillation there is a beat-to-beat change in all these parameters. Complicating conditions such as aortic regurgitation will alter ventricular diastolic pressure and further affect the timing of $S_1$ with respect to ventricular systole. The absence of a palpable $S_1$ or its graphic equivalent, the notch on the apexcardiogram, may be explained in severe MS by heavy calcification of the valve leaflets, a complication well known to result in a diminished intensity of $S_1$.

Although the delayed palpable $S_1$ can, as Cossio indicated, be strongly suggestive of MS, it is not possible to estimate at the bedside with any certainty the extent of the delay. The entire interval from the onset of the ventricular impulse to the palpable $S_1$ is usually <0.12 second. It is possible nevertheless to appreciate that the thrust and the palpable sound are occurring sequentially and not synchronously. This observation, although useful in suggesting the possibility of MS, is not specific for that condition since left atrial myxoma is also associated with an accentuated, delayed $S_1$ and, in graphic tracings, a deep notch on the apex resembling that described previously.[22] Fortunately, myxoma is usually excluded by echocardiography without difficulty. We have also found that tricuspid valve closure may be palpable in certain conditions. Recently, we studied a patient who had an atrial septal defect and mild mitral regurgitation (Fig. 3). The right ventricular impulse was prominent and there was a loud, palpable tricuspid valve closure sound ($T_1$). In this case, the notch ratio showed inspiratory variation; it was quite high (approximately 75%) at peak inspiration but diminished, as did $T_1$ amplitude, when Q-$T_1$ interval decreased from 0.095 to 0.080 second during expiration.

*Conclusion:* Palpable events at the cardiac apex are useful as a bedside physical sign of MS. The manifestation strongly suggestive of this diagnosis consists of an apical thrust due to left ventricular systole upon which is superimposed a delayed tap representing $S_1$. This sign is not present in all instances of MS since some patients lack a palpable apical impulse and some have an inaudible or very soft $S_1$ due to calcification of the valve.

A graphic equivalent of the palpable events described above can be obtained by combining phonocardiograms and apexcardiograms with an electrocardiogram. Delay in $S_1$ results in the appearance of a coincidental notch on the apexcardiogram high on the systolic upstroke. The notch ratio, an index of the extent of this delay, has a significant relation with the severity of stenosis as obtained at cardiac catheterization.

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## References

1. **Cossio P.** Choque de la punta mitral. Rev Argent Cardiol 1943;10:145–161.
2. **Kelly JJ Jr.** Diagnostic value of phonocardiography in mitral stenosis. Am J Med 955;19:862–868.
3. **Wells B.** Assessment of mitral stenosis by phonocardiography. Br Heart J 1954;16:261–266.
4. **Craige E.** Phonocardiographic studies in mitral stenosis. N Engl J Med 1957;257:650–654.
5. **Becker LC, Klaus AP, Humphries JO.** Early systolic notch in the apexcardiogram in mitral stenosis. Am Heart J 1973;86:582–586.
6. **Craige E.** Apexcardiography. In: Weissler AM, ed. Non-invasive Cardiology. New York: Grune & Stratton, 1974:8–11.
7. **Grossman W.** Cardiac Catheterization and Angiography. Philadelphia: Lea & Febiger, 1974:13–107.
8. **Corvisart JN.** Essai sur les Maladies et les Lésions Organiques du Coeur. Paris: 1806.
9. **Duroziez P.** Du rhythme pathognomique du retrecissement mitral. Arch Gen Med 1862;20:385.
10. **Friedreich A.** Traité des Maladies du Coeur. Translation of the second German edition. Paris: 1873.
11. **Bard L,** cited by Barié E. Maladies du Coeur et de l'Aorte. Paris: 1912.
12. **Fishleder BL.** Exploracion Cardiovascular y Fonomecanocardiographia. Mexico: La Prensa Medica Mexicana, 1966:575.
13. **Esper RJ, Madoery RJ.** Progresos en Auscultacion y Fonomecanocardiografia. Buenos Aires: Lopez Libreros, 1974:166.
14. **Wood P.** Physical signs. In: Wood P, ed. Diseases of the Heart and Circulation. London: Eyre and Spottiswoode, 1968:64–65.
15. **Braunwald E.** The physical examination. In: Braunwald E, ed. Heart Disease—A Textbook of Cardiovascular Medicine. Philadelphia: WB Saunders, 1980:25.
16. **Crawley IS, Morris DC, Silverman BD.** Valvular heart disease. In: Hurst JW, Logue RB, Schlant RC, Wenger NK, eds. The Heart. New York: McGraw-Hill, 1978:994.
17. **Willerson JT.** Physical examination of the patient with heart disease. In: Sanford JP, Willerson JT, Sanders CA, eds. Clinical Cardiology. New York: Grune & Stratton, 1977:102.
18. **Eddleman EE Jr.** Examination of precordial movements. In: Hurst JW, Logue RB, Schlant RC, Wenger NK, eds. The Heart. New York: McGraw-Hill, 1978:201–217.
19. **Fowler NO.** Cardiac Diagnoses and Treatment. Hagerstown, MD: Harper and Row, 1980:582.
20. **Oreshkov VI.** Q-1 or C-1 interval in the diagnosis of mitral stenosis. Br Heart J 1967;29:778–782.
21. **Willems JL, DeGeest H, Kestleloot H.** On the value of apex cardiography for timing intracardiac events. Am J Cardiol 1971;28:59–66.
22. **Craige E, Algary WP.** Left atrial myxoma: diagnosis with the help of the phonocardiogram and apexcardiogram. Arch Intern Med 1972;129:470–474.

# Coronary Vascular Reserve in Left Ventricular Hypertrophy Secondary to Chronic Aortic Regurgitation

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**Coronary vascular reserve was studied in 11 patients with severe chronic aortic regurgitation (AR). Nineteen patients with the chest pain syndrome and normal findings on cardiac catheterization served as control subjects. Resting coronary sinus flow and contrast-agent–induced hyperemia were measured by continuous thermodilution. Left ventricular (LV) dimensions and mass were obtained echocardiographically. All patients had normal coronary arteries. Resting coronary flow was increased and coronary reserve was decreased in patients with AR compared with the control subjects: 310 ± 38 versus 121 ± 13 ml/min and 56 ± 9 versus 86 ± 7.5%, respectively. The decrease in coronary vascular reserve correlated with the increase in LV mass ($r = -0.86$, $p = 0.001$) and LV wall thickness ($r = -0.83$, $p = 0.002$) and with the decrease in LV volume/mass ratio ($r = 0.761$, $p = 0.007$). There was no significant correlation between the decrease in coronary vascular reserve and LV volume ($r = 0.255$), LV peak wall stress ($r = 0.292$), LV systolic pressure ($r = -0.495$), aortic or LV diastolic pressure ($r = 0.322$ and $-0.318$, respectively), or aortic-LV diastolic gradient, nor with the voltage on the electrocardiogram (limb leads $r = -0.60$, precordial leads $r = -0.118$). Thus, coronary vascular reserve is decreased in proportion to the degree of left ventricular hypertrophy in patients with chronic AR. Patients with angina pectoris tended to have a lower coronary vascular reserve than those without angina (median 26 versus 76%, difference not significant). LV wall thickness and not LV volume is the critical component of left ventricular mass related to coronary reserve. No significant correlation between the decrease in coronary vascular reserve and the presence of angina pectoris was demonstrated.**

Aortic regurgitation (AR) imposes a load on the left ventricle, which, if applied gradually, is well tolerated for many years. During this period a number of reserve mechanisms enter into play, the most important being an increase in end-diastolic volume and an increase in stroke volume. These reserve mechanisms allow near-normal effective cardiac performance until late in the course of the disease, when progressive LV dilatation occurs and a gradual course toward end-stage disease or death follows even in the absence of overt clinical manifestations.[1] Some patients have angina pectoris at this stage, often in the presence of normal coronary arteries. The exact mechanism for the failure of these reserve mechanisms has not yet been clarified. We previously demonstrated[2] that patients with pressure overload LV hypertrophy due to aortic stenosis have a decreased coronary vascular reserve. This decrease may be related to the pathogenesis of LV decompensation and may potentiate angina pectoris. This study analyzes coronary flow dynamics and coronary flow reserve in patients with volume overload LV hypertrophy from chronic AR.

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## Methods

Eleven patients (9 men and 2 women) with chronic AR referred for diagnostic cardiac catheterization were evaluated. Their ages ranged from 24 to 63 years (mean 48). All patients had normal coronary arteriograms. All patients had 3 to 4+ (moderate to severe) or 4+ (severe) AR defined angiographically: that is, 3+ indicates that during aortography the entire left ventricle is opacified with regurgitant contrast medium but does not reach the same radiologic density as the aorta; 4+ indicates that the entire ventricle is opacified with regurgitant contrast medium and reaches the same contrast as the aorta.[3] These patients had no aortic stenosis or other valvular lesions. Two patients were taking digitalis and 9 were taking diuretics. No patient was taking beta-blocking drugs or dilators. Ten of 11 patients had symptoms.

Nineteen patients with a chest pain syndrome referred for cardiac catheterization and found to have normal coronary arteries served as control subjects. These patients had no other known cardiac disease (valvular, myocardial, or the like). Three patients were taking beta-blocking agents, 3 patients long-acting nitrates, 2 patients nitroglycerin whenever needed, and 1 patient Norpace®. Twelve patients were taking no medication.

History of angina pectoris, syncope or presyncope, and symptoms or signs of congestive heart failure including dyspnea, orthopnea, rales, and peripheral edema were recorded. LV hypertrophy on the electrocardiogram was evaluated by adding the voltage of the R wave in lead I plus the S wave in lead III and the voltages of the S wave in $V_1$ and the R wave in $V_5$.[4] S-T segment depression with asymmetric T-wave inversion, so-called strain pattern,[4] was noted when present.

Right heart catheterization with a Swan-Ganz catheter and P23D Statham transducers were used to determine right heart pressures. LV and aortic pressures were determined with a fluid-filled catheter and P23D Statham transducers. The heart rate was measured at the time of coronary blood flow determination. LV mean diastolic pressure was calculated as an average of 3 points in diastole: initial, mid, and late diastole. LV end-diastolic pressure was measured at the top of the R wave. Aortic diastolic pressure was measured as end-diastolic pressure. The aortic to LV diastolic gradient was calculated as the difference between aortic diastolic pressure and LV mean diastolic pressure. All medications were withheld at least 12 hours before catheterization.

Echocardiography was performed just before catheterization or the day before. If high quality recordings were not obtainable, the patient was not entered into the study. Dimensions of the septum, LV posterior wall and LV internal diameter were performed in diastole, before the *a* wave. They were measured in millimeters, using the standard convention.[5] LV mass was calculated using the following formula[6]: LV mass (g) = $0.77 \times 10^{-3}$ [(LVID + LVPW + IVS)$^3$ − LVID$^3$] + 2.4, where LVID = LV internal dimension in diastole, LVPW = LV posterior wall dimension in diastole, and IVS = interventricular septal dimension in diastole.

The LV volume/mass ratio was calculated by dividing the echocardiographic end-diastolic LV internal dimension by the sum of the posterior and septal wall thicknesses at end-diastole.[7] LV wall stress was evaluated as peak systolic stress by the formula[8–10]: Peak stress = (SBP × LVID) (h × [1 + (h/LVID)]), where SBP = systolic blood pressure, LVID = LV internal dimension, and h = (IVS + LVPW)/2. We used the end-diastolic h/R (mass/volume) ratio, which is quite similar to the h/R ratio at peak systolic stress.[9] Although the systolic pressure is less than the peak LV systolic pressure,[9,10] the correlation between true peak systolic stress and peak stress estimated by the foregoing formula is acceptable.[10] Echocardiographic dimensions were measured by 2 investigators who had no knowledge of the results of the coronary sinus flow measurement.

Coronary sinus blood flow was determined by the continuous thermodilution technique of Ganz et al[11] using a preshaped coronary sinus catheter with 2 thermistors and 2 pacing electrodes (Wilton Webster Laboratories). Resting coronary sinus flow was obtained before any intervention. Hyperemic flow was defined as the maximal flow recorded after contrast medium injection into the left coronary artery (5 to 10 ml). Hyperemic flow was determined 3 to 6 times in each patient. Coronary reserve was defined as the percentage of increase in coronary sinus flow and was calculated as follows: (Hyperemic flow − resting flow):(resting flow) ×100. Because resting coronary blood flow as determined by this technique represents an unknown fraction of the total LV venous outflow, primarily the percent change in flow with hyperemia was used for analysis in this study. Data from coronary sinus flow measurements were recorded at a paper speed of 2.5 or 5 mm/s with an Electronics for Medicine DR 12 recorder, and entered into a minicomputer (Texas Instruments TI 59) for calculation of flow. Flow measurements obtained by the thermodilution technique and the evocation of a constant hyperemic response with a given dye volume were previously validated in our laboratory.[2]

**TABLE I Summmary of Clinical and Hemodynamic Data (Mean ± Standard Error of the Mean)**

| | AR | Control |
|---|---|---|
| Patients (n) | 11 | 19 |
| Age (yr) (NS) | 47.4 ± 4 | 47.1 ± 1 |
| Sex | 9M, 2F | 11M, 8F |
| Angina | 4 of 11 | 4 of 19 |
| CHF | 9 of 11 | 0 of 19 |
| Syncope | 0 of 11 | 0 of 19 |
| ST-T strain | 9 of 11 | 2 of 19 |
| $R_1 + S_3$ (mm)* | 17.2 ± 2.6 | 9.42 ± 1.4 |
| $S_{V1} + R_{V5}$ (mm)* | 46.8 ± 2 | 9.42 ± 1.4 |
| Heart rate (beats/min) (NS) | 77.6 ± 2.4 | 72 ± 19 |
| LV systolic (mm Hg)* | 152.6 ± 7.1 | 123.2 ± 4.4 |
| LV mean diastolic (mm Hg)* | 11.6 ± 1.3 | 7.4 ± 0.9 |
| LV end-diastolic (mm Hg)† | 19.1 ± 2.5 | 12.5 ± 0.9 |
| Ao systolic (mm Hg)* | 145.8 ± 6.1 | 123.2 ± 4.4 |
| Ao diastolic (mm Hg)† | 64.9 + 4.1 | 72.9 ± 1.9 |
| Ao diastolic − LV diastolic (mm Hg)*,† | 52.3 ± 4 | 65.5 ± 1.9 |
| IVS (mm)* | 13.3 ± 0.7 | 9.8 ± 0.2 |
| LVPW (mm)* | 13.4 ± 0.7 | 9.8 ± 0.2 |
| LVID (mm)* | 59.9 ± 1.3 | 42.5 ± 0.8 |
| Mass (g)* | 338.9 ± 19.4 | 128.6 ± 5.4 |
| CSF, rest (ml/min)* | 309.9 ± 38.4 | 120.6 ± 13.0 |
| CSF, hyperemia (ml/min)* | 459.7 ± 45.9 | 218.7 ± 21.9 |
| CSF, percent change† | 55.6 ± 9.2 | 85.8 ± 7.5 |
| LV volume/mass ratio (NS) | 2.31 ± 0.15 | 2.2 ± 0.06 |
| LV peak systolic stress* | 895.8 ± 51 | 701.2 ± 22.9 |

* $p < 0.01$; † $p < 0.05$.

Ao = aorta; CHF = congestive heart failure; CSF = coronary sinus flow; IVS = interventricular septum; LV = left ventricle; LVID = left ventricular internal diameter; LVPW = left ventricular posterior wall; NS = not significant; $R_1 + S_3$ = sum of voltages of R in lead I and S in lead III; $S_{V_1} + R_{V_5}$ = sum of voltages of S in lead $V_1$ and R in lead $V_5$.

Means and standard errors were recorded for each measurement by groups. Comparisons between the groups for all continuous measurements were made using a 2-tailed *t* test. Pearson's product moment correlation coefficients were calculated to determine the association of all continuous measurements with the percent change in coronary sinus flow. For the frequency data, Fisher's exact test and the chi-square test were used. When each group was divided into subgroups, that is, those with and those without angina, comparisons of coronary reserve among the 4 groups were made using the Kruskal-Wallis nonparametric test.

## Results

Table I summarizes the clinical and hemodynamic data on the 30 patients by patient groups: the control subjects and those with AR. The age was similar in both groups. There was a predominance of men. Typical angina pectoris (classic, effort-induced) was present in 4 of 11 patients with AR and in 4 of 19 control subjects. Fifteen control subjects had atypical chest pain syndrome. Signs or symptoms of congestive heart failure were elicited by history or physical examination in 9 of 11 patients with AR and in none of the control subjects. No patient had syncope. Voltage in the limb leads (17.2 ± 2.6 mm) and precordial leads (46.8 ± 2 mm) of the

electrocardiogram suggested LV hypertrophy in patients with AR and not in the control group (9.4 ± 1.4 and 25.6 ± 2.1 mm, respectively). ST-T strain pattern was present in 9 of 11 patients with AR and in none of 19 control subjects. Heart rate was similar in both groups (77.6 ± 2.4 versus 72 ± 1.9 beats/min, difference not significant [NS]). LV and aortic pressures were different in both groups; those with AR had a higher LV systolic pressure (152 ± 7.1 versus 123.2 ± 4.4 mm Hg, $p < 0.01$), a higher LV mean diastolic pressure (11.6 ± 1.3 versus 7.4 ± 0.9 mm Hg, $p < 0.01$), a higher LV end-diastolic pressure (19.1 ± 2.5 versus 12.5 ± 0.9 mm Hg, $p < 0.05$), a higher aortic systolic pressure (145.8 ± 61 versus 123.2 ± 4.4 mm Hg, $p < 0.01$), and a lower aortic diastolic presure (64.9 ± 4.1 versus 72.9 ± 1.9 mm Hg, $p < 0.05$). The diastolic gradient between the aorta and the left ventricle was lower in those with AR (52.3 ± 4 versus 65.5 ± 1.9 mm Hg, $p < 0.01$).

Echocardiographic dimensions of the LV wall and LV internal diameter were larger in patients with AR (13.3 ± 0.7 and 59.9 ± 1.3 versus 9.8 ± 0.2 and 42.5 ± 0.8 mm, respectively; both $p < 0.01$). The LV mass was significantly increased in the group with AR (338.9 ± 19.4 versus 128.6 ± 5.4 g, $p < 0.01$). The LV volume/mass ratio was not significantly different in both groups (2.31 ± 0.15 versus 2.2 ± 0.06). The LV peak systolic wall stress was significantly higher in patients with AR (895.8 ± 51 versus 701.2 ± 22.9, $p < 0.01$). Coronary sinus flow at rest and during hyperemia was significantly higher in patients with AR (309 ± 38.4 and 459.7 ± 45.9 versus 120.6 ± 13 and 218.7 ± 21.9 ml/min, respectively; both $p < 0.01$); no further analyses of these values were performed, given the expected variability of the total flow measurement by the coronary sinus thermodilution technique. The percent change in coronary flow during hyperemia (coronary reserve) was significantly lower in the group with AR (55.6 ± 9.2 versus 85.8 ± 7.5%, $p < 0.0187$).

Table II indicates the correlation between the percent change in coronary sinus flow with hyperemia and 11 variables that may influence the coronary vascular reserve in patients with AR. There was a strong negative correlation between coronary reserve and left ventricular mass ($r = -0.86$) (Fig. 1). A strong negative correlation was also found between coronary reserve and LV wall thickness in diastole ($r = -0.83$). A positive correlation was found between coronary reserve and LV volume/mass ratio ($r = 0.76$). No significant correlation was found between coronary vascular reserve and LV volume in diastole ($r = 0.25$), LV peak wall stress ($r = 0.292$), and LV systolic ($r = -0.495$) or diastolic pressure ($r = -0.32$). No significant correlation was found either between coronary reserve and aortic diastolic pressure ($r = 0.32$) or the aortic-LV diastolic gradient ($r = 0.45$). The correlation between coronary vascular reserve and voltage was $r = 0.604$, $p = 0.064$ in the limb leads and $r = -0.118$, $p = 0.745$ in the precordial leads.

Four of 11 patients with AR had angina pectoris. Their coronary reserve was 20, 28, 25, and 107%. The median coronary reserve was 26% in patients with AR and angina pectoris and 66% in those with AR without angina pectoris. The median for the control patients with and without angina pectoris was 72 and 74%, respectively. Although the median coronary reserve was at least 40% lower in patients with AR and angina pectoris, the Kruskal-Wallis test ($k = 5.75$, $p < 0.07$) for testing differences in locations (medians) did not reach the alpha = 0.05 significance level. Patients with AR with and without angina pectoris had similar values for all other variables ($p > 0.05$).

**TABLE II Correlations of Percent Change in Coronary Sinus Flow (Coronary Reserve) and 11 Other Variables**

| | r | p |
|---|---|---|
| Heart rate | 0.071 | <0.834 |
| Aortic-LV diastolic gradient | 0.449 | <0.1935 |
| Aortic diastolic pressure | 0.322 | <0.3339 |
| LV diastolic pressure | −0.318 | <0.370 |
| LV systolic pressure | −0.495 | <0.122 |
| LV mass | −0.860 | <0.0007* |
| Wall thickness | −0.830 | <0.0016* |
| LVID | 0.255 | <0.4499 |
| LV volume/mass ratio | 0.761 | <0.0065* |
| LV peak wall stress | 0.292 | <0.3825 |
| Resting coronary flow | −0.640 | <0.0338* |

* Statistically significant ($p < 0.05$). r = correlation factor.

## Discussion

**Coronary vascular reserve:** Experimental studies show that volume overload LV hypertrophy is associated with decreased coronary vascular reserve. Feldman et al,[12] who studied the peak reactive hyperemic flow after 10-second coronary occlusion in dogs with acute, reversible AR, found it reduced. In addition, and of great interest, Feldman et al[12] showed that coronary reserve was further reduced by the presence of moderate (50%) coronary narrowing. Karp and Roe[13] studied the effects of chronic (2 to 6 weeks) aortic insufficiency on coronary blood flow; they showed that after temporary coronary occlusion, the overshoot flow repaid an average of 75% (range 0 to 180%) of the calculated flow debt, as compared with 365% in the control subjects. Heiss et al[14,15] studied the coronary reserve in patients with AR and other cardiomyopathies and reported a lower reserve in patients with aortic insufficiency and aortic stenosis than in control subjects. Heiss also showed a positive correlation between coronary reserve and the coronary arteriovenous oxygen difference.

In this study of patients with AR we found an increase in resting coronary sinus flow and a decrease in coronary vascular reserve as compared with those in control subjects (Table I). The decrease in coronary reserve correlated negatively with the increase in resting coronary flow, suggesting that the coronary circulation can adapt to the increased myocardial oxygen requirements of LV hypertrophy by increasing the resting flow, but that it is unable to modify its capacity for maximal coronary flow, so that the increase in resting flow is obtained at the expense of the coronary reserve.

To determine whether the decrease in coronary vascular reserve was the result of LV hypertrophy per se or the result of the specific hemodynamic alterations of chronic AR, the correlation between the decrease in coronary vascular reserve and all other variables measured in this study was analyzed. Table II presents a

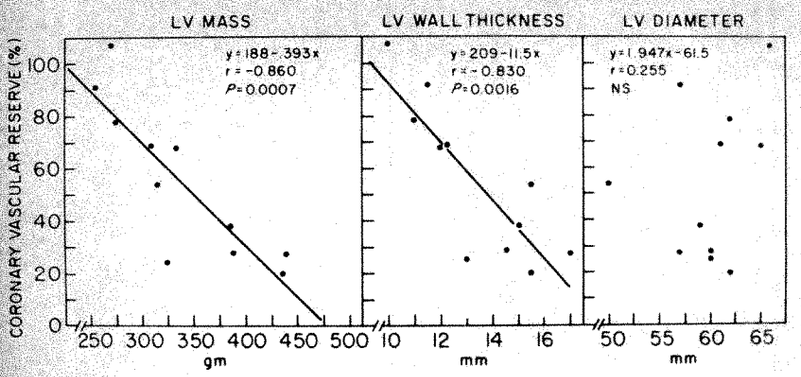



**FIGURE 1.** Correlation between coronary vascular reserve and LV mass in patient with AR.

summary of the most important variables in determining or limiting coronary flow and their correlation with coronary vascular reserve. We found that the LV mass was negatively correlated with the coronary reserve ($r = -0.86$, $p < 0.001$), the patients with the largest mass having the lowest coronary reserve. The increase in LV mass (weight) in aortic insufficiency is the result of a thickened LV wall, encompassing a dilated LV chamber. When analyzing these 2 components separately (Fig. 1), we found a strong negative correlation between coronary reserve and LV wall thickness ($r = -0.83$, $p < 0.001$), but no significant correlation between coronary reserve and LV internal dimension ($r = 0.26$, $p = NS$), suggesting that wall thickness is more important than LV volume in determining coronary vascular reserve in patients with LV hypertrophy secondary to chronic AR.

The ratio between LV diameter and thickness (volume/mass ratio) was similar in the group with AR and the control group (Table I). When analyzed as a continuous function, volume/mass ratio correlated positively with coronary vascular reserve (Table II), the patients with the lowest volume/mass ratio having the lowest coronary vascular reserve. This finding can be explained by the predominant role played by wall thickness in reducing coronary vascular reserve.

Peak systolic stress is a major determinant of myocardial oxygen consumption[16] and hence of coronary blood flow. In asymptomatic or compensated AR, peak systolic stress remains normal[8-10] and end-systolic stress increases.[10] In symptomatic or decompensated AR, peak systolic stress is increased.[14-17] In our study, peak systolic stress was increased in the group with AR as compared with the control group but no strong correlation was found between the increase in peak systolic stress and the decrease in coronary vascular reserve ($r = 0.45$, $p = NS$). This inability to increase coronary vascular reserve along with the increase in peak systolic stress is consistent with our finding of impaired coronary vascular reserve in LV hypertrophy.

Aortic and LV diastolic pressures as well as the aortic-LV diastolic gradient are major determinants of diastolic coronary blood flow. These pressures were significantly different in the group with aortic insufficiency from those in the control group, but we found no significant correlation between the decrease in coronary vascular reserve and the increase in LV diastolic pressures, the decrease in aortic diastolic pressures, or the decrease in the aortic-LV gradient (Table II). Experimentally it has been observed[10,18,19] that a change in the diastolic/systolic ratio of coronary flow occurs with aortic insufficiency: with increasing degrees of AR the systolic component of coronary blood flow becomes more important and the diastolic component decreases; in acute severe AR, all coronary blood flow becomes systolic, with reversal of coronary flow (retrograde flow) during diastole. We could not evaluate the contribution of systolic coronary flow to total coronary blood flow in this study. The lack of significant correlation between coronary vascular reserve and diastolic pressures may be related to the independence of this systolic component from the diastolic pressures, or the result of the predominant effect of LV mass on coronary vascular reserve.

The LV systolic pressure was significantly higher in the group with AR than in the control group (Table I), but we found no significant correlation between the increase in LV systolic pressure and the decrease in coronary reserve, suggesting that other variables outweighed its effect on myocardial oxygen consumption and coronary blood flow.

Of the variables analyzed then, the LV mass, wall thickness, and volume/mass ratio were the only significant determinants of coronary vascular reserve.

**Chest pain:** The mechanism of angina pectoris is a subject of great interest, especially in patients with aortic valvular disease. It has been shown[2,20,21] that patients with aortic stenosis and LV hypertrophy have a decreased coronary vascular reserve. We propose that this decrease in coronary vascular reserve may be related to the pathogenesis of angina pectoris in these patients. Bertrand[22] evaluated the supply/demand ratio in AR by measuring the diastolic pressure-time index over the systolic pressure-time index (DPTI/SPTI)[23] and found it significantly decreased in those with angina pectoris but found no relation between exercise-induced angina and the DPTI/SPTI ratio. The value of the DPTI/SPTI ratio is controversial,[24] making these observations difficult to interpret.

In this study of severe symptomatic AR, the median coronary reserve was 26% in those with angina pectoris and 66% in those without angina pectoris (NS). The

median for the control patients with and without angina was 72.3, and 73.8% respectively. We also compared the clinical data, hemodynamic values, and echocardiographic dimensions in those with and without angina pectoris and found no statistically significant differences. Perhaps with a larger patient population statistical significance will be achieved. Interestingly, 3 of the 4 patients with angina pectoris had the lowest values for coronary vascular reserve, that is, 20, 25, and 28%; these patients had the highest resting coronary blood flow, suggesting that they had undergone vasodilation at rest and had lost the capacity to increase coronary flow appropriately in situations of increased demand.

## Limitations of the Study

**Determination of LV mass by echocardiography:** There is no precise method to measure LV mass in vivo with absolute accuracy. In our study, LV mass was determined echocardiographically. Studies by Devereux and Reichek[5] in normal hearts and hearts with LV hypertrophy validated the echocardiographic calculation of LV mass in patients who later came to autopsy, finding a correlation of 0.92 for LV mass by echocardiography versus LV mass at autopsy. Grossman et al[9] reported good agreement between dimensions determined by echocardiography and by angiographic methods. Abdulla et al[25] failed to find a good correlation between angiographic and echocardiographic determination of LV mass in AR, but they did not use biplane angiography in all cases. Even if the determination of LV mass in our study did not represent accurately the true anatomic LV mass, the directional changes observed and their relation to coronary vascular reserve should remain a valid conclusion.

**Coronary sinus flow measurement may not represent total LV venous outflow:** In the human heart, coronary sinus flow is highly representative of the total LV efflux.[26,27] Also, coronary sinus flow as determined by the continuous thermodilution technique accurately represents total LV coronary flow.[28,29] A possible source of error in estimating total coronary sinus flow stems from the fact that in some cases the posterior ventricular vein drains very near the ostium of the coronary sinus, so that its flow is not included in the measurements obtained.[11] The flow measured may decrease artifactually if the thermodilution catheter is advanced too far into the coronary sinus or may increase artifactually if it is too close to the right atrium, especially in cases of elevated right atrial pressure.[30]

These considerations would not influence the conclusions of our study, because our analysis was based not so much on the total flow per se, but rather on the percent change in flow seen during contrast-agent–induced hyperemia. The percent change should be the same for total or less than total coronary sinus flow.

**Contrast agents may not induce maximal coronary vasodilation:** A major limitation in our study could exist if the contrast agent produced less than a maximal increase in coronary conductance, because in that case the total coronary vascular reserve could not be evaluated by this method. Existing information is controversial in this respect. In the experimental situation, the increase in coronary conductance produced by contrast agents is equivalent to a 10 to 15 second occlusion of the coronary artery ($r = 0.86$),[31,32] similar to the effect of an intracoronary bolus injection of adenosine triphosphate (ATP) or papaverine, but lower than the effect of a prolonged infusion of ATP or papaverine.[31] This comparison has not been made in human beings. The hyperemic reaction to contrast agent injection is greater than the increased flow necessary to repay the oxygen debt, as proved by an increase in coronary sinus oxygen saturation without a change in myocardial oxygen consumption[33] and a concomitant increase in the forearm flow,[34] suggesting an important reflex component in the contrast-agent–induced hyperemia.

Although the effect of contrast agents on the coronary conductance may be to produce near-maximal vasodilation, the effects of contrast agents on cardiac and circulatory hemodynamics[35,36] may influence qualitatively and quantitatively the hyperemic reaction, and maximal coronary flow may not be obtained. Agents that increase coronary conductance without major changes in hemodynamic variables seem better suited for the study of coronary reserve in human subjects. We have currently started a study with such an agent, that is, intravenous dipyridamole.

Even if contrast agents had not induced maximal increase in coronary sinus flow in our study, analysis of the directional changes observed, as well as analysis of the factors determining such changes, such as LV dimensions and hemodynamic variables may remain valid.

**Dose response to contrast agent:** If the hyperemic response is dose related, patients with LV hypertrophy could have a reduced response because they get a lower amount of contrast agent applied per gram of myocardium. We previously demonstrated that this is not the case when $\geq 5$ ml of contrast agent is injected.[2]

**Effect of drugs on coronary blood flow:** Although all drug therapy was discontinued at least 12 hours before the study, some drugs may have a residual effect on coronary blood flow and this effect may influence our results.

**The control group may not be truly normal:** This group of patients had chest pain syndrome with normal coronary arteries. None of them had clinical or laboratory findings that would suggest the presence of underlying coronary artery spasm. Patients in whom coronary artery spasm was suspected had provocative testing with ergonovine maleate and were not included in this study. However, we did not evaluate dynamic changes in coronary tone, myocardial biopsy, blood elements physiology, and hormonal or other variables that could alter coronary blood flow and explain the cause of the chest pain. If such an alteration in coronary blood flow were demonstrated, a better control group would be necessary.

*Conclusions:* Patients with chronic AR and LV hypertrophy seem to have an increased resting coronary flow and a decreased coronary vascular reserve. The decrease in coronary vascular reserve was significantly

correlated with the degree of LV hypertrophy, represented in our study by LV mass, LV wall thickness, and LV volume/mass ratio. The decrease in coronary vascular reserve had no significant correlation with the hemodynamic changes attributable to AR, suggesting that LV hypertrophy per se was the principal determinant of the restricted coronary reserve found in this study.

Although not proven, it seems reasonable to propose that the limitation in the coronary vascular reserve may be one of the underlying mechanisms responsible for the clinical deterioration of patients with advanced AR. Whether the altered capacity to appropriately increase coronary blood flow participates in the pathogenesis of the syndrome of angina pectoris in patients with AR and normal coronary arteries remains unanswered. Our study shows a trend that supports the hypothesis of a limited coronary vascular reserve being a cause of angina pectoris, but the population size and limitations of the methods do not allow for a definite conclusion.

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## References


1. **Spagnuolo M, Kloth H, Taranta A, Doyle E, Pasternak B.** Natural history of rheumatic aortic regurgitation: criteria predictive of death, congestive heart failure and angina in young patients. Circulation 1971;44:368–380.
2. **Pichard AD, Gorlin R, Smith H, Ambrose J, Meller J.** Coronary flow studies in patients with left ventricular hypertrophy of the hypertensive type: evidence for an impaired coronary vascular reserve. Am J Cardiol 1981;47: 547–554.
3. **Sellers RD, Levy MJ, Amplatz K, Lillehei CW.** Left retrograde cardioangiography in acquired cardiac disease. Am J Cardiol 1964;14:437–447.
4. **Romhilt DW, Estes EH.** Point-score system for the ECG diagnosis in left ventricular hypertrophy. Am Heart J 1968;75:752–758.
5. **Devereux RB, Reichek N.** Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977;55:613–618.
6. **McFarland TM, Alam M, Goldstein S, Pickard SD, Stein PD.** Echocardiographic diagnosis of left ventricular hypertrophy. Circulation 1978;57: 1140–1144.
7. **Gaasch WH.** Left ventricular radius to wall thickness ratio. Am J Cardiol 1979;43:1189–1194.
8. **Hood WP Jr, Rackley CE, Rolett EL.** Wall stress in the normal hypertrophied human left ventricle. Am J Cardiol 1968;22:550–558.
9. **Grossman W, Jones D, McLaurin LP.** Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975;56:56–64.
10. **Wilson JR, Reichek N, Hirshfeld J, Keller CA.** Non-invasive assessment of load reduction in patients with asymptomatic aortic regurgitation. Am J Med 1980;68:664–674.
11. **Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC.** Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971;44:181–195.
12. **Feldman RL, Nichols WW, Pepine CJ, Conti R.** Influence of aortic insufficiency on the hemodynamic significance of a coronary artery narrowing. Circulation 1979;60:259–268.
13. **Karp RB, Roe BB.** Effect of aortic insufficiency on phasic flow patterns in the coronary artery. Ann Surg 1966;164:959–966.
14. **Heiss HW.** Die Koronarreserve. In: Roskamm R, Reindell H, eds. Das chronisch Kranke Herz, International Symposium. Stuttgart, New York: FK Schattauer Verlag, 1973:63.
15. **Heiss HW, Wink K, Barmeyer J, Keull J, Reindell H.** Myocardial oxygen consumption and substrate uptake in man during physiological and pathological volume load. Basic Res Cardiol 1977;72:293–298.
16. **Strauer BE.** Myocardial oxygen consumption in chronic heart disease: role of wall stress, hypertrophy and coronary reserve. Am J Cardiol 1979;44: 730–740.
17. **Osbakken M, Bove AA, Spann JF.** Left ventricular function in chronic aortic regurgitation with reference to end-systolic pressure volume and stress relations. Am J Cardiol 1981;47:193–198.
18. **Pichard AD, Martinez E, Squire A, Goldman M.** Coronary blood flow in experimental aortic regurgitation. Unpublished data.
19. **Folts JD, Rowe GG.** Coronary and hemodynamic effects of temporary acute aortic insufficiency in intact anesthetized dogs. Circ Res 1974;35:238–246.
20. **Marcus M, Doty D, Wright C, Easthman C.** Mechanism of angina in patients with aortic stenosis and normal coronary arteries (abstr). Circulation 1980;62:III:III-111.
21. **Fallen EL, Elliot WC, Gorlin R.** Mechanism of angina in aortic stenosis. Circulation 1967;36:480–488.
22. **Bertrand ME, Lablanche JM, Tilmant PY, Thieulex FP, Delforge MR, Carre AG.** Coronary sinus flow at rest and during isometric exercise in patients with aortic valve disease. Mechanisms of angina pectoris in presence of normal coronary arteries. Am J Cardiol 1981;47:199–205.
23. **Buckberg GD, Fixler DE, Archie JC.** Experimental subendocardial ischemia in dogs with normal coronary arteries. Circ Res 1972;30:67–81.
24. **Hoffman JIE.** The myocardial supply-demand ratio. A critical review. Am J Cardiol 1978;58:327–332.
25. **Abdulla MA, Frank MJ, Canedo MI, Stefadouros MA.** Limitations of echocardiography in the assessment of left ventricular size and function in aortic regurgitation. Circulation 1980;61:148–155.
26. **Hood, WB.** Regional venous drainage of the human heart. Br. Heart J 1968;30:105–109.
27. **James TN.** Anatomy of the heart: normal and pathologic, as related to cardiac function. In Gordon BL, ed. Clinical Cardiopulmonary Physiology. New York: Harper & Row, 1960.
28. **Alfonso S.** A thermodilution flowmeter. J Appl Physiol 1966;21:1883–1886.
29. **Weisse AB, Regan TJ.** A comparison of thermodilution coronary sinus blood flows and krypton myocardial blood flow in the intact dog. Cardiovasc Res 1974;8:526–533.
30. **Mathey DG, Chatterjee K, Tyberg JV, Lekven J, Brundage B, Parmley WW.** Coronary sinus reflux. A source of error in the measurement of thermodilution coronary sinus flow. Circulation 1978;57:778–786.
31. **Bookstein JJ, Higgins CG.** Comparative efficacy of coronary vasodilatory methods. Invest Radiol 1977;12:121–127.
32. **Yamazaki H, Aya S, Horikawa M, Matsumura N, Kanamura Y.** Effects of radioopaque material on coronary reserve. Jpn Heart J 1975;16:57–64.
33. **Griggs DJ Jr, Nakamura Y, Leunissen RLA, Klasparian H, Novack P.** Effects of radiopaque material on ischemic coronary flow and myocardial oxygen consumption (abstr). Clin Res 1966;14:247.
34. **Zelis R, Camdill CC, Baggette K, Mason DT.** Reflex vasodilation induced by coronary angiography in human subjects. Circulation 1976;53:490–493.
35. **Wolf GL, Gerlins ED, Wilson WJ.** Depression of myocardial contractility induced by hypertonic coronary injections in the isolated perfused dog heart. Radiology 1973;107:655–658.
36. **Cohn PF, Horn HR, Teichholz LE, Kreulen TH, Herman MV, Gorlin R.** Effects of angiographic contrast medium on left ventricular function in coronary artery disease. Am J Cardiol 1973;32:21–26.

# Regurgitation of Prosthetic Heart Valves: Dependence On Heart Rate and Cardiac Output

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**Prosthetic heart valves exhibit closure and leakage backflow; however, no well-controlled study to evaluate the influence of factors such as cardiac output and heart rate on backflow has been reported to date. Four clinically used prosthetic aortic valves (size 27 mm)—St. Jude Medical, Björk-Shiley Spherical Disc, Björk-Shiley Convexo Concave, and Starr-Edwards model 1260—were studied in the aortic chamber of a pulse duplication system at heart rates of 50, 80, 110, and 140 beats/min, cardiac output of 2, 4, 6, and 8 liters/min, and mean aortic pressure of 100 mm Hg. Regurgitation was calculated in percentage and found to vary directly with heart rate and inversely with cardiac output. The range of values obtained were 5.5% for the Starr-Edwards model 1260 valve at 110 beats/min and 8 liters/min, to 37.5% for the Björk-Shiley Convexo Concave valve at 140 beats/min and 2 liters/min. Regurgitation was also calculated in milliliters/stroke and ranged from 3.4 ml/stroke for the Starr-Edwards model 1260 valve at 140 beats/min and 2 liters/min, to 17.3 ml/stroke for the Björk-Shiley spherical disc valve at 50 beats/min and 2 liters/min. Regurgitation associated with prosthetic heart valves may present a problem clinically, particularly under conditions of low cardiac output and tachycardia.**

Since the pioneering work of Hufnagel and Harvey[1] in 1952, and Harken et al[2] and Starr and Edwards[3] in 1960, considerable effort has been devoted to the design, development, and testing of prosthetic heart valves.[4] The goal continues to be a heart valve which functions with the efficiency of a normal human heart valve. Major problems associated with tissue and mechanical prosthetic heart valves include thromboembolism, hemolysis, tissue overgrowth, infection, calcification, valve wear, and excessive pressure gradients.[5–10]

One problem not generally considered when selecting a prosthetic heart valve is the volume of backflow (regurgitation) associated with the particular design. For the patient with poor cardiac performance, the amount of backflow may be critical when heart rates and cardiac outputs differ from the norm. Backflow associated with prosthetic heart valves is composed of 2 categories: (1) closure backflow (which is required to close the valve), and (2) leakage backflow (which occurs after the valve is closed) (Fig. 1).

Although studies of backflow associated with prosthetic heart valves under various test conditions have been reported, a detailed analysis of the interrelationship of backflow, heart rate, and cardiac output has heretofore not been performed.

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## Methods

Four different currently used clinical prosthetic aortic valves were employed in this study. All valves were equivalent to a 27 mm mounting diameter. The study included the following valves: a Björk-Shiley spherical disc, Björk-Shiley Convexo Concave disc, St. Jude Medical, and Starr-Edwards model 1260. Each valve was independently studied in the aortic chamber of a pulse duplication system which models the left heart as described by Wieting et al[5] in 1966 (Fig. 2.)

The chamber geometry was obtained by sectioning room temperature vulcanizing (RTV) silicone rubber injection molded castings. The aortic sinuses are modeled as an axisymmetric bulge due to ease of manufacturing. A schematic diagram of the aortic valve test chamber is shown in Figure 3. A Björk-Shiley spherical disc 29 mm mitral valve was used

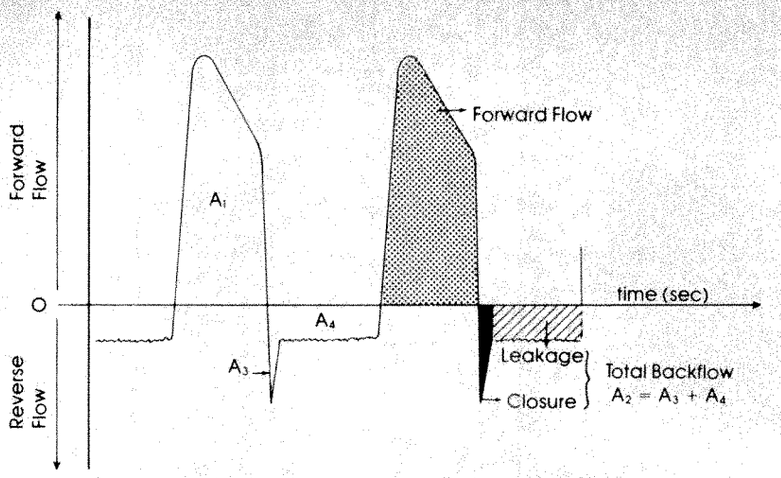



**FIGURE 1.** Typical aortic flow versus time tracing, illustrating categories of backflow.

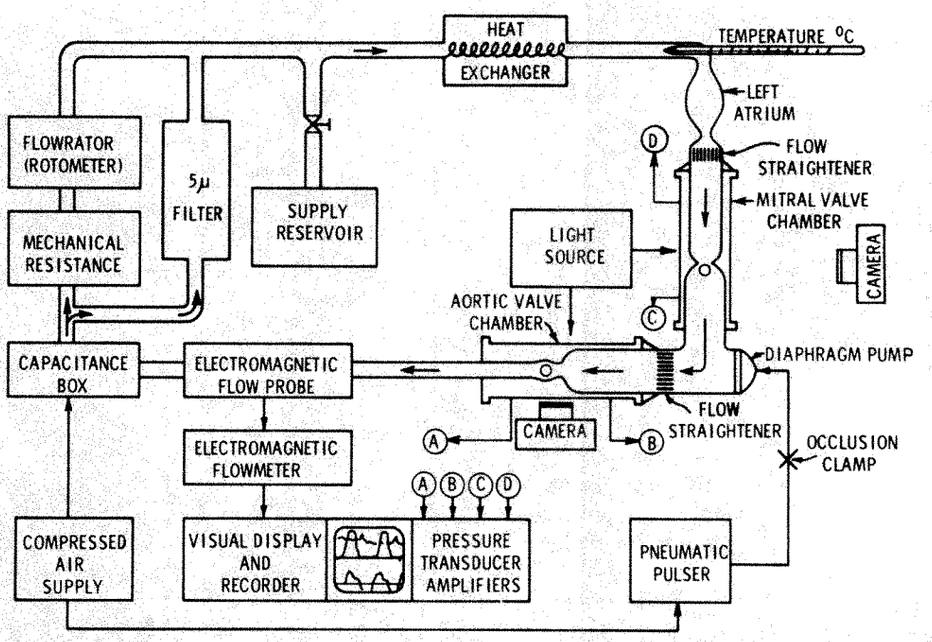



**FIGURE 2.** Schematic diagram of the pulse duplication system as designed by Wieting et al[5] in 1966.

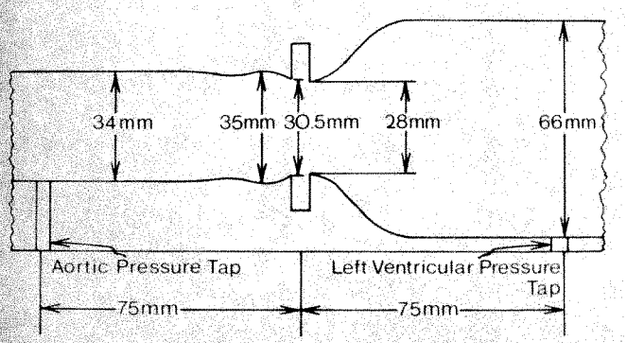



**FIGURE 3.** Schematic diagram illustrating cross-sectional flow areas of the aortic valve testing chamber.

in the mitral chamber for all studies. The valves were tested in an aqueous glycerol blood analog fluid composed of 36.7% glycerol by volume. The specific gravity of this solution at 25°C is 1.1 with a viscosity of 3.5 centipoise. The pulse duplication system was adjusted until the left atrial, left ventricular, and aortic pressures resembled physiologic waveforms. These pressures were measured with 3 Ailtech MS20 physiologic pressure transducers. Aortic flow was measured with a Carolina square wave electromagnetic flowmeter, model 501, using a 26 mm diameter cannulating iron-core flow probe, model EP 695. The pressure and flow signals were filtered at 30 Hz and monitored and recorded on a Honeywell Electronics for Medicine VR-6 Simultrace recorder using paper speeds of 100 mm/s.

Heart rates and cardiac outputs used were as follows: heart rate 50 beats/min, cardiac output 2 and 4 (liters/min); rate 80 beats/min, output 2, 4, and 6 liters/min; rate 110 beats/min,

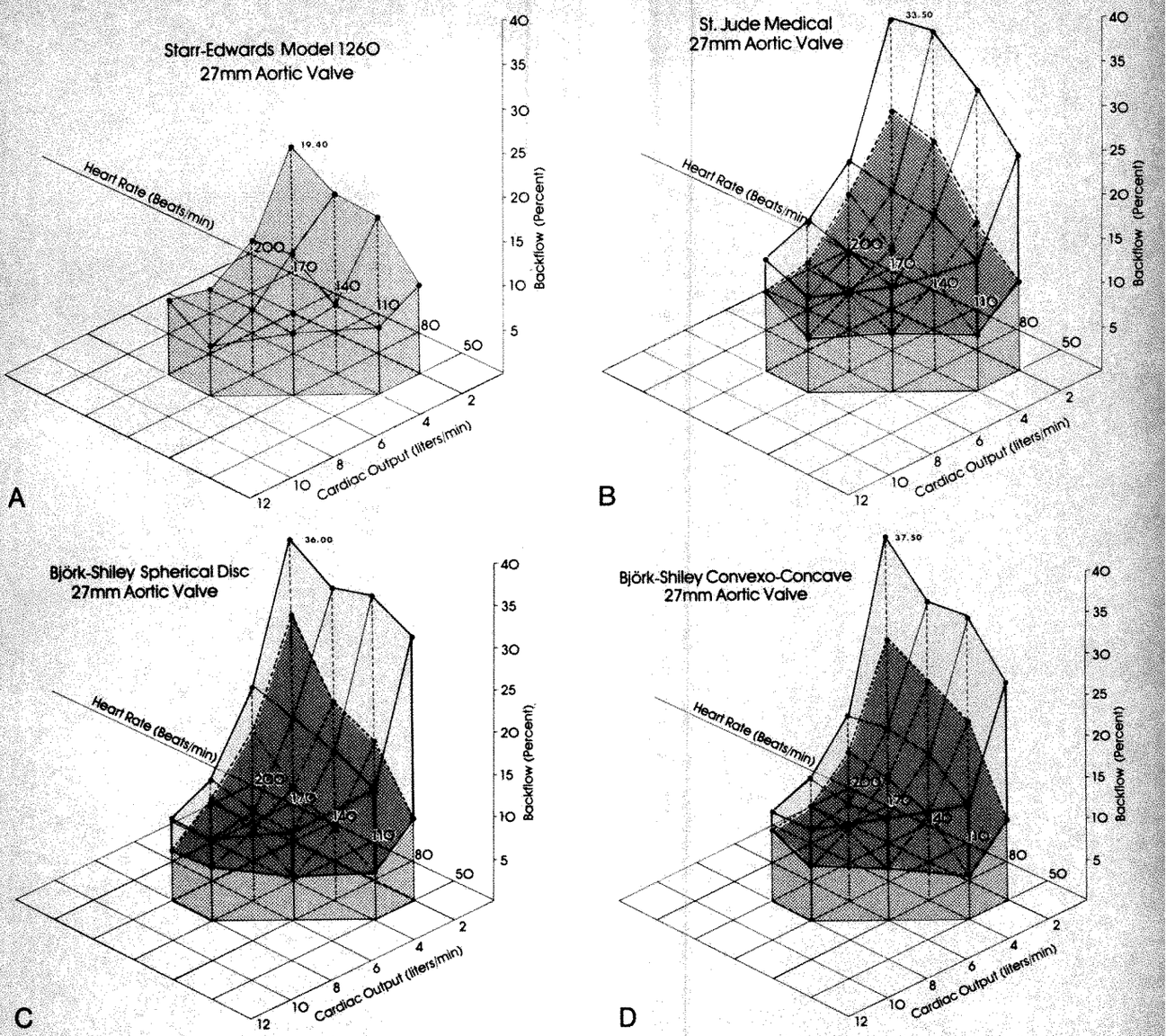



**FIGURE 4.** Three-dimensional graphic representation of backflow expressed in percentage as dependent upon cardiac output and heart rate for the following aortic valve prostheses: **A**, Starr-Edwards model 1260; **B**, St. Jude Medical; **C**, Björk-Shiley spherical disc; and **D**, Björk-Shiley Convexo Concave. In each graph, the upper surface represents the total backflow. The lower surface in **B, C,** and **D** represents closure backflow. The volume of backflow shown between the 2 surfaces in **B, C,** and **D** is the backflow that occurs while the valve is closed (leakage backflow). Since the Starr-Edwards model 1260 valve has no leakage backflow, the closure backflow is the total backflow.

output 2, 4, 6, and 8 liters/min; and rate 140 beats/min, output 2, 4, 6, and 8 liters/min. Systolic durations, corresponding to the Q-T interval of the electrocardiogram for each heart rate setting, were selected as reported by Burton.[11] The resulting values are as follows: heart rate 50 beats/min, systolic duration 420 ms; rate 80 beats/min, duration 350 ms; rate 110 beats/min, duration 290 ms; and rate 140 beats/min, duration 260 ms.

Throughout the range of simulated heart rates and cardiac outputs, the mean aortic pressure was maintained at 100 ± 2 mm Hg; mean left atrial pressure was maintained at physiologic levels, not exceeding 18 mm Hg at the rapid heart rate and high cardiac output settings.

Backflow results were analyzed by planimetry techniques in 2 major categories: (1) percent backflow, and (2) backflow measured in milliliters/stroke. In each major category, total backflow was divided into closure and leakage backflow (Fig. 1.) The percent backflow was measured using the following formula[5]: Percent backflow = $(A_n/A_1) \times 100\%$ (n = 2, 3, 4) where $A_1$ is the area under the forward flow versus time curve, $A_2$ is the area of total backflow, $A_3$ is the area of backflow during valve closure, and $A_4$ is the area of backflow during valve leakage. Backflow in milliliters/stroke is obtained from the following formula: Backflow (ml/stroke) = $[A_n/(A_1 - A_2)] \times (CO/HR)$ (n = 2, 3, 4), where $A_1$, $A_2$, $A_3$, and $A_4$ are as just described, CO is the mean flow rate in milliliters/minute, and HR is the pulse rate in beats/minute.

## Results

The percent backflow results are shown graphically in Figure 4. The upper surface represents the total percent backflow at each setting. The lower surface in Figure 4 (B, C, and D) illustrates the percent backflow

**TABLE I Results for the St. Jude Medical and Starr-Edwards Model 1260 Valves Expressed in Percent Total Backflow**

| | | St. Jude Medical | | | | Starr-Edwards Model 1260 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Heart Rate (beats/min) | | | | Heart Rate (beats/min) | | | |
| | | 50 | 80 | 110 | 140 | 50 | 80 | 110 | 140 |
| Cardiac Output (liters/min) | 2 | 24.3 | 29.1 | 33.5 | 32.8 | 9.6 | 15.5 | 16.1 | 19.3 |
| | 4 | 14.3 | 17.5 | 17.7 | 19.2 | 7.4 | 7.4 | 11.2 | 11.0 |
| | 6 | . . . | 11.9 | 13.5 | 14.6 | . . . | 7.5 | 7.5 | 7.3 |
| | 8 | . . . | . . . | 9.8 | 12.0 | . . . | . . . | 5.5 | 8.2 |

**TABLE II Results for the Björk-Shiley Spherical Disc and Björk-Shiley Convexo Concave Valves Expressed in Percent Total Backflow**

| | | Björk-Shiley Spherical Disc | | | | Björk-Shiley Convexo Concave | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Heart Rate (beats/min) | | | | Heart Rate (beats/min) | | | |
| | | 50 | 80 | 110 | 140 | 50 | 80 | 110 | 140 |
| Cardiac Output (liters/min) | 2 | 30.3 | 33.4 | 32.6 | 36.0 | 26.0 | 32.3 | 32.0 | 37.5 |
| | 4 | 16.0 | 17.6 | 19.2 | 20.6 | 14.0 | 17.3 | 17.6 | 17.4 |
| | 6 | . . . | 10.4 | 11.0 | 11.9 | . . . | 12.0 | 11.6 | 12.7 |
| | 8 | . . . | . . . | 8.9 | 8.9 | . . . | . . . | 10.9 | 10.6 |

**TABLE III Valve With the Highest Percent Backflow at Each Setting**

| | | Heart Rate (beats/min) | | | |
|---|---|---|---|---|---|
| | | 50 | 80 | 110 | 140 |
| Cardiac Output (liters/min) | 2 | BSSD | BSSD | SJM | BSCC |
| | 4 | BSSD | BSSD | BSSD | BSSD |
| | 6 | . . . | BSCC | SJM | SJM |
| | 8 | . . . | . . . | BSCC | SJM |

BSCC = Björk-Shiley Convexo Concave; BSSD = Björk-Shiley Spherical Disc; SJM = St. Jude Medical.

required to close the valve or closure backflow. The volume between the lower and upper surfaces in these figures represents backflow occurring while the valve is closed—leakage backflow. It is obvious that under conditions of low cardiac outputs and high heart rates, backflow greatly increases, reaching 37.5% for the Björk-Shiley Convexo Concave aortic valve. The Starr-Edwards prosthesis exhibited the lowest percent backflow of the valves studied at a heart rate of 140 beats/min and a cardiac output of 2 liters/min, having a total backflow of 19.3%. The valves generally have percent backflow which varies directly with heart rate and inversely with cardiac output.

The actual values for percent backflow are presented in Tables I and II. The valve which exhibited the highest percent backflow at each setting is summarized in Table III. The Starr-Edwards model 1260 aortic valve has the lowest total percent backflow at each setting.

A graphic representation of the backflow in milliliters/stroke is shown in Figure 5. The backflow in milliliters/stroke remains relatively constant along a plane of constant heart rate. This analysis suggests that there is a true inverse relation between percent backflow and cardiac output: that is, the amount of backflow in volume remains constant with constant heart rates, but the denominator becomes smaller, leading to larger percent values. The actual values for backflow in milliliters/stroke are presented in Tables IV and V.

## Discussion

**In vitro studies:** Natural human heart valves have net backflows which are not measurable.[5,12,13] The anatomic configuration of these valves takes advantage of flow inertia to promote rapid closure. After closure, natural human heart valves seal tightly and do not allow retrograde flow.

By their nature, however, all prosthetic heart valves require a certain amount of backflow to effect closure.[14,15] One major consideration for closure backflow is the drag force exerted on the occluder by the retrograde flow. As shown in Figure 4, the closure backflow is greater for the Björk-Shiley Convexo Concave valve than for the Björk-Shiley spherical disc valve. Leakage

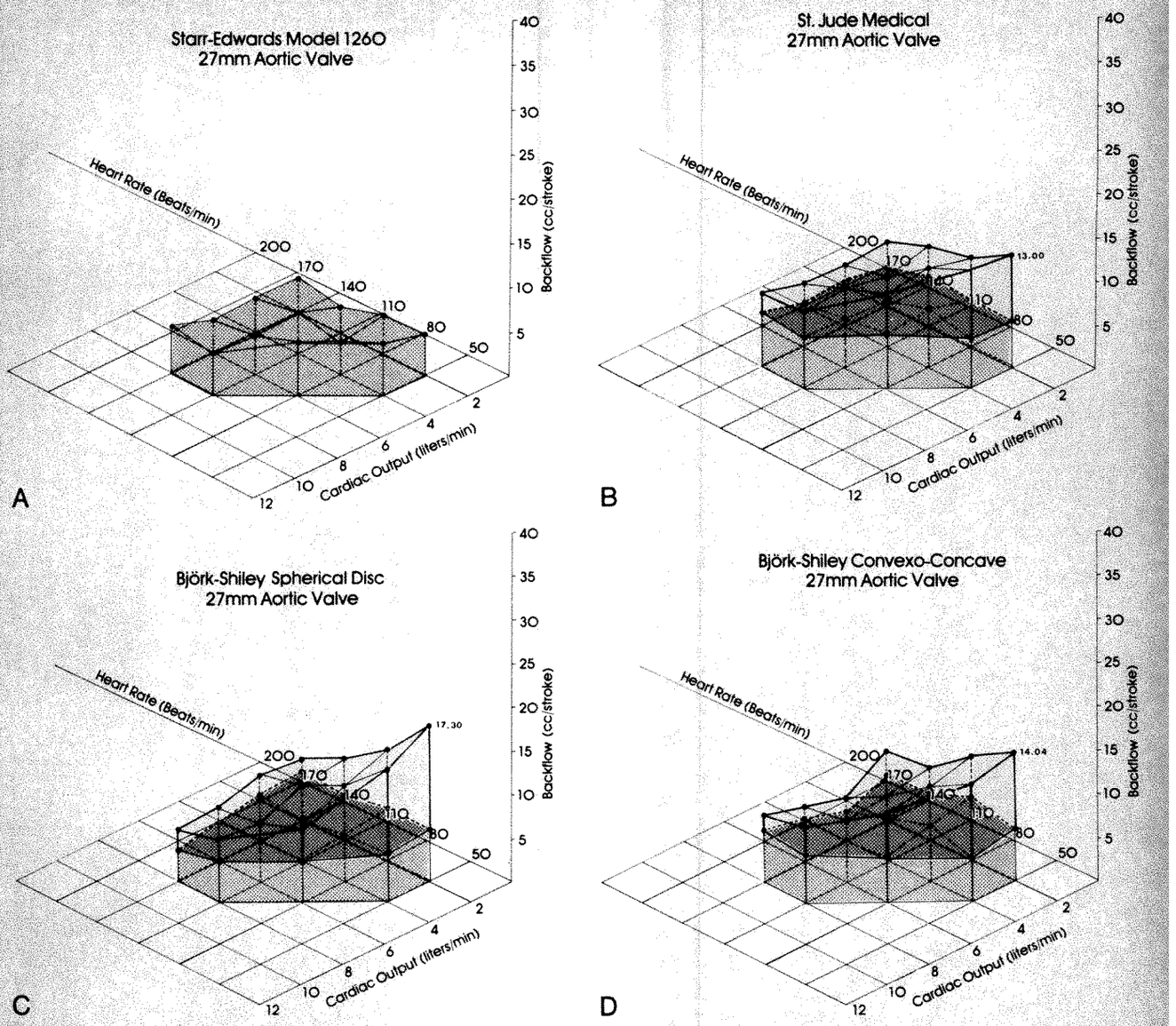



**FIGURE 5.** Three-dimensional graphic representation of backflow expressed in milliliters/stroke (cc/stroke) as dependent upon cardiac output and heart rate for the following aortic valve prostheses: **A,** Starr-Edwards model 1260; **B,** St. Jude Medical; **C,** Björk-Shiley spherical disc; and **D,** Björk-Shiley Convexo Concave. In each graph, the upper surface represents total backflow. The lower surface in **B, C,** and **D** represents closure backflow. The volume of backflow shown between the 2 surfaces in **B, C,** and **D** is the backflow that occurs while the valve is closed (leakage backflow). Since the Starr-Edwards model 1260 valve has no leakage backflow, the closure backflow is the total backflow.

backflow, however, is slightly greater in the Björk-Shiley spherical disc valve than in the Convexo Concave model. One possible explanation for the higher closure backflow is that the Björk-Shiley Convexo Concave occluder presents less drag to the reverse flow and therefore closes slower. Drag forces during closure are greater when the occluder presents a concave surface to the reverse flow, similar to a sail in the wind. Drag forces during closure are least when the occluder is streamlined in the direction of retrograde flow.

The results of this study indicate much lower backflows for the Starr-Edwards model 1260 valve than for the other prostheses studied. The major reason for this finding is the absence of leakage. The absence of leakage backflow stems from the orifice seating design of this prosthesis. Other prostheses studied—the St. Jude Medical, Björk-Shiley spherical disc, and Björk-Shiley Convexo Concave—have built into their design a "controlled leakage" which tends to increase total backflow.

Total backflow results obtained are consistent with those reported by Wright[14] at varying heart rates with a constant stroke volume. Although valves sizes in this study were larger than those used by Wright in the simulated mitral valve position, the values obtained are within the range of experimental error. Work by Baehr (unpublished data) in the aortic position of a similar test apparatus with size 25 mm aortic valves supports these

**TABLE IV Results for the St. Jude Medical and Starr-Edwards Model 1260 Valves Expressed in Milliliters/Stroke**

| | | St. Jude Medical | | | | Starr-Edwards Model 1260 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Heart Rate (beats/min) | | | | Heart Rate (beats/min) | | | | |
| | | 50 | 80 | 110 | 140 | 50 | 80 | 110 | 140 | Category of Backflow |
| Cardiac Output (liters/min) | 2 | 5.1 | 5.1 | 5.8 | 4.7 | 4.2 | 4.6 | 3.4 | 3.4 | Closure |
| | | 7.9 | 4.9 | 3.4 | 2.3 | NM | NM | NM | NM | Leakage |
| | | 13.0 | 10.3 | 9.2 | 7.0 | 4.2 | 4.6 | 3.4 | 3.4 | Total |
| | 4 | 5.7 | 6.3 | 5.1 | 5.4 | 6.3 | 4.0 | 4.6 | 3.5 | Closure |
| | | 7.6 | 4.3 | 2.7 | 1.3 | NM | NM | NM | NM | Leakage |
| | | 13.3 | 10.6 | 7.8 | 6.7 | 6.3 | 4.0 | 4.6 | 3.5 | Total |
| | 6 | ... | 6.0 | 5.3 | 5.0 | ... | 6.1 | 4.4 | 3.4 | Closure |
| | | ... | 4.1 | 3.2 | 2.3 | ... | NM | NM | NM | Leakage |
| | | ... | 10.1 | 8.5 | 7.3 | ... | 6.1 | 4.4 | 3.4 | Total |
| | 8 | ... | ... | 5.1 | 5.7 | ... | ... | 4.3 | 5.1 | Closure |
| | | ... | ... | 2.8 | 2.1 | ... | ... | NM | NM | Leakage |
| | | ... | ... | 7.9 | 7.8 | ... | ... | 4.3 | 5.1 | Total |
| Mean at constant heart rate | | 5.4 | 5.8 | 5.3 | 5.2 | 5.2 | 4.9 | 4.2 | 3.9 | Closure |
| | | 7.8 | 4.4 | 3.0 | 2.0 | NM | NM | NM | NM | Leakage |
| | | 13.2 | 10.2 | 8.3 | 7.2 | 5.2 | 4.9 | 4.2 | 3.9 | Total |

NM = not measurable.

findings of markedly increased backflows at low cardiac output and fast heart rates.

Although most investigators have not divided backflow analysis into the 2 types of backflow, several studies have been carried out on the leakage component. Bellhouse and Bellhouse[16] found that a leakage of 5.7% at a cardiac output of 5 liters/min associated with the Björk-Shiley spherical disc mitral valve, which is consistent with the results obtained in this study. On the other hand, Björk and Henze[17] evaluated leakage through a Björk-Shiley spherical disc prosthesis using a column of test fluid (human blood) with variable height. They found that the leakage flow rate at a pressure of 100 mm Hg was 7.5 ml/s for a 27 mm valve. This leakage flow rate when converted into leakage backflow is 5.9 ml/stroke at a heart rate of 50 beats/min and 1.3 ml/stroke at a heart rate of 140 beats/min. The values obtained by Björk and Henze are lower than those obtained in this study in a pulse duplicator system with a blood analog test fluid.

**In vivo results:** Many investigators have stated that an obligatory closing backflow exists in mechanical prosthetic heart valves[13,15,16,18,19]; however, few have reported the magnitude of this backflow.[13,15,19] Levang et al[20] studied the transvalvular regurgitation of Björk-Shiley spherical disc aortic valves after implantation in humans using 2 techniques. One technique employed an electromagnetic flow probe placed around the ascending aorta perioperatively. This technique, however, lacks specificity in assessing transvalvular regurgitation. Reverse flow due to coronary blood flow was estimated and subtracted from the overall reverse flow waveform. The transvalvular regurgitant fraction was found to be 7% for a size 27 mm Björk-Shiley spherical disc aortic valve. They divided the backflow into closure and leakage components and found that

**TABLE V Results for the Björk-Shiley Spherical Disc and Björk-Shiley Convexo Concave Valves Expressed in Milliliters/Stroke**

| | | Björk-Shiley Spherical Disc | | | | Björk-Shiley Convexo Concave | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Heart Rate (beats/min) | | | | Heart Rate (beats/min) | | | | |
| | | 50 | 80 | 110 | 140 | 50 | 80 | 110 | 140 | Category of Backflow |
| Cardiac Output (liters/min) | 2 | 5.5 | 6.0 | 5.2 | 6.0 | 5.3 | 7.1 | 5.9 | 5.7 | Closure |
| | | 11.7 | 6.8 | 3.6 | 1.9 | 8.8 | 4.7 | 2.6 | 2.7 | Leakage |
| | | 17.3 | 12.8 | 8.8 | 7.9 | 14.1 | 11.8 | 8.5 | 8.4 | Total |
| | 4 | 5.3 | 5.0 | 5.0 | 5.4 | 4.8 | 6.2 | 5.4 | 4.6 | Closure |
| | | 10.0 | 5.6 | 3.7 | 2.0 | 8.2 | 4.3 | 2.4 | 1.4 | Leakage |
| | | 15.3 | 10.6 | 8.7 | 7.4 | 13.0 | 10.5 | 7.8 | 6.0 | Total |
| | 6 | ... | 4.6 | 5.1 | 4.6 | ... | 5.5 | 5.3 | 4.8 | Closure |
| | | ... | 4.1 | 1.6 | 1.2 | ... | 4.6 | 1.8 | 1.4 | Leakage |
| | | ... | 8.7 | 6.7 | 5.8 | ... | 10.1 | 7.1 | 6.2 | Total |
| | 8 | ... | ... | 5.0 | 3.5 | ... | ... | 5.6 | 5.7 | Closure |
| | | ... | ... | 2.0 | 2.1 | ... | ... | 3.3 | 1.1 | Leakage |
| | | ... | ... | 7.0 | 5.6 | ... | ... | 8.9 | 6.8 | Total |
| Mean at constant heart rate | | 5.4 | 5.2 | 5.1 | 4.9 | 5.0 | 6.3 | 5.5 | 5.2 | Closure |
| | | 10.9 | 5.5 | 2.7 | 1.8 | 8.5 | 4.5 | 2.6 | 1.7 | Leakage |
| | | 16.3 | 10.7 | 7.8 | 6.7 | 13.5 | 10.8 | 8.1 | 6.9 | Total |

approximately half of the total backflow occurs during each phase at a heart rate of 72 beats/min. In addition to the perioperative flow recordings, postoperative cineaortography was performed and the transvalvular leakage was graded from 0 to IV according to the degree of contrast filling of the left ventricle. Used clinically, however, this technique lacks the quantitative measure that a well-controlled in vitro study would yield. In Levang's series of 47 patients with Björk-Shiley spherical disc prostheses, 42 patients had a grade I transvalvular regurgitation, 4 patients had a grade II transvalvular regurgitation, and 1 patient had a grade III transvalvular regurgitation. The patient with the grade III transvalvular regurgitation was found to have a 30% regurgitation during the perioperative flow measurement.

Williams et al,[13] using an electromagnetic flow probe placed upstream from the normal mitral valve, found that in dogs, regurgitation associated with normal valve closure was negligible when compared to the approximate 4% associated with a Starr-Edwards mitral valve prostheses at low heart rates. Nolan and co-workers[19,21,22] reported that closure backflow in calves varied from 1.3 to 3.6 ml for disc and ball-type mitral valve prostheses as measured with an electromagnetic flow probe attached to the orifice of the prosthesis. These figures are slightly lower than the 4.5 ml measured in this study for a Starr-Edwards prosthesis in the aortic position. In vivo studies reported by Frater[23] indicated the obligatory closing backflow was approximately 3.1 ml for eccentrically opening mitral valve prostheses, such as the Björk-Shiley spherical disc valve. In Frater's work the amount of obligatory backflow did not vary significantly as the heart rate was increased, while the percentage of backflow increased as the heart rate increased. The 3.1 ml obtained by Frater for an eccentrically opening mitral valve is lower than the 5.1 to 5.5 ml found for the Björk-Shiley valves in this study. The amount of fluid required, however, in order to close a prosthetic valve in the mitral position is lower than that required for the closure of an aortic prosthetic valve (unpublished data).

**Clinical significance:** When evaluating a valvular lesion hemodynamically, both the decrease in pressure and the regurgitation should be assessed. Clinically significant incompetence occurs at regurgitant flows as low as 20 to 30% of the forward stroke volume.[24] In this study, all prostheses exhibited some degree of backflow at all pulse duplicator settings. The backflow in the "normal" range of operation was approximately 10%, which is not considered clinically significant. However, the hinged leaflet valves have total regurgitant fractions >20% once cardiac output is <4 liters/min and heart rate is >110 beats/min. At rates equivalent to clinical tachycardia, closure backflow is the major component of regurgitation, while the leakage backflow is the major component of regurgitation at rates equivalent to clinical bradycardia.

The physician should be aware of the possible problems which may be associated with prosthetic valves with high regurgitant fractions. Specifically, for a patient with tachycardia and low cardiac output, backflow may present an enormous demand on the cardiac energy supply. In this case, the valve which has a low closure backflow would be hemodynamically favorable. However, a patient with bradycardia presents a different type of problem. In this patient, the obligatory closure backflow is small compared with the large volume of leakage backflow. At these rates, leakage backflow may represent as much as 65 to 75% of the total backflow. For this patient, a prosthesis which possesses little or no leakage backflow would be hemodynamically favorable.

It is reasonable to speculate that diastolic augmentation with an intraaortic balloon pump may be associated with excess backflow in patients with prosthetic valves which have a large amount of leakage backflow. From this study and others,[17,24] the slower the heart rate and the higher the closing transvalvular pressure, the greater the amount of leakage backflow.

**Conclusion:** Regurgitation of the 4 prosthetic valves studied is dependent on heart rate and cardiac output. During tachycardia, closure backflow dominates, whereas, during bradycardia leakage backflow dominates. Regurgitation also varies inversely with cardiac output. Regurgitation of prosthetic valves does not appear to be significant for the patient with heart rates and cardiac outputs in the normal range. Mean aortic pressures were maintained at a constant level in this study. Because mean aortic pressure fluctuates in vivo, further analysis of the regurgitation of prosthetic aortic valves should be made with varying mean aortic pressures.

Total backflows >30% were measured for the 3 hinged leaflet valves (St. Jude Medical, Björk-Shiley spherical disc, and Björk-Shiley Convexo Concave). These high percent backflows measured in vitro could be clinically significant, particularly at increased heart rates and low cardiac outputs.

The Starr-Edwards model 1260 ball valve had the smallest backflow measured both in percentage and in milliliters/stroke. A major factor responsible for the lower backflow is the absence of leakage backflow with this orifice seating ball valve; however, the closure backflow for the Starr-Edwards valve was also less than that associated with the hinged leaflet valves.

Based on the results of this study, backflow associated with prosthetic heart valves may be a matter of even greater concern when surgically replacing more than 1 diseased or malfunctioning cardiac valve. Backflow associated with 2 or more prosthetic valves could result in an increased work load of >50% on the heart in order to maintain suitable cardiac output. For this reason, it is imperative that future prosthetic heart valves be designed to minimize backflow.

## References


1. **Hufnagel CA, Harvey WP.** Surgical correction of aortic insufficiency: preliminary report. Bull Georgetown U Med Center 1953;6:60–61.
2. **Harken DE, Soroff HS, Taylor WJ, Lefemine AA, Gupta SK, Lunzer S.** Partial and complete prosthesis in aortic insufficiency. J Thorac Cardiovasc Surg 1969;40:744–762.
3. **Starr A, Edwards ML.** Mitral replacement: clinical experience with a ball-valve prosthesis. Ann Surg 1960;154:726–740.
4. **Lefrak EA, Starr A.** Cardiac Valve Prostheses. New York: Appleton-Century-Crofts, 1979:3–37.
5. **Wieting DW, Hall CW, Kreisle LF, Liotta D, DeBakey ME.** Design of a

system for analyzing flow behavior of prosthetic human heart valves. Cardiovasc Res Cent Bull 1966;5:41–56.
6. **Wright JTM, Temple LJ.** An improved method for determining the flow characteristics of prosthetic mitral heart valves. Thorax 1971;26:81–88.
7. **Magilligan DJ Jr, Lewis JW Jr, Jara FM.** Spontaneous degeneration of porcine xenografts. Ann Thorac Surg 1980;30:259–266.
8. **Harrison EC, Roschke EJ, Meyers HI, Edmiston WA, Chan LS, Tatter D, Lau FYK.** Cholelithiasis: a frequent complication of artificial heart valve replacement. Am Heart J 1978;95:483–488.
9. **Yoganathan AP, Corcoran WH, Harrison EC, Carl JR.** The Björk-Shiley prosthesis: flow characteristics, thrombus formation and tissue overgrowth. Circulation 1978;58:70–76.
10. **Merendino KA, Monhas DR.** Man-made gallstones—a new entity following cardiac valve replacement. Ann Surg 1973;177:694–704.
11. **Burton AC.** Physiology and Biophysics of the Circulation. Chicago: Yearbook Medical, 1965:123.
12. **Nolan SP, Fisher RD, Dixon SH, Williams WH, Morrow AG.** Alterations in left atrial transport and mitral valve blood flow resulting from aortic regurgitation. Am Heart J 1970;79:668–675.
13. **Williams BT, Worman RK, Jacobs RR, Schenk WG Jr.** An in vivo study of blood flow patterns across the normal mitral valve. J Thorac Cardiovasc Surg 1970;59:824–829.
14. **Wright JTM.** An in vivo assessment of the hydraulic characteristics of the Mark II Abrams-Lucas mitral valve prosthesis. Thorax 1977;32:296–302.
15. **Frater RWM.** Discussion in Prosthetic Heart Valves. In: Yoganathan AP, Harrison EC, Corcoran WH, eds. The 14th annual meeting of the Association of the Advancement of Medical Instrumentation, Las Vegas, NV. May 21, 1979, Department of Chemical Engineering, California Institute of Technology, Pasadena, CA: 1979:246.
16. **Bellhouse BJ, Bellhouse FH.** Fluid mechanical performance of five prosthetic mitral valves. In: Kalmanson D, ed. The Mitral Valve: A Pluridisciplinary Approach. Acton, MA: Publishing Sciences Group, 1976:247–259.
17. **Björk VO, Henze A.** Flow dynamics across the Björk-Shiley tilting disc valve in the mitral position. In Ref 16:239–245.
18. **Folts JD, Young WD, Rowe GG.** Phasic flow through normal and prosthetic mitral valves in unanesthetized dogs. J Thorac Cardiovasc Surg 1971; 61:235–241.
19. **Nolan SP, Stewart S, Fogarty TJ, Dixon SJ Jr, Morrow AG.** In vivo studies of instantaneous blood flow across mitral ball-valve prostheses: effects of cardiac output and heart rate on transvalvular energy losses. Ann Surg 1969;169:551–559.
20. **Levang OW, Levorstad K, Hauglend T.** Aortic valve replacement: a randomized study comparing the Björk-Shiley and Lillehei-Kaster disc valves. Scand J Thorac Cardiovasc Surg 1980;14:7–19.
21. **Nolan SP, Stewart S, Fogarty TJ, Morrow AG.** Instantaneous blood flow through ball valve prostheses in the tricuspid position. Arch Surg 1968; 97:969–975.
22. **Nolan SP.** Flow characteristics of mitral valvular prostheses: ball, disc and xenograft. In Ref 16:291–297.
23. **Frater RWM.** Discussion: part V. In Ref 16:300–301.
24. **Morrow AG, Brawley RK, Braunwald E.** Effects of aortic regurgitation on left ventricular performance. Circulation 1965;31,32:Suppl I:I-80–I-95.

# Noninvasive Detection of Active Pericardial Bleeding Using Cardiac Blood Pool Scintigraphy

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**The diagnosis of active pericardial bleeding has traditionally depended on an invasive documentation by needle aspiration, angiography, or direct inspection. Blood pool scintigraphy performed in 2 patients just before and after the development of hemopericardium revealed unique images in which acute pericardial bleeding manifested itself by an additional blood pool adjacent to the cardiac chambers. With appropriate attention to technical factors, such distinctive images should be highly specific for active bleeding into the pericardial sac.**

Active pericardial bleeding is a described complication of blunt or sharp cardiac trauma,[1,2] pacemaker or catheter perforation,[3] open heart surgery,[4] acute myocardial infarction,[5] rupture of the heart or aorta,[6,7] neoplastic disease of the pericardium,[8] drugs that alter clotting mechanisms,[9] and pericarditides of viral, tubercular,[10] or uremic[11] origin. When bleeding accompanies inflammatory conditions of the pericardium, no special management is usually needed beyond an awareness of its possibility and an avoidance of medications that may exacerbate the hemorrhage. In other cases, however, active pericardial hemorrhage may be life-threatening. Situations of this type may arise secondary to pacemaker or catheter perforation, early after cardiac surgery, early after infarction, or with retrograde aortic dissection, where the detection of bleeding may presage impending cardiac tamponade. Traditionally, the diagnosis has depended on a strong clinical suspicion followed by invasive documentation by needle aspiration, angiography, or direct inspection.

Nuclear techniques may be useful for the detection of bleeding, in that red blood cells are labelled with a radionuclide, thereby allowing their localization to various intra- or extravascular spaces. In active pericardial bleeding, an additional blood pool encircling all or part of the myocardium may be expected. However, this finding has not yet been reported and in our experience is an uncommon observation. Because this may simply reflect the infrequent application of blood pool imaging in suspected hemopericardium, we believe it important to draw attention to scintigraphic findings when cardiac blood pool imaging is performed in patients with active pericardial bleeding.

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## Reports of Patients

**Patient 1:** A 76-year-old man was referred for exercise radionuclide ventriculography because of recent onset of typical angina. Results of physical examination were within normal limits. As the patient was being prepared for the exercise test, chest pain accompanied by a heart block typical of the Mobitz II pattern occurred. After injection of 25 mCi of technetium-99m–labelled red blood cells, a resting radionuclide ventriculogram was normal (Fig. 1A). The exercise study was deferred in view of the ischemia-induced heart block, and the patient underwent temporary pacemaker insertion. Difficulty in obtaining regular capture required numerous repositionings of the electrode within the right ventricle. Approximately 1 hour after pacemaker insertion, a sharp pleuritic anterior chest pain suddenly developed that was quite unlike the angina. The pacing threshold of the ventricular demand pacemaker concomitantly increased, and there was intermittent loss of ability to capture. A 2-dimensional echocardiogram revealed a small anterior and posterior pericardial effusion and also suggested that the tip of the pacemaker wire was outside the right ventricular chamber, as described previously.[3,12,13] A diagnosis of pacemaker perforation was made, and the wire was repositioned inside the right ventricle. Four hours after injection of the technetium-99m–labelled red blood cells, repeat scintigraphic images revealed a halo of increased radioactivity around the entire heart (Fig. 1B). The subsequent course was uneventful.

**Patient 2:** A 59-year-old woman was referred for surgical therapy of mitral stenosis. Valvuloplasty and double aortocoronary saphenous vein bypass grafting were performed. The pericardium was left open

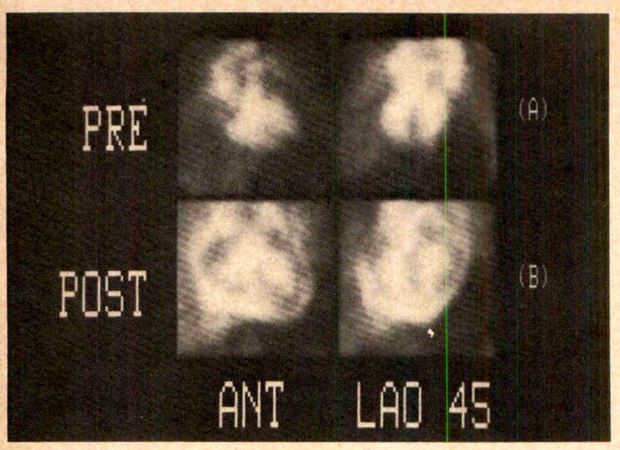



**FIGURE 1.** Patient 1. **A,** anterior (ANT) and left anterior oblique (LAO) 45° cardiac blood pool scintigrams taken at rest with patient supine. **B,** same views 4 hours later, after a temporary transvenous pacemaker tip had penetrated the right ventricular wall. A "halo" of activity surrounding the heart has developed, consistent with the presence of radioactively labelled red blood cells within the pericardial space.

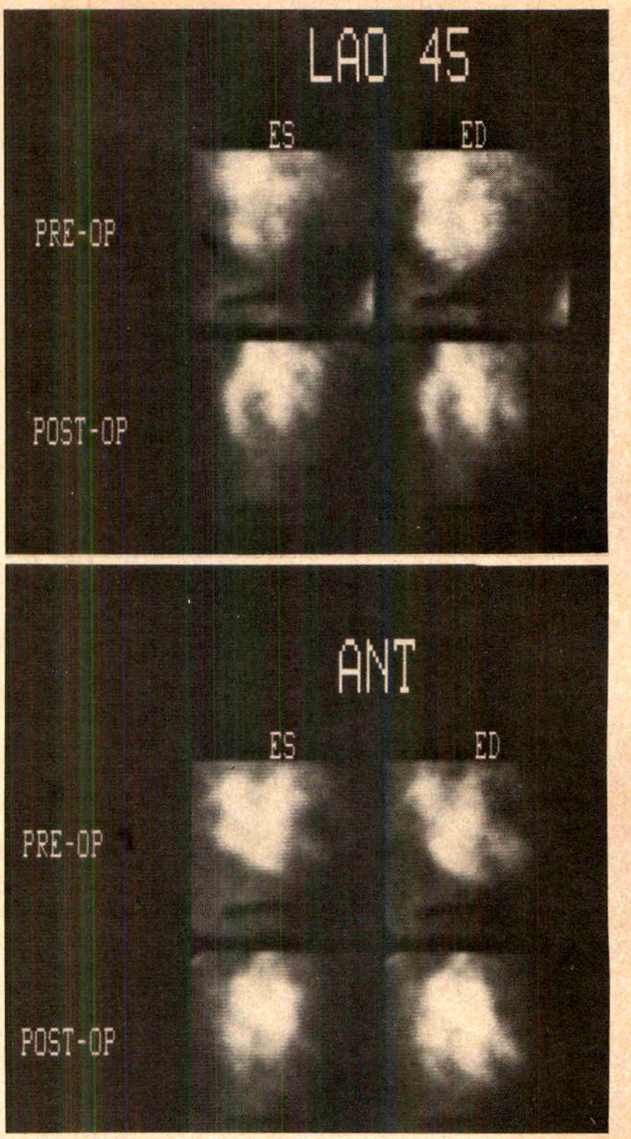



**FIGURE 2.** Patient 2. Cardiac blood pool scintigrams taken at rest with the patient supine, before open heart surgery (PRE-OP), and just before the development of tamponade (POST-OP). ES = end-systole; ED = end-diastole.

and 2 chest tubes were placed in the pericardial space. By 8 hours postoperatively, 1,100 ml of blood had been lost from the chest tubes. The neck veins were distended, and the cardiac index was only 1.9 liters/min/$m^2$ and the blood pressure 100/50 mm Hg. Because the pulmonary capillary wedge pressure was 12 mm Hg, blood, colloid, and plasma expanders were given, with a rapid increase in the right atrial pressure (to 24 mm Hg), and little change in the pulmonary capillary wedge pressure, cardiac index, or blood pressure. Chest X-ray showed a larger cardiac silhouette than preoperatively, with a prominent right heart border. A diagnosis of right atrial tamponade[14] was suspected and the patient returned to the operating room. On opening of the sternum, cardiac index and blood pressure increased and the right atrial pressure decreased precipitously, changing its waveform from a finely undulating line to a recognizable atrial pressure tracing with steep $x$ and $y$ descents. Fresh blood and well-formed clots were seen throughout the pericardial cavity, with a marked accumulation over the right coronary artery graft, clearly compressing the right atrium. The source of bleeding was a small area on the right atrium.

Equilibrium radionuclide ventriculography using technetium-99m–labelled red blood cells had been performed approximately 48 hours preoperatively and again about 3 hours postoperatively (Fig. 2). The postoperative wall motion study differed from the preoperative one in that the end-diastolic volume of the left ventricle was much smaller and a faint halo of increased radioactivity surrounded the entire heart, both findings probably representing blood outside of and compressing the cardiac chambers. There was a marked accumulation of radioactivity along the free border of the right ventricle and right atrium. In the preoperative anterior views, the right atrium virtually disappeared during ventricular diastole, as the labelled blood left it to fill the right ventricle. In the postoperative images, the area of the right atrium emitted a large number of counts that did not vary with the cardiac cycle, indicating a large volume of labelled blood lying outside the atrial chamber and compressing it to a fraction of its normal size. Post-reoperative images were similar to those taken before the first operation.

## Discussion

In equilibrium blood pool scintigraphy, red blood cells are labelled with a radiopharmaceutical agent that emits gamma rays detectable by a scintillation camera. A parallel-hole collimator is placed between the patient and the camera to allow localization of count origins and thus the development by a computer of an image of the blood pool within the region of viewing interest. In the usual situation in which cardiac imaging is performed, the labelled red blood cells remain within the vascular space and the resulting images are therefore of the cardiac chambers and the great vessels, with "background radioactivity" resulting from the pulmonary vascular bed and scatter from radioactivity contained within the cardiac chambers. The myocardium surrounding the cardiac chambers will not be as great a source of gamma rays and so will appear as a rim of relative darkness. With a large pericardial effusion, this rim of darkness will be thicker than expected.[15] If pericardial bleeding is active, an additional radioactive blood pool encircling all or part of the myocardium would be expected. If the blood is flowing into a closed and healthy pericardium with or without excessive

pericardial fluid, the blood should distribute rather uniformly throughout the pericardial space with a slightly greater concentration in the dependent areas, as in Patient 1. When the bleeding is brisk and the pericardium is diseased, absent, or open, the formation of blood clots may lead to an uneven distribution of blood, as in Patient 2.

In the detection of bleeding, the radionuclear label must be nearly completely bound to red blood cells, for unbound isotopes may distribute freely throughout extra- as well as intravascular spaces and may even accumulate in various serous cavities. Indeed, the differentiation of transudative from exudative pericardial effusions has been attempted on the basis of how fast an injected bolus of free technetium-99m diffused into the pericardial space of patients with known effusions.[16] Radioactivity emanating from the pericardium will not be specific for active pericardial bleeding if the technetium-99m has been labelled to albumin, because this bond is not stable and a large portion of the tracer will be free to redistribute throughout extravascular spaces within 1 hour of injection.[17] Moreover, there will be situations other than active bleeding in which albumin itself would extravasate into the pericardial space. Because in the absence of bleeding, red blood cells remain exclusively intravascular, tagged red cells are the ideal agent for blood pool imaging. At our institution, an in vitro method for labelling red blood cells with technetium-99m is employed.[18] This method routinely provides >95% labelling efficiency which persists at this high level for at least 30 minutes after injection.[19] It is not certain that this degree of binding will continue for a prolonged period, but preliminary studies here have established a comparable binding efficiency for at least 4 hours from the time of injection. An in vivo method[20] for labelling erythrocytes is more commonly employed for convenience and availability, but has a lower intravascular retention of activity at 30 minutes than does the in vitro method.[19] Therefore, we believe the in vitro method holds more promise if blood pool imaging is to become a reliable test for the detection of bleeding.

Blood pool scintigraphy is not yet a proven sensitive method for detecting pericardial bleeding. Also unknown is the amount of bleeding required before the described scintigraphic appearances may be anticipated. However, these are reasonable areas for investigation, because a reliable method of either detecting or ruling out pericardial bleeding would find clinical use if it even occasionally eliminated the need for a more invasive diagnostic approach. In addition, because technetium-99m has a half-life in excess of 6 hours, visualization of bleeding may be possible as late as 24 hours after injection of the labelled red blood cells. Therefore, repeated imaging may be of help in detecting slow or intermittent pericardial hemorrhage.

This present documentation should serve to direct attention to other possible uses of blood pool imaging in the detection of active bleeding. Recent reports have demonstrated its usefulness in the diagnosis and localization of acute gastrointestinal bleeding[21] and in the localization of active pulmonary hemorrhage.[22] Presumably, this procedure may also permit the noninvasive diagnosis of bleeding into joints, pleural spaces, and meninges.

## References


1. **Callaham M.** Acute traumatic cardiac tamponade: diagnosis and treatment. JACEP 1978;7:306–310.
2. **Wray TM, Prochaska J, Fisher RD, Shaker IJ.** Traumatic pericardial hematoma simulating tricuspid valve obstruction. Johns Hopkins Med J 1975;137:147–150.
3. **Basman MM, Merin G.** Pericardial tamponade due to perforation with a permanent endocardial pacing catheter. J Thorac Cardiovasc Surg 1977; 74:51–54.
4. **Nelson RM, Jenson CB, Smoot WM.** Pericardial tamponade following open-heart surgery. J Thorac Cardiovasc Surg 1969, 58:510–516.
5. **Darsee JR, Braunwald E.** Diseases of the pericardium. In: Braunwald E, ed. Heart Disease. Philadelphia: WB Saunders, 1980:1558.
6. **Gobel FL, Visudh-Arom K, Edwards JE.** Pseudoaneurysm of the left ventricle leading to recurrent pericardial hemorrhage. Chest 1971;59:23–27.
7. **Hirst AE, Barbour BH.** Dissecting aneurysm with hemopericardium. N Engl J Med 1958;258:116–120.
8. **Cortes FM.** The Pericardium and Its Disorders. Springfield, IL: Charles C Thomas, 1971:298.
9. **Fell SC, Rubin IL, Enselberg CD, Hurwitt ES.** Anticoagulant induced hemopericardium with tamponade. N Engl J Med 1965;272:670–674.
10. **Heimann HL, Binder S.** Tuberculous pericarditis. Br Heart J 1940:2: 165–176.
11. **Buja LM, Friedman CA, Roberts WC.** Hemorrhagic pericarditis in uremia. Clinicopathologic studies in six patients. Arch Pathol 1970;90:325–330.
12. **Meyer JA, Millar K.** Perforation of the right ventricle by electrode catheters: a review and report of nine cases. Ann Surg 1968;168:1048–1060.
13. **Harris A.** Pacemaker "heart sound." Br Heart J 1967;29:608–609.
14. **Bateman T, Gray R, Chaux A, Lee M, DeRobertis M, Berman D, Matloff J.** Right atrial tamponade complicating cardiac operation: clinical, hemodynamic, and scintigraphic correlates. J Thorac Cardiovasc Surg 1982; 84:413–419.
15. **Kriss JP.** Diagnosis of pericardial effusion by radioisotopic angiocardiography. J Nucl Med 1969; 10:233–241.
16. **Yeh SH, Liu RS, Liu OK.** Pertechnetate (Tc-99m) sequential scintiphotography: aid in differentiating exudative from transudative pericardial effusions. J Nucl Med 1982;23:386–390.
17. **Kitani K, Taplin GV.** Rapid hepatic-turnover of radioactive human serum albumin in sensitized dogs. J Nucl Med 1974;15:938–942.
18. **Eckelman W, Richards P, Hauser W, Atkins H.** Technetium-labelled red blood cells. J Nucl Med 1971;12:22–24.
19. **Hegge FN, Hamilton GW, Larson SM, Ritchie JL, Richards P.** Cardiac chamber imaging: a comparison of red blood cells labelled with Tc-99m in vitro and in vivo. J Nucl Med 1978;19:129–134.
20. **Pavel DG, Zimmer AM, Patterson VN.** In vivo labelling of red blood cells with Tc-99m: a new approach to blood pool visualization. J Nucl Med 1977;18:305–308.
21. **Winzelberg GG, Froelich JW, McKusick KA, Waltman AC, Greenfield AJ, Athanasoulis CA, Strauss HW.** Radionuclide localization of lower gastrointestinal hemorrhage. Radiology 1981;139:465–469.
22. **Winzelberg GG, Laman D, Sachs M, Miller WH.** Detection of pulmonary hemorrhage with technetium-labelled red cells. J Nucl Med 1981;22: 884–885.

# Assessment of the Cardiac Effects of Hemodialysis With Systolic Time Intervals and Echocardiography

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**The acute effects of hemodialysis on left ventricular (LV) function were studied with the use of externally recorded LV systolic time intervals and echocardiography; 10 patients with normal or near-normal predialysis LV function and no circulatory congestion were studied. Hemodialysis significantly decreased the LV ejection time (LVET) from 270 ± 9 ms to 237 ± 10 ms ($p < 0.001$); no significant change was noted in the preejection period (PEP). The PEP/LVET ratio increased from 0.41 ± 0.05 to 0.45 ± 0.06 ($p < 0.05$). The LV end-diastolic dimension decreased from 5.3 ± 0.3 cm to 4.8 ± 0.3 cm ($p < 0.001$). Fractional shortening and ejection fraction did not change significantly, but hemodialysis slightly increased mean $V_{CF}$ from 1.2 ± 0.1 $s^{-1}$ to 1.4 ± 0.1 $s^{-1}$ ($p < 0.005$). Hemodialysis was associated with a 17% decrease (87 ± 8 ml to 72 ± 7 ml; $p < 0.001$) in LV stroke volume as calculated from echocardiographic data. Small changes in heart rate and blood pressure were insignificant. We conclude that the postdialysis reduction in stroke volume was due primarily to an acute decrease in LV preload; dialysis also appears to be associated with a small increase in the LV contractile state.**

The effect of chronic renal failure and hemodialysis on cardiac function has been the subject of several reports. Early studies primarily used the classic measurements of cardiac output and stroke volume,[1-3] but more recently the effect of hemodialysis on left ventricular function has been studied with noninvasive techniques.[4-6] The latter methods not only allow determination of LV end-diastolic volume or dimension, systolic ejection fraction, and cardiac output, but also provide information regarding changes in the LV contractile state.[7,8] Noninvasive methods have an obvious advantage over invasive techniques partly because they make it possible to monitor LV performance serially in chronically dialyzed patients during diagnostic or therapeutic intervention. The externally recorded systolic time interval and the echocardiographic LV study are complementary in that each provides information the other does not.[7-9]

Hemodialysis in patients with chronic renal failure is reported to cause a reduction in stroke volume as reflected by a decrease in LV ejection time. However, we were unable in those studies to estimate changes in ejection fraction or LV contractile state.[4] The purpose of the present study was to examine the effects of hemodialysis on LV function using both systolic time intervals and the echocardiographic (echo) LV study. Specifically, we wish to define the mechanisms responsible for the postdialysis reduction in LV stroke volume.

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## Methods

Ten patients with chronic renal failure maintained by long-term hemodialysis at the Hemodialysis Unit of the New England Medical Center Hospital were studied. All 10 patients were active and ambulatory, and none had evidence of pulmonary congestion or more than a trace of peripheral edema. No patient was taking digitalis. The patients were studied immediately before and after hemodialysis (4 to 5 hours) in the recumbent position. Dialysis was performed using a 1.0 $m^2$ parallel plate kidney and a variable degree of positive pressure ultrafiltration. Blood flow was typically 250 to 300 ml/min.

Echocardiograms were obtained with a Smith Kline Ekoline 20A ultrasonoscope using a 2.25 MHz, 0.5 inch transducer focused at 7.5 cm. LV dimensions were measured at end-diastole and end-systole, and the fractional change in LV dimension (or circumference) was calculated as (DED − DES)/DED, where DED = dimension at end-diastole and DES = dimensions at end-systole. Mean normalized velocity of circumferential fiber shortening (mean $V_{CF}$ expressed in circumferences per second [circ/s]) was calculated as follows: Mean $V_{CF}$ = (DED − DES)/DED·LVET, where LVET = LV

**TABLE I Left Ventricular Echocardiographic and Systolic Time Interval Data Before and After Hemodialysis**

| Case | Age (yr) & Sex | Weight (kg) | | DED (cm) | | FS (%) | | $V_{CF}$ ($s^{-1}$) | | LVET (ms) | | PEP (ms) | | HR (beats/min) | | BP (mm Hg) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C | D | C | D | C | D | C | D | C | D | C | D | C | D | C | D |
| 1 | 57F | 63.4 | 61.2 | 4.6 | 4.0 | 30 | 33 | 1.1 | 1.3 | 285 | 260 | 105 | 100 | 64 | 70 | 145/80 | 115/70 |
| 2 | 46F | 64.5 | 62.7 | 5.6 | 5.1 | 29 | 29 | 1.0 | 1.1 | 290 | 260 | 120 | 120 | 75 | 80 | 160/100 | 140/80 |
| 3 | 45M | 69.5 | 67.0 | 5.8 | 5.4 | 34 | 33 | 1.2 | 1.3 | 290 | 260 | 120 | 110 | 85 | 85 | 200/93 | 200/90 |
| 4 | 47F | 64.0 | 63.0 | 5.5 | 5.1 | 35 | 29 | 1.0 | 1.1 | 300 | 270 | 110 | 110 | 85 | 85 | 135/75 | 140/80 |
| 5 | 70M | 57.5 | 56.5 | 6.3 | 6.0 | 25 | 24 | 1.0 | 1.1 | 240 | 220 | 160 | 170 | 85 | 85 | 118/78 | 110/70 |
| 6 | 32F | 59.5 | 59.0 | 4.1 | 4.0 | 38 | 38 | 1.4 | 1.4 | 280 | 270 | 60 | 60 | 75 | 65 | 110/50 | 110/50 |
| 7 | 35F | 72.4 | 70.6 | 4.5 | 4.1 | 38 | 39 | 1.3 | 1.7 | 285 | 235 | 105 | 105 | 75 | 83 | 160/105 | 150/100 |
| 8 | 48M | 65.0 | 63.0 | 5.5 | 5.0 | 40 | 42 | 1.6 | 2.0 | 245 | 200 | 105 | 80 | 71 | 85 | 100/60 | 100/60 |
| 9 | 24M | 76.9 | 74.9 | 5.2 | 4.5 | 42 | 43 | 1.7 | 1.9 | 265 | 215 | 100 | 75 | 88 | 97 | 140/90 | 120/70 |
| 10 | 41M | 61.7 | 60.7 | 5.5 | 5.1 | 26 | 24 | 1.2 | 1.3 | 215 | 180 | 135 | 125 | 95 | 112 | 140/70 | 150/84 |
| | Average | 65.4 | 63.9 | 5.3 | 4.8 | 34 | 33 | 1.2 | 1.4 | 270 | 237 | 112 | 106 | 80 | 85 | 141/80 | 134/75 |
| | SE | 1.9 | 1.8 | 0.3 | 0.3 | 2 | 2 | 0.1 | 0.1 | 9 | 10 | 8 | 9 | 3 | 5 | 9/6 | 9/5 |
| | P value | <0.001 | | <0.001 | | NS | | <0.005 | | <0.001 | | NS | | NS | | NS | |

BP = blood pressure; C = control (before dialysis); D = dialysis (after dialysis); DED = left ventricular dimension at end-diastole; FS = fractional shortening; HR = heart rate; LVET = left ventricular ejection time; NS = not significant; PEP = preejection period; SE = standard error; $V_{CF}$ = mean velocity of circumferential fiber shortening.

ejection time measured from the carotid pulse tracing recorded simultaneously with the echocardiographic study. Our methods, including the rationale for the normalized velocities and the limitations of these echocardiographic techniques, are detailed in previous reports.[7–9] LV volume was estimated from the method of Teichholz et al.[10]

Externally monitored LV systolic time intervals were recorded at a paper speed of 100 mm/s using standard methods.[11] Lead II of the electrocardiogram was recorded simultaneously with the phonocardiogram and the carotid pulse tracing. Electromechanical systole ($QS_2$) was measured from the onset of the QRS complex of the electrocardiogram to the first high-frequency component of the second heart sound; the LV ejection time was measured from the rapid upstroke to the incisural notch on the carotid pulse tracing; the preejection period (PEP) was derived by subtracting LVET from the $QS_2$ interval.

Echocardiographic and systolic time interval measurements were averaged over 12 cardiac cycles, and the heart rate was obtained from the average R-R interval of the 12 QRS complexes. Blood pressure was measured by cuff sphygmomanometer. All data are presented as the average ±1 standard error of the mean; statistical analyses were performed using a paired *t* test.

Patients were selected for this study only if they were free of clinical evidence of LV disease and had normal or near-normal echocardiographic and systolic time interval data before hemodialysis. Both the echocardiographic and systolic time interval data were clearly normal in 7 of the 10 patients. One patient (Patient 5) had left bundle branch block and abnormal systolic time intervals, in part secondary to conduction delay. Patients 8 and 10 had abnormal systolic time intervals and normal echocardiographic measurements.

## Results

The echocardiographic and systolic time interval data are presented in Table I, and a representative study is shown in Figure 1. Body weight and LV end-diastolic dimension decreased in every patient (both $p < 0.001$), but fractional shortening did not show a consistent tendency to increase or decrease; there was a small and statistically significant ($p < 0.005$) increase in circumferential fiber shortening velocity ($V_{CF}$). LV end-diastolic volume decreased from 143 ± 18 ml to 119 ± 17 ml ($p < 0.001$), and stroke volume decreased from 87 ± 8 ml to 72 ± 7 ml ($p < 0.001$).

The LV ejection time decreased in every patient ($p < 0.001$), but there was no significant change in the preejection period; the PEP/LVET ratio increased from 0.41 ± 0.05 to 0.45 ± 0.06 ($p < 0.05$). The heart rate tended to increase and arterial pressure tended to decrease, but these changes did not achieve statistical significance.

The average blood urea nitrogen level decreased from 89 ± 4 to 48 ± 7 mg/dl ($p < 0.001$); serum calcium increased from 8.9 ± 0.2 to 9.4 ± 0.1 mg/dl ($p < 0.02$); serum potassium decreased from 5.2 ± 0.3 to 4.0 ± 0.2 mEq/liter ($p < 0.005$).

## Discussion

The major hemodynamic change associated with hemodialysis was a decrease in stroke volume due to a reduction in LV preload; there was no change in fractional shortening, but our data indicate an increase in contractility after dialysis.

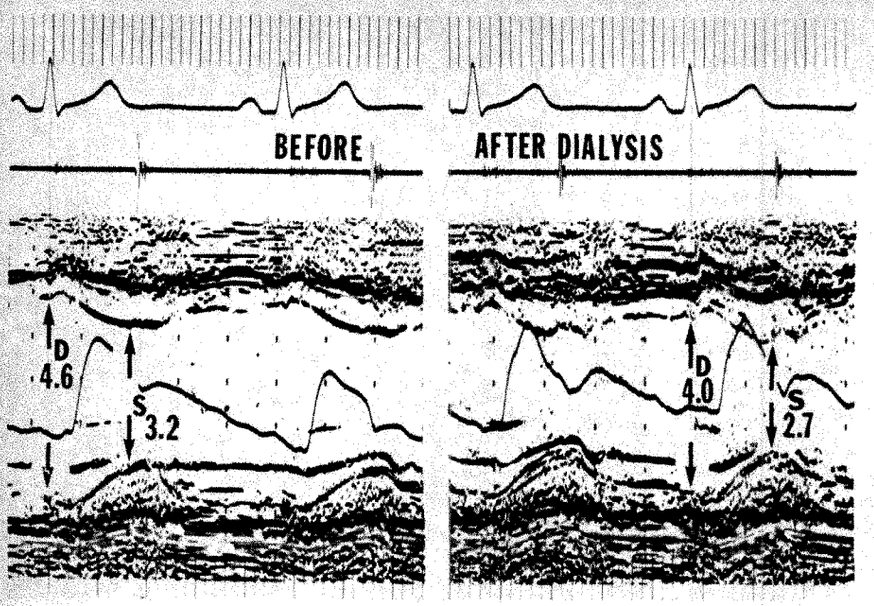



**FIGURE 1.** Echocardiographic LV studies before and after hemodialysis (Patient 1). With dialysis, the LV dimension at end-diastole (D) decreased from 4.6 to 4.0 cm and the systolic dimension (S) from 3.2 to 2.7 cm. See text for details.

Hemodialysis resulted in a highly significant decrease in LV ejection time, no change in the preejection period, and a small but significant increase in the PEP/LVET ratio. If these data were interpreted without the information provided by the echocardiographic LV study, it might be concluded that the decrease in LVET, which implies a postdialysis rejection in stroke volume,[4] was due to a decline in the systolic ejection fraction, because an increase in the PEP/LVET ratio suggests a decrease in the ejection fraction.[11] It is well known that decreased LV preload commonly accompanies hemodialysis, and although it might also contribute to a reduction in LVET, the relative contributions of these 2 factors (decreased preload and ejection fraction) are impossible to assess from systolic time interval data alone. The echocardiogram provides important information in this regard. The echocardiographic LV study confirmed a reduction in preload, but no change in fractional shortening indicates no change in the systolic ejection fraction. Thus, the suggestion that the ejection fraction decreased with dialysis (on the basis of an increase in the PEP/LVET ratio, as described earlier) is not supported by the measured echocardiographic fractional shortening. Not only does the echocardiographic LV study identify the basis for the postdialysis reduction in LVET, namely, a 17% decrease in LV end-diastolic volume and a 24% decrease in stroke volume, but also the combination of both techniques provides additional insight into the cardiac effects of hemodialysis.

LV mean circumferential fiber shortening velocity calculated from the echocardiographic dimension data and the LVET has been used as an index of LV contractile state, but it is well known that mean $V_{CF}$ is sensitive to acute alterations in LV afterload[8]: that is, an increase in LV contractile state or a decrease in afterload, or both, will result in an increase in mean $V_{CF}$. In our 10 patients, the decrease in LV systolic pressure was minimal (and statistically nonsignificant), but the decrease in LV systolic dimension and volume was highly significant. Because afterload (systolic wall stress) is directly related to systolic pressure and radius, a postdialysis reduction in afterload is apparent. For this reason the postdialysis increase in $V_{CF}$ must be interpreted with caution. The increase in $V_{CF}$ was likely due in part to a reduction in afterload, and perhaps to an increase in contractility, but we would not conclude, as have others,[5] that the increase in $V_{CF}$ can be taken as evidence of an increase in LV contractile state alone. However, there is some evidence of an increase in contractility which is not apparent on analysis of the echocardiographic LV study; the absence of a change in PEP is not consistent with a pure decrease in preload. The PEP is determined by the rate of development of LV isovolumic pressure (LV dP/dt) and the level of aortic diastolic pressure (aortic valve opening pressure); LV dP/dt increases with an increase in preload or an increase in contractile state (and vice versa), or both.[11] Arterial pressure did not change significantly, but with a decreased preload, the expected change in the PEP should have been an increase (if there were no change in contractility). The PEP did not change, and the lack of such a change is likely due to the opposing effects of a decrease in preload (which should increase the PEP) and an increase in contractility (which should decrease the PEP). Although this may be weak evidence for an increase in the LV contractile state, the acute increase in serum calcium as well as a potential reduction in uremic toxins or an improvement in electrolyte balance, or both, might be expected to augment LV contractility. Alternatively, a reflex increase in sympathetic tone as a consequence of the reduced stroke volume could have caused the increase in contractility.

The findings in our 10 patients complement those recently reported with radionuclide left ventriculography. Hung et al[6] found that the systolic ejection fraction remained unchanged in 15 patients with a

normal predialysis ejection fraction; their methods did not allow measurement of end-diastolic or stroke volume, but did suggest that the *combination* of an acute decrease in preload (which should reduce the systolic ejection fraction) and afterload (which should increase the systolic ejection fraction) might explain the absence of a change in the ejection fraction. Our findings of a postdialysis reduction in preload and afterload and no change in the ejection fraction confirm the hypothesis of Hung et al.[6] In contrast to the findings in patients with normal LV function, these investigators and others[5] showed that the systolic ejection fraction may increase in patients with a low predialysis ejection fraction.

It thus appears that the cardiac effects of hemodialysis in patients with normal LV function are primarily related to variations in LV preload and the Frank-Starling mechanism. In addition, dialysis appears to be associated with a small increase in LV contractile state. Both the externally recorded systolic time intervals and the echocardiographic LV study are influenced by hemodialysis and both provide useful information about the functional state of the left ventricle, especially when used together. It should be emphasized that any single assessment of LV function in patients with chronic dialysis may not be truly representative of the functional state of the left ventricle because of the lack of a steady state. Serial studies may be useful in this regard.

## References


1. **Goss JE, Alfrey AC, Vogel JHK, Holmes JH.** Hemodynamic changes during hemodialysis. Trans Am Soc Artif Intern Organs 1967;13:68–74.
2. **Hampers CL, Skillman JJ, Lyons JH.** Hemodynamic evaluation of bilateral nephrectomy and hemodialysis in hypertensive man. Circulation 1967; 35:272–288.
3. **del Greco F, Simon NM, Roguska J, Walker C.** Hemodynamic studies in chronic uremia. Circulation 1969;40:87–95.
4. **Bornstein A, Zambrano SS, Morrison RS, Spodick DH.** Cardiac effects of hemodialysis: noninvasive monitoring by systolic time intervals. Am J Med Sci 1975;269:189–192.
5. **Fernando HA, Friedman HS, Zaman Q, Celis A, Masih E, Stein R, Yap A.** Echocardiographic assessment of cardiac performance in patients on maintenance hemodialysis. Cardiovasc Med 1979;4:459–472.
6. **Hung J, Harris PJ, Uren RF, Tiller DJ, Kelly DT.** Uremic cardiomyopathy: effect of hemodialysis on left ventricular function in end stage renal failure. N Engl J Med 1980;302:547–551.
7. **Quinones MA, Gaasch WH, Alexander JK.** Echocardiographic assessment of left ventricular function with special reference to normalized velocities. Circulation 1974;50:42–51.
8. **Quinones MA, Gaasch WH, Cole JS, Alexander JK.** Echocardiographic determination of left ventricular stress velocity relations in man. With reference to the effects of loading and contractility. Circulation 1975;51: 689–700.
9. **Andrias CW, Gaasch WH, Deane LV, Bornstein AB.** Assessing positive inotropic action through systolic time intervals and echocardiography. Cardiovasc Med 1979;4:563–570.
10. **Teichholz LE, Kreulen T, Herman MV, Gorlin R.** Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence or absence of asynergy. Am J Cardiol 1976;37:7–11.
11. **Lewis RP, Rittgers SE, Forester WF, Boudoulas H.** A critical review of the systolic time intervals. Circulation 1977;56:146–158.

# Normal Left Atrial Function Determined by 2-Dimensional Echocardiography

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**To obtain normal values for left atrial function noninvasively, volumes of the left atrium and ventricle were calculated in 52 volunteers by 2-dimensional echocardiography. A light pen digitizing and computation system, controlled by a microprocessor, was used to outline the left atrium and ventricle in orthogonal apical views. Then, to calculate end-systolic and end-diastolic atrial and ventricular volumes, a modified Simpson's rule formula was used. End-systolic left atrial volume (mean ± standard deviation) was 37 ± 11.7 ml or 21 ± 6.6 ml/m$^2$. The change in left atrial volume from end-systole to end-diastole was 24 ± 7.6 ml or 13.5 ± 4.3 ml/m$^2$, which represented 37 ± 12.9% of left ventricular stroke volume. The mean fractional emptying of the left atrium was 65 ± 8.9% and the conduit volume was 41 ± 14.0 ml or 23 ± 7.9 ml/m$^2$. These values are similar to those reported in studies in which left atrial function was calculated from contrast angiography.**

Harvey[1] first proposed that atrial function made an important contribution to ventricular filling. Although some denied this contribution,[2-4] later studies supported Harvey's proposal by demonstrating the influence of atrial function on ventricular filling and stroke volume.[5,6]

Levophase and transseptal contrast angiography have provided data about absolute left heart volumes, which were then used to determine left atrial function.[7-16] However, these techniques require cardiac catheterization, which precludes their routine clinical use. M-mode echocardiography, a noninvasive technique, has been a reliable indicator of angiographically determined left atrial size expressed as an area,[17,18] but can only imply left atrial function indirectly.[19,20] Gated radionuclide angiography also provides a noninvasive means of assessing normal left atrial function.[21] However, it provides information about relative and not absolute changes in atrial volume, and there are potential errors because of atrioventricular overlap, the technique for background correction, and the differential tissue attenuation of left atrial and ventricular photons. Bough et al[21] attempted to eliminate the last potential error by using M-mode echocardiography to determine the comparative depths of the left atrium and ventricle. Because patients are frequently referred for 2-dimensional echocardiography to assess valvular lesions or left ventricular performance, it would be preferable to derive information relating to left atrial function from these same echocardiograms rather than to perform an additional test.

Although previous studies have indicated that left atrial and left ventricular volumes measured from apical and parasternal 2-dimensional echocardiograms correlate with the respective angiographic volumes or radionuclide techniques,[22-24] routine clinical application of quantitative 2-dimensional echocardiography, a noninvasive technique, has been hampered by the lack of normal values.[25] To obtain normal values, we used this method to calculate absolute left atrial volumes. We then determined left atrial function expressed as the change in left atrial volume from end-systole to end-diastole, the ratio of this change to left ventricular stroke volume, the left atrial fractional emptying, and the left atrial conduit volume.

## Methods

Sixty-three subjects volunteered for the study. Eleven were excluded: 2 had hypertension, 2 chronic obstructive pulmonary disease, 4 mitral valve prolapse, and 3 left ventricular or atrial echocardiograms of suboptimal quality. Thus, 52 normal volunteers (29 male and 23 female) aged 20 to 66 years (mean 37 ± 11.0), none of whom had a history of cardiac disease or hypertension or any clinical evidence of cardiac abnormality, were included. The average subject's body surface area was

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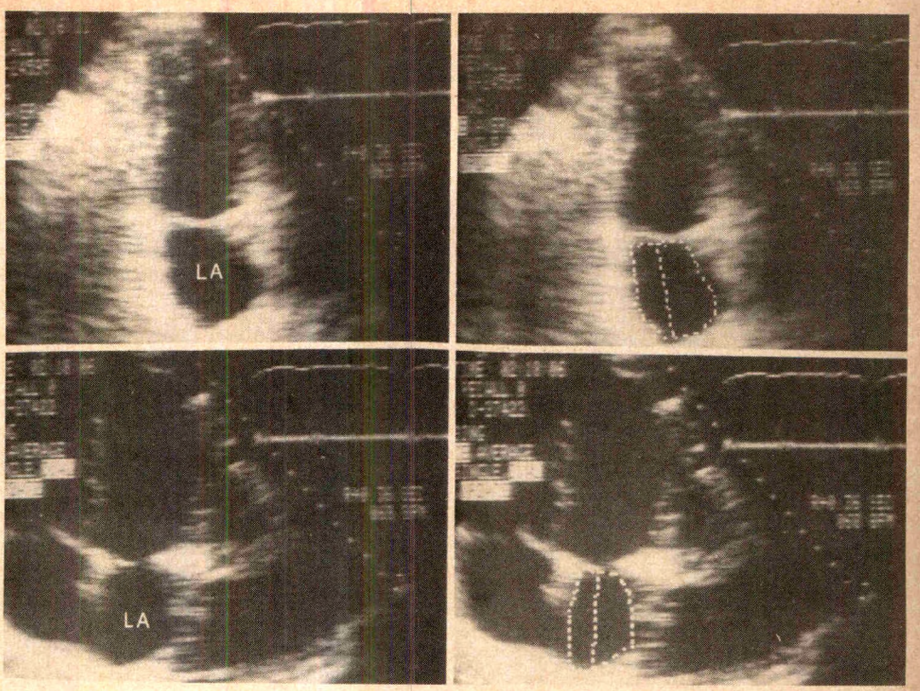



**FIGURE 1.** Determination of left atrial volumes in a normal subject from apical 2-chamber views (**above**) and 4-chamber views (**below**) at end-systole. The left atrial outlines, traced with a light pen, are **on the right.** LA = left atrium.

1.78 ± 0.21 $m^2$. Regional wall motion, wall thickness, and cardiac valves were normal as were blood pressure and the 12-lead electrocardiogram.

Two-dimensional echocardiograms were recorded with Varian 3000 or 3400 phased array 84° sector scanners and 2.25 MHz, 32 element transducers. The images were generated at 32 frames/second and recorded with standard video techniques at 64 fields/second for later playback and analysis in the stop-action mode. The 2- and 4-chamber views were used for end-systolic and end-diastolic volume measurements because they are orientated in 2 orthogonal planes. These views were obtained with the patient in the extreme left lateral recumbent position with respiration suspended at end expiration. This is important because changes in position and phase of respiration may affect the volume of the heart chambers. The transducer was angled to qualitatively maximize atrial or ventricular size separately and to obtain clear outlines of each chamber at end-systole and end-diastole. End-systole was defined by advancing the videotape, frame by frame, to obtain maximal atrial and minimal ventricular size (usually at the end of the T wave of the electrocardiogram just before the mitral valve opening). End-diastole was determined by obtaining minimal atrial and maximal ventricular size (usually at the peak of the R wave of the electrocardiogram just after closure of the mitral leaflet). After an optimal image was identified, volume measurements were repeated 3 times and averaged from a single cardiac cycle.

Left atrial volumes were obtained in the following way using a light pen digitizing and computation system controlled by a microprocessor.[26] The atrial outline was traced along the inner border of the atrial wall (Fig. 1). However, when dropout of the atrial septum occurred, the outline was completed by a straight line drawn between the 2 inner borders of the adjacent clear echoes. Instead of using the inner surface along the coapted leaflets of the mitral valve, a straight line connecting both sides of the leaflet attachments to the mitral valve anulus was taken as the border of the atrial outline. Care was taken to exclude both the pulmonary veins and the atrial appendage from the atrial perimeter. To calculate atrial end-systolic and end-diastolic volumes, a modified biplane Simpson's rule formula was used.[27] Change in left atrial volume was calculated from the difference between end-systolic and end-diastolic left atrial volume. Fractional emptying of the left atrium was then computed by dividing the change in left atrial volume by the left atrial volume at end-systole. Left atrial conduit volume was derived by subtracting the change in left atrial volume from the left ventricular stroke volume. To calculate left atrial volume, we previously determined that the intraobserver correlation and estimate of reliability was 0.95 and 3.0 ml and the interobserver correlation and estimate of reliability was 0.89 and 7.2 ml.[23]

To determine left ventricular stroke volume, 2- and 4-chamber views were obtained so that left ventricular volumes could be calculated. The plane of each of these views was chosen to maximize left ventricular size. Attempts were made to optimize visualization of the endocardium by careful transducer and gain manipulations, by changes in the angle of the subject's trunk, and by alterations in the phase of the subject's respiration. Ventricular volumes were computed in a similar manner to that described for left atrial volumes with the use of a modified Simpson's rule formula.[27] In tracing the left ventricular endocardium, minor irregularities were ignored and the papillary muscles were excluded (Fig. 2). Left ventricular stroke volume was computed from the difference between left ventricular end-diastolic and end-systolic volumes. Intraobserver variability in ventricular volume measurement in our laboratory was determined as ±4%, and correlation coefficients for measurements obtained by 2 different observers (interobserver variability) were 0.82 for end-diastolic volume, 0.95 for end-systolic volume, and 0.95 for ejection fraction.[23]

The heart rate of each subject at the time of echocardiographic study was noted. To assess whether left atrial function was influenced by heart rate, standard methods were used to compute correlation coefficients between heart rate and each of the following variables: change in left atrial volume, ratio of the change in left atrial volume to left ventricular stroke volume, fractional left atrial emptying, and conduit volume. A p value $<0.05$ was considered significant. All results are expressed as the mean value ± standard deviation.

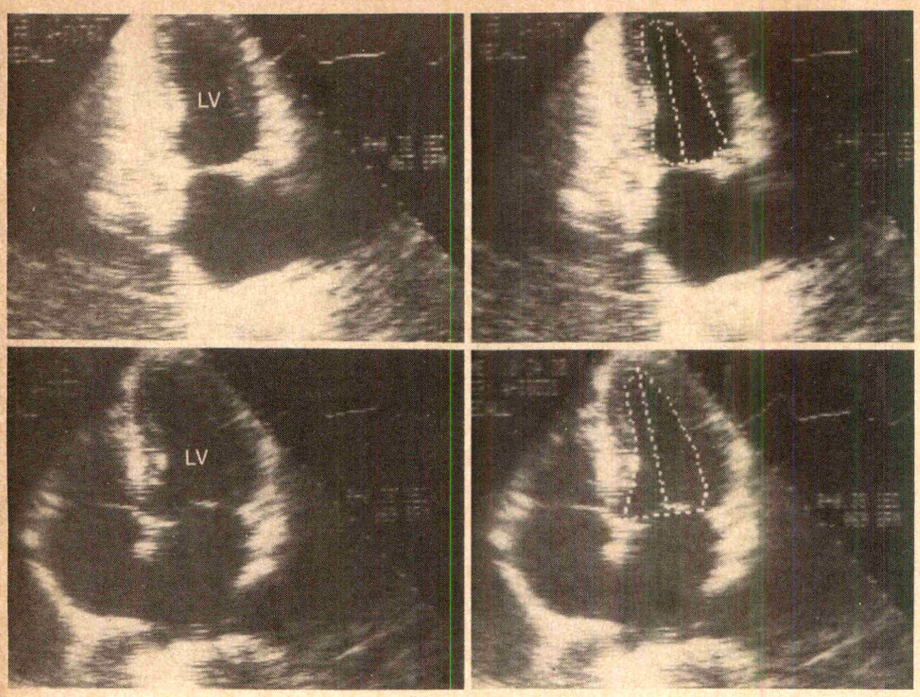



**FIGURE 2.** Determination of left ventricular volumes in a normal subject from apical 2-chamber views (**above**) and 4-chamber views (**below**) at end-systole. The outlines of the left ventricular endocardium, traced with a light pen, are **on the right.** LV = left ventricle.

## Results

The mean maximal left atrial volume (end-systolic volume) was 37 ± 11.7 ml or 21 ± 6.6 ml/m$^2$. Mean change in left atrial volume was 24 ± 7.6 ml or 13.5 ± 4.3 ml/m$^2$ and the mean fractional emptying was 65 ± 8.9% (Table I). It was determined from statistical analysis that correction for body surface area was not necessary when left atrial volume was measured in a normal population. To be complete, both values are presented here.

Mean left ventricular end-diastolic, end-systolic, and stroke volumes were 97 ± 17.8 ml or 54.5 ± 10 ml/m$^2$, 32 ± 10.7 ml or 18 ± 6 ml/m$^2$, and 65 ± 14.3 ml or 36.5 ± 8 ml/m$^2$. Thus, the change in left atrial volume was 37 ± 12.9% of left ventricular stroke volume. Mean left atrial conduit volume, calculated by subtracting the change in left atrial volume from left ventricular stroke volume, was 41 ± 14.0 ml or 23 ± 7.9 ml/m$^2$ and represented 63% of the left ventricular stroke volume.

Mean heart rate was 67 ± 11.3 beats/min (range 45 to 100). The correlation coefficient between heart rate and change in left atrial volume was 0.03, between heart rate and the ratio of the change in left atrial volume to left ventricular stroke volume 0.11, between heart rate and fractional emptying 0.21, and between heart rate and conduit volume 0.21. None of these correlations was significant.

**TABLE I Normal Values for Left Atrial Volume and Function in 52 Volunteers**

| Variable | Mean | SD | Range |
|---|---|---|---|
| LA volume at end-systole | | | |
| ml | 37 | 11.7 | 15–66 |
| ml/m$^2$ | 21 | 6.6 | |
| LA volume at end-diastole | | | |
| ml | 13 | 5.7 | 3–29 |
| ml/m$^2$ | 7.3 | 3.2 | |
| Change in LA volume | | | |
| ml | 24 | 7.6 | 10–45 |
| ml/m$^2$ | 13.5 | 4.3 | |
| Fractional emptying (%) | 65 | 8.9 | 44–82 |
| LV stroke volume | | | |
| ml | 65 | 14.3 | 39–136 |
| ml/m$^2$ | 36.5 | 8.0 | |
| Change in LA volume/LV stroke volume (%) | 37 | 12.9 | 11–71 |
| Conduit volume | | | |
| ml | 41 | 14.0 | 16–114 |
| ml/m$^2$ | 23 | 7.9 | |

LA = left atrial; LV = left ventricular; SD = standard deviation.

## Discussion

**Normal values for left atrial function:** Our study provides the normal values for left atrial function in a sample population by means of 2-dimensional echocardiography (Table I). The results we obtained with echocardiography agree with those previously obtained with contrast angiography. The only exception is that our mean maximal left atrial volume (37 ml or 21 ml/m$^2$) underestimates the means derived from angiographic studies, which range from 55 to 66 ml.[7,8,13,16] However, previously reported echocardiographic determinations of left atrial and left ventricular volumes also underestimate the values obtained by angiography.[22,23] Whether the underestimation is due primarily to the angiographic or echocardiographic method is not known. The change we found in left atrial volume (24 ml or 13.5 ml/m$^2$) is similar to that documented in previous studies using contrast angiography (20 to 33 ml).[8,12,13] In addition, the mean fractional emptying value of 65% that we obtained is similar to the means

obtained from contrast angiography, which range from 37 to 75%.[7,8,13–16] In contrast, the value for fractional left atrial emptying obtained from radionuclide angiography, 39%,[21] is in the lower end of the range of these contrast angiographic studies. For the ratio between the change in left atrial volume and left ventricular stroke volume, our mean echocardiographic value (37%) was similar to the mean contrast angiographic values which ranged from 21 to 52%,[8,12–16] whereas the radionuclide measurement of 53%[21] was at the upper end of the range of these reported means.

The mean value for maximal left atrial volume that we obtained is almost identical to that calculated with a single plane formula from 2-dimensional echocardiograms.[29] This similarity occurred despite the echocardiograms being analyzed retrospectively and the transducer not being angled to maximize the left atrial dimension. However, the combination of only a 1 ml smaller maximal left atrial volume and a 3 ml larger change in left atrial volume resulted in a 10% higher value for fractional emptying than in our study. The reason for this is not apparent, but perhaps the transducer angle had a greater effect on reducing left atrial minimal volume and thus resulted in spuriously greater changes in left atrial volume.

Values for the change in left atrial volume, the ratio of the change in left atrial volume to left ventricular stroke volume, fractional emptying, and left atrial conduit volume did not correlate significantly with heart rate in our sample population. However, it may be expected that at very high heart rates, the relative contribution of left atrial conduit volume to left ventricular stroke volume would decrease, and the ratio of the change in left atrial volume to left ventricular stroke volume would approach unity.

**Limitations of the method:** Two-dimensional echocardiography may be limited by an inability to obtain adequate echocardiograms for volumetric analysis of the left ventricle and left atrium. Obtaining adequate echocardiograms relies not only on the skill and experience of the technician, but also on the physical habitus of the patient, especially the anatomic relations of the heart, lung, and chest wall. In certain subjects it may be impossible to visualize portions of the left ventricular endocardium, particularly the anterior left ventricular wall in the 2-chamber view in diastole. To overcome this limitation, we found that when the subject takes a small breath and then stops respiration, the anterior wall is more easily visualized than it is during full expiration. Although the left atrium is usually easier to outline than the endocardium of the left ventricle, dropout of the anterior atrial wall echoes in the 2-chamber view may cause errors in atrial volume measurement.

Even when adequate echocardiograms are recorded, other potential limitations are introduced because our method for determining both left atrial and ventricular volumes is time consuming and is based on certain geometric assumptions. Nevertheless, even in the presence of segmental left ventricular contraction abnormalities or left atrial enlargement, volumes calculated with Simpson's rule correlate well with left ventricular and atrial volumes from contrast angiography and radionuclide techniques.[22–24]

In contrast to left atrial and ventricular volumes, which are calculated directly, left atrial conduit volume can only be calculated indirectly from the difference between left ventricular stroke volume and the change in left atrial volume. This limitation, common to other techniques that estimate left atrial conduit volume, is due to the assumption that the left ventricular stroke volume is derived entirely from the left atrium. Obviously, the left atrial conduit volume would be overestimated in subjects with aortic regurgitation or a ventricular septal defect with a right to left shunt.

Because volumetric calculations of 2-dimensional echocardiograms require expertise and take considerable time, it may be impractical for some laboratories to obtain quantitative data for routine clinical use. To overcome these limitations, computerized technology[30,31] may decrease the time commitment that is necessary at present and may permit routine clinical use of 2-dimensional echocardiography to assess left atrial function.

**Clinical applications:** The relative importance and contribution of left atrial function vary in different disease states. These variations may become useful in distinguishing pericardial constriction from pericardial effusion, chronic from acute mitral regurgitation, predominantly mitral from predominantly aortic regurgitation, and predominantly mitral stenosis from predominantly mitral regurgitation. For example, in patients with pericardial constriction, fractional emptying of the left atrium is less than that in patients with pericardial effusions and in normal subjects.[7] Patients with chronic mitral regurgitation not only have an enlarged left atrium but also have large changes in left atrial volume[8,9] which correlate with the severity of chronic regurgitation.[10] Furthermore, patients with chronic mitral regurgitation have a larger left atrial volume and a greater change in left atrial volume than do patients with acute mitral regurgitation.[8] In contrast to patients with mitral regurgitation, patients with aortic regurgitation have low values for the change in left atrial volume relative to left ventricular stroke volume.[8] Also, patients with mitral stenosis have a lower change in left atrial volume than do patients with mitral regurgitation.[10] Calculation of left atrial function may not only be important in assessing pericardial and mitral and aortic valvular disease, but may also be clinically useful in patients with left ventricular abnormalities, such as left ventricular hypertrophy, in which altered ventricular compliance may affect left atrial emptying.

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## References

1. **Harvey W.** Anatomical studies on the motion of heart and blood. Springfield, IL: Charles C Thomas, 1949:40.
2. **Henderson Y.** The volume curve of the ventricles of the mammalian heart, and the significance of this curve in respect to the mechanism of the heart beat and the filling of the ventricles. Am J Physiol 1906;16:325–367.

3. **Henderson Y, Johnson FE.** Two modes of closure of the heart and valves. Heart 1912;4:69–82.
4. **Lewis T.** Fibrillation of the auricles: its effects upon the circulation. J Exp Med 1912;16:395–420.
5. **Straub H.** The diastolic filling of the mammalian heart. J Physiol 1910; 40:378–388.
6. **Gesell RA.** Auricular systole and its relation to ventricular output. Am J Physiol 1911;29:32–63.
7. **Preger L, Dayem MKA, Goodwin JF, Steiner RE.** Angiographic studies of pericardial disease. Lancet 1965;2:701–706.
8. **Hawley RR, Dodge HT, Graham TP.** Left atrial volume and its changes in heart disease. Circulation 1966;34:989–996.
9. **Sasayama S, Takahashi M, Osakada G, Hirose K, Hamashima H, Nishimura E, Kawai C.** Dynamic geometry of the left atrium and left ventricle in acute mitral regurgitation. Circulation 1919;60:177–186.
10. **Kennedy JW, Yarnall SR, Murray JA, Figley MM.** Quantitative angiocardiography. IV. Relationships of left atrial and ventricular pressure and volume in mitral valve disease. Circulation 1970;41:817–824.
11. **Santer HJ, Dodge HT, Johnson RR, Graham TP.** The relationship of left atrial pressure and volume in patients with heart disease. Am Heart J 1964;67:635–642.
12. **Grant C, Bunnell IL, Greene DG.** The reservoir function of the left atrium during ventricular systole. An angiocardiographic study of atrial stroke volume and work. Am J Med 1964;37:36–43.
13. **Murray JA, Kennedy JW, Figley MM.** Quantitative angiocardiography. II. The normal left atrial volume in man. Circulation 1968;37:800–804.
14. **Graham TP, Jarmakani MM, Canent RV, Capp MP, Spach MS.** Characterization of left heart volumes and mass in normal children and in infants with intrinsic myocardial disease. Circulation 1968;38:826–837.
15. **Soloff LA, Zatuchni J, Mark GE.** Relationship of left atrial volume to pulmonary artery and wedge pressures in mitral stenosis. Circulation 1957; 15:430–433.
16. **Bjork L, Lodin H.** Angiographic determination of left atrial and left ventricular volumes in normal children and adults. Acta Radiol (Diagn) 1965;3:577–580.
17. **Hirata T, Wolfe SB, Popp R, Helman CH, Feigenbaum H.** Estimation of left atrial size using ultrasound. Am Heart J 1969;78:43–52.
18. **TenCate FJ, Kloster FE, vanDorp WG, Meester GT, Roelandt J.** Dimensions and volumes of left atrium and ventricle determined by single beam echocardiography. Br Heart J 1972;36:737–746.
19. **Strunk BL, Fitzgerald JW, Lipton M, Popp R, Barry WH.** The posterior aortic wall echocardiogram: its relationship to left atrial volume change. Circulation 1976;54:744–750.
20. **Strunk BL, London EJ, Fitzgerald J, Ropp RL, Barry WH.** The assessment of mitral stenosis and prosthetic mitral valve obstruction, using the posterior aortic wall echocardiogram. Circulation 1977;55:885–891.
21. **Bough EW, Gandsman EJ, Shulman RS.** Measurement of normal left atrial function with gated radionuclide angiography. Am J Cardiol 1981;48: 473–478.
22. **Schabelman S, Schiller NB, Silverman NH, Ports TA.** Left atrial volume estimation by two-dimensional echocardiography. Cathet Cardiovasc Diagn 1981;7:165–178.
23. **Schiller NB, Acquatella H, Ports TA, Drew D, Goerke J, Ringertz H, Silverman N, Brundage B, Botvinick E, Boswell R, Carlsson E, Parmley W.** Left ventricular volume from paired biplane two-dimensional echocardiography. Circulation 1979;60:547–555.
24. **Starling MR, Crawford MH, Sorensen SG, Levi B, Richards KL, O'Rourke RA.** Comparative accuracy of apical biplane cross-sectional echocardiography and gated equilibrium radionuclide angiography for estimating left ventricular size and performance. Circulation 1981;63:1075–1084.
25. **Henry WL.** Evaluation of ventricular function using two-dimensional echocardiography. Am J Cardiol 1982;49:1319–1323.
26. **Daigle R, Paineter W, Anderson W, Schiller NB.** A light pen measurement system for cross-sectional echocardiography. Ultrasound Med 1977;4: 447–478.
27. **Goerke RJ, Carlsson E.** Calculation of right and left cardiac ventricular volumes: method using standard computer equipment and biplane angiocardiograms. Invest Radiol 1967;2:360–367.
28. **Wang Y, Heilbron D, Gutman J, Wahr D, Schiller NB.** Clinical quantitative echocardiography. I. End systolic atrial volume in a normal population (abstr). Am J Cardiol 1982;49:905.
29. **Gehl LG, Mintz GS, Kotler MN, Segal BL.** Left atrial volume overload in mitral regurgitation: a two-dimensional echocardiographic study. Am J Cardiol 1982;49:33–38.
30. **Garcia E, Gueret P, Bennett M, Corday E, Zwehl W, Meerbaum S, Corday S, Swan HJC, Berman D.** Real time computerization of two-dimensional echocardiography. Am Heart J 1981;101:783–792.
31. **Skorton DJ, McNary CA, Child JS, Newton FC, Shah PM.** Digital image processing of two-dimensional echocardiograms: identification of the endocardium. Am J Cardiol 1981;48:479–486.

# Myocardial Function in Rocky Mountain Spotted Fever: Echocardiographic Assessment

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**Nine patients with Rocky Mountain spotted fever underwent M-mode echocardiographic examination. Increased left ventricular dimension was found in 2 patients and decreased left ventricular shortening fraction in 7. Diminished mean velocity of circumferential fiber shortening, increased left ventricular systolic time intervals ratio, and increased mitral valve E point to ventricular septal separation were found in 6 patients. One patient died and at necropsy diffuse myocarditis was present. Repeat echocardiographic examination was available in the remaining 8 patients at follow-up (mean 10 months). Abnormal E mitral point to ventricular septal separation remained in 3 patients and decreased left ventricular shortening fraction in 2; in 1 there was also increased left ventricular end-diastolic dimension. Thus abnormal left ventricular function and chamber enlargement are frequently present in patients with Rocky Mountain spotted fever.**

Rocky Mountain spotted fever is a serious infectious disease that continues to occur in various areas of the United States. Over 1,000 cases were reported to the Center for Disease Control in 1980,[1] and a high case-fatality ratio (7 to 11%) persists despite the availability of adequate chemotherapeutic agents (tetracycline and chloramphenicol). Although data are available regarding the clinical and anatomic cardiac manifestations of Rocky Mountain spotted fever,[2,3] the effect of the disease on myocardial function has not been reported. Thus, a prospective analysis of the echocardiographic findings in patients with Rocky Mountain spotted fever was undertaken.

## Methods

From 1980 to 1982, 9 consecutive, unselected children—5 girls and 4 boys with an average age of 8.25 years (range 4 to 14)—were admitted to a children's hospital with clinical evidence of Rocky Mountain spotted fever. The criteria for diagnosis were similar to those previously reported[3] and are presented in Table I.

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One patient died and necropsy examination was performed. Clinical, electrocardiographic, and radiologic data were available for study in each patient. M-mode echocardiograms were obtained at the time of admission in each patient and at late follow-up (mean 10 months) in 8 survivors. Normal control subjects were 15 boys and 10 girls with body surface areas similar to that of the study subjects. Echocardiograms were recorded with a Hoffrel 101 ultrasonoscope with use of either a 3.5 or 5 MHz nonfocused transducer. Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), left ventricular shortening fraction (LVSF), mean velocity of circumferential fiber shortening (VCF), and left ventricular preejection period to left ventricular ejection time ratio (LPEP/LVET) were measured using standard techniques.[4,5] E mitral point to ventricular septal separation (EPSS) was measured as previously reported by Massie et al.[6] Statistical analysis of data for EPSS and LVSF in the studied subjects and control group was done by contigency table analysis. Results are expressed as mean ± standard deviation.

## Results

*Clinical cardiac data:* Inappropriate sinus tachycardia for the degree of fever was present in all but 1 patient (Case 2) and gallop rhythm in 2 (Cases 2 and 6). A precordial murmur (grade 2/6 holosystolic) was heard in 3 patients (Cases 2, 6, and 8). Cardiac enlargement by radiogram was present in 2 patients (Cases 7 and 9). First degree atrioventricular block was present in 3 patients (Cases 1, 5, and 7), and left ventricular hyper-

**TABLE I Criteria for Diagnosis of Rocky Mountain Spotted Fever**

| Case | Age (yr) & Sex | Clinical | Tick * | Serum Sodium (mEq/liter) | Platelets ($mm^3$) | Acute/Conval Weil Felix | Acute/Conval Latex Agglutination | Acute/Conval Complement Fixation |
|---|---|---|---|---|---|---|---|---|
| 1 | 4F | +† | ? | 131 | 250,000 | +‡ | – | – |
| 2 | 9M | + | ? | 135 | 500,000 | + | +§ | – |
| 3 | 12M | + | 0 | 137 | 200,000 | + | – | – |
| 4 | 9F | + | ? | 128 | 40,000 | + | + | – |
| 5 | 5F | + | + | 131 | 125,000 | | – | 0 |
| 6 | 6F | + | + | 126 | 14,000 | – | – | 0 |
| 7‖ | 10M | + | + | 126 | 23,000 | – | – | 0 |
| 8 | 7F | + | + | 135 | 300,000 | – | – | – |
| 9 | 14M | + | + | 124 | 15,000 | + | 0 | – |

* Tick found on patient; questionable = ticks on pet or in environment. † Typical centripetal rash and central nervous system manifestations. ‡ Four-fold rise or single titer 1:320. § Four-fold rise. ‖ Fatal case.
+ = positive or present; 0 = negative or absent; – = not done; ? = questionable.

**TABLE II Echocardiographic Findings**

| Case | LVEDD (cm) | LVESD (cm) | LVSF (%) (Normal 35.2 ± 3.1) | VCF (Normal 1.36 ± 0.07) | LPEP/LVET (Normal 0.25 ± 0.03) | EPSS (mm) (Normal ≤4) |
|---|---|---|---|---|---|---|
| 1 | 3.1 (3.1) | 2.2 (2.1) | 29 (32) | 1.0 (–) | 0.31 (–) | 5 (1) |
| 2 | 4.1 (3.8) | 3.1 (3.0) | 24 (21) | 1.1 (1.1) | 0.31 (0.27) | 6 (6) |
| 3 | 2.9 (2.9) | 2.1 (2.0) | 27 (31) | 1.1 (1.3) | 0.27 (0.26) | 4 (0) |
| 4 | 4.1 (3.9) | 3.1 (2.9) | 24 (25) | 1.0 (1.3) | 0.36 (0.31) | 8 (6) |
| 5 | 3.2 (3.3) | 2.6 (2.1) | 18 (36) | 0.78 (1.4) | 0.43 (0.27) | 13 (7) |
| 6 | 3.4 (3.5) | 2.6 (2.2) | 23 (37) | 0.93 (–) | 0.26 (–) | 9 (2) |
| | Normal 2.5–3.8 Mean 3.3 | Normal 1.6–2.6 Mean 2.2 | | | | |
| 7* | 4.1 | 3.0 | 26 | 1.2 | 0.27 | 3 |
| 8 | 3.2 (3.0) | 2.0 (2.0) | 37 (33) | 1.7 (1.4) | 0.33 (–) | 2 (0) |
| 9 | 3.5 (3.2) | 2.6 (2.2) | 25 (31) | 1.6 (1.3) | 0.43 (0.25) | 9 (4) |
| | Normal 3.4–4.2 Mean 3.8 | Normal 2.1–2.7 Mean 2.4 | | | | |

* Fatal case.
EPSS = E mitral point to ventricular septal separation; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricle end-systolic dimension; LVSF = left ventricle shortening fraction; LPEP/LVET = left ventricular preejection period to left ventricular ejection time ratio; VCF = mean velocity of circumferential fiber shortening; figures in parentheses = findings at follow-up; – = not available.

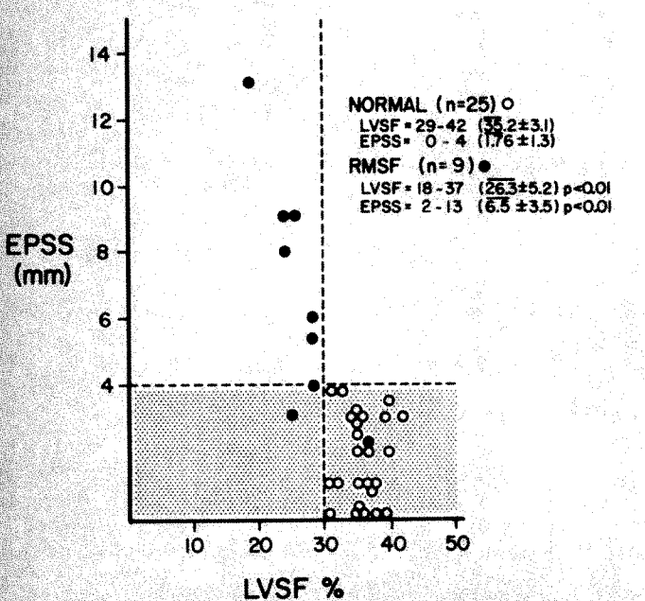



**FIGURE 1.** Comparison of mitral valve E point to ventricular septal separation (EPSS) and left ventricular shortening fraction (LVSF) in patients with Rocky Mountain spotted fever (RMSF) (**closed circles**) and normal subjects (**open circles**).

trophy in 1 (Case 2). Echocardiographic findings are presented in Table II. Data on left ventricular dimension was subdivided into 2 sections according to the body surface area. Comparison of EPSS and LVSF shows a significant difference between study and control subjects (Fig. 1).

In 2 cases (Patients 4 and 5) abnormal echocardiographic findings were the presenting manifestation before any clinical sign of cardiac involvement was detected. In the fatal case, myocarditis in combination with diffuse vasculitis and left ventricular enlargement was found at autopsy.

Follow-up echocardiograms (Table II) revealed decreased LVSF and LVEF in Patients 2 and 4; the latter also showed residual left ventricular enlargement and increased LPEP/LVET ratio. Although EPSS decreased in most patients, it was still abnormal at follow-up in 3 patients (Cases 2, 4, and 5).

## Discussion

Rocky Mountain spotted fever is an acute, potentially lethal illness caused by Rickettsia rickettsii and transmitted by ticks. The disease is characterized by generalized vasculitis involving many organs and systems.

Myocarditis and multifocal myocardial necrosis are frequently present, and this may play a significant role in the final outcome of some cases. Although a definitive diagnosis of myocardial disease can be made only after histologic examination of the myocardium, echocardiography offers a reliable way to evaluate chamber dimensions as well as myocardial performance in this disease. Inappropriate sinus tachycardia for the degree of fever was a common finding in our cases; nevertheless, variables such as LVSF, LPEP/LVET, and EPSS are not influenced by a wide variation in heart rate. On admission, left ventricular enlargement was found in 2 patients and abnormal left ventricular dimension remained in 1. LVSF was reduced at initial evaluation in 7 cases and remained abnormally low at late follow-up in 2. EPSS, a qualitative index of left ventricular ejection fraction, was abnormally elevated on admission in 6 cases and remained abnormal in 3. Although there has been some controversy as to whether EPSS is independent of left ventricular size, in our experience as well in others[7] increased left ventricular dimension does not affect EPSS unless depressed left ventricular function was also present. This variable appears to be an adequate index of depressed left ventricular ejection independent of the size of the chamber, in the absence of mitral valve stenosis or aortic valve regurgitation.

Although quantification of left ventricular dysfunction may not influence management in Rocky Mountain spotted fever it appears useful in identifying the patient with severe illness. The degree of left ventricular impairment correlated with the severity of the illness in all but Patients 2 and 5. These patients had substantial left ventricular dysfunction but only mild illness with normal or mildly decreased serum sodium and platelet levels. On the other hand, and except in patient 5, the severity of left ventricular dysfunction on admission correlated with the presence of residual abnormalities at follow-up. Patients 3, 6, and 9 had mild reduction of left ventricular function and no abnormalities were present at follow-up; Patients 2 and 4 presented with significant left ventricular dysfunction and residual abnormalities persisted.

The clinical recognition of myocardial involvement in Rocky Mountain spotted fever may be delayed if a high index of suspicion is not maintained. The initial echocardiogram in Patients 4 and 5 showed abnormal left ventricular performance before any clinical sign of cardiac involvement was detected. These findings suggest that myocardial dysfunction may be present early in the disease and it may require a variable length of time to manifest itself clinically. Thus, besides clinical examination and electrocardiography, echocardiography might be necessary if early identification of myocardial involvement is to be achieved. Although most patients recovered and the initial clinical manifestations disappeared, residual echocardiographic abnormalities suggests chronic disturbance in left ventricular function in some cases. The long-term prognosis for this group is unknown. In patients with Rocky Mountain spotted fever, close monitoring and aggressive therapeutic approach are essential if the high case fatality ratio is to be reduced. Treatment with tetracycline or chloramphenicol must be initiated before serologic confirmation.

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## References

1. Summary. Cases of specific notifiable disease: United States. Morbid Mortal Week Rep 1980;29:607.
2. **Marin-Garcia J, Gooch III WM, Coury DL.** Cardiac manifestations of Rocky Mountain spotted fever. Pediatrics 1981;67:358–361.
3. **Bradford WD, Hackel DB.** Myocardial involvement in Rocky Mountain spotted fever. Arch Pathol Lab Med 1978;102:357–359.
4. **Gutgesell HP, Paquet M, Duff DF, McNamara DG.** Evaluation of left ventricular size and function by echocardiography. Circulation 1977;56:457–462.
5. **Sahn DJ, DeMaria A, Kisslo J, Weyman A.** Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–1083.
6. **Massie BM, Schiller NB, Ratshin RA, Parmley WW.** Mitral-septal separation: new echocardiographic index of left ventricular function. Am J Cardiol 1977;39:1008–1016.
7. **Child JS, Krivokapich J, Perloff JK.** Effect of left ventricular size on mitral E point to ventricular septal separation in assessment of cardiac performance. Am Heart J 1981;101:797–805.

# Mechanisms for Decreased Exercise Capacity After Bed Rest in Normal Middle-Aged Men

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**The mechanisms responsible for the decrease in exercise capacity after bed rest were assessed in 12 apparently healthy men aged 50 ± 4 years who underwent equilibrium gated blood pool scintigraphy during supine and upright multistage bicycle ergometry before and after 10 days of bed rest. After bed rest, echocardiographically measured supine resting left ventricular end-diastolic volume decreased by 16% ($p < 0.05$). Peak oxygen uptake during *supine* effort after bed rest was diminished by 6% (p = not significant [NS]), whereas peak oxygen uptake during *upright* effort declined by 15% ($p < 0.05$). After bed rest, increases in heart rate were also greater during exercise in the upright than in the supine position ($p < 0.05$). Values of left ventricular ejection fraction increased normally during both supine and upright effort after bed rest and were higher than corresponding values before bed rest ($p < 0.05$). After bed rest, increased left ventricular ejection fraction and heart rate largely compensated for the reduced cardiac volume during supine effort, but these mechanisms were insufficient to maintain oxygen transport capacity at levels during upright effort before bed rest. These results indicate that orthostatically induced cardiac underfilling, not physical deconditioning or left ventricular dysfunction, is the major cause of reduced effort tolerance after 10 days of bed rest in normal middle-aged men.**

Bed rest contributes to reduced physical working capacity of patients after myocardial infarction.[1–3] To develop effective strategies against bed rest deconditioning it is important to characterize those factors that contribute to a reduced functional capacity after prolonged bed rest. We previously found in normal middle-aged men that peak oxygen transport capacity ($VO_2$ max) declined more significantly during upright than supine exercise after 10 days of bed rest.[4] This finding indicated that orthostatic factors played an important role in the decline in exercise capacity of these subjects after bed rest. Previous investigations of the effects of bed rest,[5–9] including the classic work of Saltin et al in 1968,[10] have been limited to young persons aged 19 to 25 years whose responses to bed rest may differ significantly from those of older persons who are at risk for myocardial infarction. Saltin et al found a decrease in exercise stroke volume during supine as well as upright effort after bed rest.[10] Because this finding could not be accounted for by orthostatic factors, these investigators suggested that prolonged bed rest adversely affects ventricular function. To evaluate this problem, we measured left ventricular function with radionuclide angiography in the same normal middle-aged men as in our previous report and compared their cardiovascular and left ventricular functional responses with upright and supine effort before and after 10 days of bed rest.

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## Methods

The 12 apparently healthy male subjects of the present report, aged 45 to 55 years, were previously described.[4] Significant abnormalities were excluded by a screening evaluation consisting of a detailed history, physical examination, complete blood count, urinary analysis, chest X-ray, resting electrocardiogram, maximal bicycle exercise test, and a chemistry panel consisting of measurements of fasting glucose, serum electrolytes, uric acid, cholesterol, calcium, phosphate,

and renal and liver function tests. Screening exercise testing was performed with the patient in the upright position on a Monark bicycle ergometer, the initial work load of 30 W increasing in 30-W increments every 3 minutes until voluntary physical exhaustion. Resting 12-lead electrocardiograms were normal in all 12 subjects and no chest discomfort, ischemic S-T segment depression, or significant ventricular arrhythmias were noted during or after the screening exercise test. The 12 subjects aged 50 ± 4 years gave written informed consent to participate as paid volunteers for the 15-day study. No subject was taking medication at the time of the study. Subjects were not allowed to smoke during the study or within 2 weeks before the start of the study.

The study group of 12 subjects was admitted to the Clinical Research Center of the Stanford University Hospital. During a 4-day ambulatory control period, subjects underwent M-mode echocardiographic imaging of the heart during supine rest. On the morning of the second day before bed rest, subjects performed 1 supine and 1 upright maximal exercise test on a bicycle ergometer. The 2 tests were separated by a 60-minute rest period. Six subjects were randomly assigned to perform supine exercise initially and 6 performed upright exercise initially. The same sequence was retained during testing after bed rest.

Supine and upright exercise testing consisted of 4 uninterrupted stages (I, II, III, and IV [maximum]) of exercise approximating 20, 45, 70, and 100% of the work loads utilized during the prehospital screening evaluation. Absolute work loads for these 4 stages were 250 ± 73, 525 ± 121, 835 ± 135, and 1,156 ± 194 kg/min, respectively. The same work loads, which were performed before and after bed rest, were designed to produce exhaustion during the 12 minutes available for radionuclide imaging of left ventricular function during exercise.

Upright testing was performed on a Schwinn electrically braked bicycle ergometer and supine exercise testing on a padded table with a Collins electrically braked bicycle ergometer. The physiologic comparability of work loads provided by these 2 ergometers were checked by $VO_2$ measurement before bed rest in these same 12 subjects. Oxygen uptake and heart rate were measured during the last 30 seconds of each work load. Heart rate was counted from an electrocardiographic record. Subjects used a Daniels respiratory valve and the volume of expired gas was measured with a Parkinson-Cowan high velocity low resistance meter. The composition of the expired air was determined by a Beckman E2 oxygen analyzer and a Godard capnograph carbon dioxide oxygen analyzer.

Equilibrium-gated cardiac blood pool scintigraphy was also performed during supine and upright exercise testing in 10 of the 12 subjects. Problems with computer acquisition prevented radionuclide data collection in the other 2 subjects. In vivo red cell labeling was achieved using the method of Pavel et al[11]; 15 mg of cold stannous pyrophosphate was injected intravenously, followed 30 minutes later by an intravenous injection of 20 to 25 mCi of technetium-99m pertechnetate. A gamma camera (Ohio Nuclear Series 120), fitted with a parallel hole, high resolution collimator, was positioned against the left chest wall for ideal separation of right and left ventricles in the left anterior oblique projection. For count data acquisition, the gamma camera was interfaced with an Informatek Simis IV computer. Radionuclide data were collected with the patient lying on the exercise table or sitting upright at rest on the bicycle for 4 minutes and during ≤12 minutes of graded bicycle ergometry.

All studies were subsequently analyzed automatically, that is, without operator intervention, using a previously reported series of algorithms.[12,13] The first step in processing was to combine the data from individual minutes at rest or at the same exercise level. All subjects completed 3 minutes of stage III exercise, during which values of heart rate averaged 88% of peak heart rate. Radionuclide data were omitted for stage IV (max) effort because an insufficient percentage of subjects (58%) was able to sustain exercise for up to 3 minutes of this peak work level both before and after bed rest. Subtraction of noncardiac background activity was achieved by a threshold technique.[12] Motion and phase analysis and edge detection algorithms were then used for automatic identification of the left ventricular end-diastolic region of interest.[13] The left ventricular time-activity curve was then obtained from this region and left ventricular ejection fraction was calculated from the standard formula: Ejection fraction = (end-diastolic counts − end-systolic counts)/end-diastolic counts.

Observer variability in the determination of ejection fraction was essentially removed because the studies were analyzed without operator intervention. Left ventricular stroke counts (end-diastolic − end-systolic counts), being the count correlates of stroke volume, were used to measure *relative* changes in left ventricular stroke volumes from rest to exercise during each study. Regional left ventricular function was assessed by analysis of wall motion: from static display of superimposed end-diastolic and end-systolic variables and regional ejection fraction images.

During the 10 days of bed rest, the subjects remained in the horizontal position continuously. M-mode echocardiographic imaging of the heart was repeated in the supine position 1 day before the end of bed rest. On the morning of the 10th day of bed rest, subjects repeated the same sequence of upright and supine exercise testing that they had undergone before bed rest. Before performing upright exercise, subjects sat on the exercise table with their legs dangling while blood pressure and heart rate stabilized. The interval between assumption of the sitting posture and the beginning of upright exercise averaged 17 ± 10 minutes. Initial orthostatic hypotension was often observed but no subject experienced syncope before upright exercise. No significant complications were noted during or after exercise testing.

**Statistical analysis:** The effects of test order, supine or upright position, and bed rest were tested using analysis of variance. If significance was found, paired $t$ testing was utilized for paired comparisons. Differences were considered significant for p values $<0.05$.

## Results

Test order did not have a statistically significant effect on values of oxygen uptake, heart rate, systolic blood pressure, or heart rate-systolic pressure product before and after bed rest.

**Effects of bed rest on cardiac volume:** Left ventricular end-diastolic volume measured echocardiographically in the supine position decreased 16%, from a baseline mean value of 121 ± 7 ml to 100 ± 9 ml after bed rest ($p < 0.05$).

**Effects of bed rest on oxygen uptake and exercise hemodynamics:** Values of oxygen uptake during all levels of submaximal and peak upright effort were significantly lower after bed rest and the decrease in oxygen uptake was significantly greater than during supine effort ($p < 0.05$, Fig. 1). Values of oxygen uptake during peak *upright* effort decreased by 15.1% from values before bed rest (21.9 ± 4.3 versus 25.8 ± 5.2 ml/kg/min, $p < 0.05$), whereas oxygen uptake during peak *supine* exercise after bed rest decreased only 6.1% (23.1 ± 4.7 versus 24.6 ± 5.1 ml/kg/min, respectively, NS). During

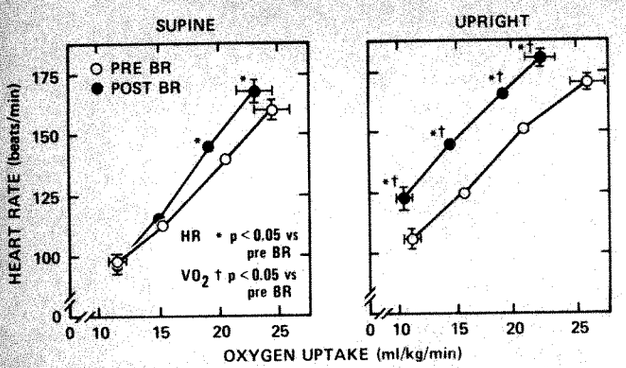



**FIGURE 1.** Changes in heart rate and oxygen uptake induced by bed rest. Values expressed are mean ± standard error of the mean. HR = heart rate; POST BR = after bed rest; PRE BR = before bed rest; $VO_2$ = oxygen uptake.

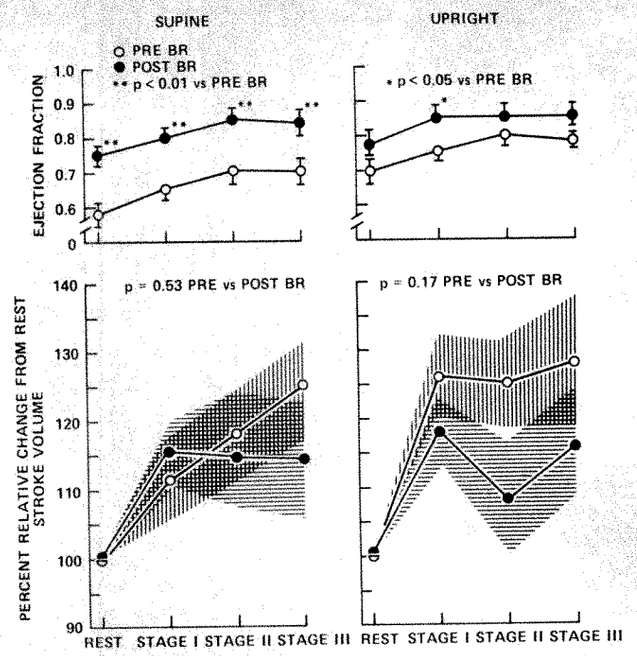



**FIGURE 2.** Changes induced by bed rest in left ventricular ejection fraction and stroke volume during rest and stages I to III of exercise. Values expressed are mean ± standard error of the mean. POST BR = after bed rest; PRE BR = before bed rest.

submaximal and peak upright effort after bed rest, heart rates were 10 to 21 beats/min higher than before bed rest ($p < 0.05$) (Fig. 1). In contrast, during supine effort after bed rest, heart rates were significantly augmented only during the last submaximal and peak work levels, by 5 and 8 beats/min, respectively ($p < 0.05$). Systolic blood pressures measured in either position were not significantly different after bed rest. Because of the augmentation of heart rate, the rate-pressure products during all levels of submaximal upright effort and during stage III of supine effort were increased after bed rest ($p < 0.05$). After bed rest, the rate-pressure products at all levels of submaximal upright effort were significantly higher than during submaximal supine effort ($p < 0.05$).

**Effect of bed rest on left ventricular function:** Before and after bed rest values of left ventricular ejection fraction at supine rest and during supine exercise were higher when the supine test was performed second than when it was performed first ($p < 0.01$). The test order did not significantly influence values of ejection fraction measured at upright rest or during upright effort.

Before bed rest the mean left ventricular ejection fraction at rest was lower in the supine than in the upright position (0.58, range 0.42 to 0.72 versus 0.69, range 0.53 to 0.84, respectively [$p < 0.01$]). In 3 subjects, values of left ventricular ejection fraction were <0.50 at supine rest. All subjects had values of ejection fraction >0.50 at upright rest and none demonstrated regional contraction abnormalities in either position. Left ventricular ejection fraction increased significantly between rest and stage III exercise: from 0.58 ± 0.11 to 0.70 ± 0.13 ($p < 0.001$) in the supine position and from 0.69 ± 0.10 to 0.78 ± 0.05 ($p < 0.001$) in the upright position. Only 1 subject failed to show a ≥0.05 increase in ejection fraction during stage III exercise: from 0.62 to 0.63 during supine effort and from 0.70 to 0.74 during upright exercise.

Values of rest and exercise left ventricular ejection fraction increased after bed rest: to 0.75 ± 0.08 and 0.77 ± 0.13 during supine and upright rest, respectively, and 0.84 ± 0.12 and 0.85 ± 0.11 during stage III supine and upright effort, respectively (Fig. 2, top). The higher values of ejection fraction after bed rest were significant at rest and during all levels of submaximal supine effort ($p < 0.01$). Values of left ventricular ejection fraction in the upright position increased after bed rest but these changes were statistically significant only at the stage I exercise level ($p < 0.05$). However, values of rest and exercise left ventricular ejection fractions were already significantly higher in the upright than supine position before bed rest ($p < 0.01$). Regional contraction abnormalities were not observed during supine or upright effort before or after bed rest.

Left ventricular end-systolic volume decreased normally ($p < 0.05$) during supine and upright exercise before and after bed rest. The augmentation of left ventricular stroke volume with exercise tended to be lower after bed rest than before—especially in the upright position (Fig. 2, bottom): The increase in left ventricular stroke volume at stage III effort was 125 ± 25% and 127 ± 26% of resting values during supine and upright effort, respectively, before bed rest versus 114 ± 29% and 116 ± 19%, respectively, during effort after bed rest (NS).

## Discussion

A decrease in physical working capacity in the supine position reflects central (cardiac) and peripheral (circulatory and musculoskeletal) deconditioning effects of bed rest, whereas a further decrease in physical working capacity in the upright position reflects the additional influence of orthostatic stress.

The exact mechanisms and the extent of their contribution to the decrease in exercise capacity after bed rest have not been fully defined in previous studies, because left ventricular function has not been measured, and the effects of bed rest on the cardiovascular responses to upright and supine exercise have not been directly compared in the same subjects as in the present study. For example, in the study by Saltin et al,[10] supine effort was performed on a bicycle ergometer and was submaximal whereas upright effort was performed on a treadmill and was maximal.

The extent of physical deconditioning in our normal middle-aged subjects was small, as evidenced by the small nonsignificant decrease in peak oxygen uptake during supine effort after bed rest. The 6% decrease in $VO_2$ max seen in our subjects was lower than the 9 to 13% decrease reported previously in young subjects during supine effort after 2 to 4 weeks of bed rest.[5–7] This may partially reflect the longer duration of bed rest in these studies as well as the fact that younger subjects are likely to be more athletically conditioned beforehand and thus subject to greater physical deconditioning. In other studies of young subjects, decreases in $VO_2$ max of 28% and 22% have been observed during upright effort after a similar duration of bed rest[9,10] and this decrease appears substantially larger than that measured during supine effort after bed rest. In the present study, we found that the decrease in peak oxygen uptake during upright effort was 2.5 times as large as that seen during supine effort after 10 days of bed rest. This finding suggests the importance of orthostatic factors.

Because Saltin et al noted a reduction in rest and exercise stroke volume even in the supine position, which could not be attributed to impairment of venous return as in the upright position, these authors postulated that bed rest might adversely affect myocardial function.[10] Blood volume decreases as much as 600 to 700 ml after 1 or more weeks of enforced immobilization.[6,10,14] In fact, in our subjects we found that echocardiographically measured left ventricular end-diastolic volume diminished 16% in the supine position and presumably more in the upright position, although this was not measured. Saltin and other investigators[10,14] have also found on chest radiography a substantial decrease in total heart volume during prolonged bed rest. Although venous return is facilitated in the supine position, a diminished volume may contribute to the decrease in stroke volume, peak cardiac output, and $VO_2$ max even during supine exercise. This decrease in cardiac volume is likely to be greater in young, athletically conditioned subjects. For example, in the study of Saltin et al the 2 subjects who were best conditioned before bed rest had the highest absolute values of heart volume and the greatest absolute decrease in heart volume after bed rest. In our middle-aged subjects we found no evidence for an adverse effect of bed rest on left ventricular function: Left ventricular ejection fraction was augmented during supine and upright exercise testing after bed rest. The augmentation of both left ventricular ejection fraction and exercise heart rate appeared to be compensatory mechanisms for a lower cardiac volume (preload) after bed rest. During supine effort after bed rest, these compensatory mechanisms appeared to be largely adequate because peak oxygen uptake did not decline significantly.

However, hypovolemia leads to even greater cardiac underfilling in the upright position because another 300 to 800 ml of blood is sequestered in the legs[15,16] and this orthostatic stress may be further accentuated after bed rest.[17] Even before bed rest, levels of heart rate and left ventricular ejection fraction in our subjects were higher at upright rest than at supine rest. We attribute this to a normal increase in sympathetic nervous activity in response to orthostatic stress.[17] After bed rest, values of ejection fraction at upright rest were even closer to their physiologic maximum, thus limiting the extent to which a further increase in left ventricular ejection fraction during upright effort could contribute to sustaining stroke volume. Thus, despite augmentation of their left ventricular ejection fraction and heart rate to levels equal to or exceeding those during supine exercise, our subjects were unable to compensate for cardiac underfilling and their $VO_2$ max decreased 15% after bed rest. The importance of orthostatic factors is underscored in the recent study by Convertino et al.[18] These investigators measured a 14% decrease in $VO_2$ max during upright bicycle effort in subjects after 14 days of bed rest but only a 5% decrease in subjects exposed to a reverse gradient garment simulating the effects of standing for 3 hours/day during this interval. Exposure to orthostatic effects also partially reversed the loss of plasma volume associated with bed rest.[18]

**Clinical implications:** Although our normal subjects manifested no deterioration in cardiac function, bed rest resulted in an augmented heart rate and rate-pressure product during submaximal effort. These factors are associated with increased myocardial oxygen demands[19,20] which are potentially hazardous to patients with coronary heart disease, especially those recovering from myocardial infarction. The findings of the present study indicate that these adverse effects of bed rest deconditioning can be largely obviated by early exposure to gravitational stress. This underscores the importance of sitting and of early ambulation in preventing or limiting unnecessary physical debility after myocardial infarction. Formal programs of in-hospital rehabilitation emphasizing exercise training may not be necessary for this purpose.

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## References

1. **Levine SA, Lown B.** "Armchair" treatment of acute coronary thrombosis. JAMA 1952;148:1365–1369.
2. **Fareeduddin K, Abelmann WL.** Impaired orthostatic tolerance after bed rest in patients with myocardial infarction. N Engl J Med 1969;280:345–350.
3. **Wenger NK.** The physiologic basis for early ambulation after myocardial infarction. In: Wenger NK, Brest AN, eds. Exercise and the Heart. Philadelphia: FA Davis, 1976;107–115.
4. **Convertino V, Hung J, Goldwater D, DeBusk RF.** Cardiovascular responses to exercise to middle-aged men after 10 days of bed rest. Circulation 1982;65:134–140.
5. **Georgievskii VS, Kakurin LI, Katkovskii BS, Senkevich YA.** Maximum

oxygen consumption and functional state of the circulation in simulated zero gravity. In: Lauer NV, Kolchinskaya AZ, eds. The Oxygen Regime of the Organism and Its Regulation. Kiev: Naukova Dimka, 1966:181–184.
6. **Stremel RW, Convertino VA, Bernauer EM, Greenleaf JE.** Cardiorespiratory deconditioning with static and dynamic leg exercise during bed rest. J Appl Physiol 1976;41:905–909.
7. **Convertino VA, Stremel RW, Bernauer EM, Greenleaf JE.** Cardiorespiratory responses to exercise after bed rest in men and women. Acta Astonautica 1977;4:895–905.
8. **Taylor HL, Henschel A, Brozek J, Keys A.** Effects of bed rest on cardiovascular function and work performance. J Appl Physiol 1949;2:233–239.
9. **Miller PB, Johnson RL, Lamb LE.** Effects of moderate physical exercise during four weeks of bedrest on circulatory functions in man. Aerospace Med 1965;36:1077–1082.
10. **Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Wildenthal K, Capman CB.** Response to exercise after bedrest and after training. Circulation 1968;38:Suppl VII:VII-1–VII-78.
11. **Pavel DG, Zimmer AM, Patterson VN.** In-vivo labeling of red blood cells with $^{99m}Tc$: a new approach to blood pool visualization. J Nucl Med 1977;18:305–308.
12. **Goris ML, Briandet PA, Thomas AJ, McKillop JH, Sneed P, Wiklander DP.** A thresholding for radionuclide angiocardiography. Invest Radiol 1981; 16:115–119.
13. **Goris ML, McKillop JH, Briandet PA.** A fully automated determination of the left ventricular region of interest in nuclear angiocardiography. Cardiovasc Intervent Radiol 1981;4:117–123.
14. **Taylor HL, Erickson L, Henschel A, Keys A.** The effect of bed rest on blood volume of normal young men. Am J Physiol 1945;144:227–232.
15. **Sjostrand T.** The regulation of blood distribution in man. Acta Physiol Scand 1952;26:312–327.
16. **Bevegard S, Holmgren A, Jonsson B.** The effect of body position on the circulation at rest and during exercise with special reference to the influence on the stroke volume. Acta Physiol Scand 1960;49:279–298.
17. **Chobanian AV, Lille RD, Tercyak A, Blevins P.** The metabolic and hemodynamic effects of prolonged bed rest in normal subjects. Circulation 1974;49:551–559.
18. **Convertino VA, Sandler H, Webb P, Annis JF.** Effect of induced venous pooling on cardiorespiratory responses to exercise after bed rest. Am J Physiol, in press.
19. **Nelson RR, Gobel FL, Jorgensen CR, Wang K, Wang Y, Taylor HL.** Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. Circulation 1974;50:1179–1189.
20. **Gobel FL, Nordstrom LA, Nelson RR, Jorgensen CR, Wang Y.** The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 1978;57:549–556.

# Cardiac Performance in Thyrotoxicosis: Analysis of 10 Untreated Patients

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**This study attempts to define cardiac performance at rest and during exercise in patients with untreated thyrotoxicosis. We studied 7 women and 3 men, aged 23 to 59 years (40 ± 10, mean ± standard deviation [SD]) and compared the results with those obtained in 12 normal subjects. In patients with thyrotoxicosis, the rhythm was sinus and the only untoward symptom was palpitations; the resting electrocardiographic results were normal in 8 patients and showed left ventricular hypertrophy in 2 patients; the left ventricular ejection fraction and volumes (measured by radionuclide ventriculography) were normal at rest. During exercise, 1 patient had dyspnea and 7 had leg fatigue; 2 were asymptomatic. Also, 7 patients had ≥5% increase in left ventricular ejection fraction, 2 had no change, and 1 had a decrease. In all 10 patients, the exercise ejection fraction was ≥60%. All normal subjects had a ≥5% increase in ejection fraction during exercise. There were no significant differences at rest between patients with thyrotoxicosis and normal subjects in blood pressure, ejection fraction, end-diastolic volume, stroke volume, end-systolic volume, or cardiac output, but the heart rate was significantly higher in patients with thyrotoxicosis (91 ± 10 versus 80 ± 12 beats/min, p <0.05). During exercise, there were no significant differences between patients with thyrotoxicosis and normal subjects in blood pressure, end-diastolic volume, stroke volume, end-systolic volume, or cardiac output. The exercise ejection fraction was significantly lower in patients with thyrotoxicosis than in normal subjects (68 ± 10% versus 75 ± 4%, p <0.05). *Cardiac performance is normal at rest in patients with thyrotoxicosis, but during exercise abnormal left ventricular reserve occurs in some patients.***

Thyroid hormones have profound effects on the metabolism of all tissues of the body, including the heart.[1,2] Thyrotoxicosis is more common in women than in men. Palpitations, dyspnea, tachycardia, and an increase in systolic pressure occur in approximately 30% of these patients. Also, many patients have an increase in the cardiac index, systolic ejection rate, coronary blood flow, and pulse pressure, but a decrease in systemic vascular resistance as well as in the systolic ejection and preejection periods.[3–10] The cardiac changes might be partly due to an increase in metabolic demand caused by the peripheral effects of thyroid hormones, but the cardiac output has been reported to be greater than the total body oxygen consumption, indicating some direct action on the heart as well. Atrial fibrillation might be seen in some patients.

The effects of thyroid hormones on the heart are either direct or indirect. The direct effects are complex and may include increased synthesis of myosin as well as alteration of the structure of myosin, such that the new myosin has better contractile properties.[11–14] Thyroid hormones are also known to enhance the enzymatic activity of the myocardium. The indirect effects are due either to increased activity of the sympathoadrenal system or enhanced cardiac response to normal sympathetic stimulation. Thus, tachycardia and the increase in cardiac output and contractility can be reduced by beta-adrenergic blocking agents.[15,16] The presence of low or normal levels of norepinephrine, epinephrine, and dopamine beta hydroxylase in the plasma and urine suggests that the function of the

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**TABLE I Laboratory Data in Patients With Hyperthyroidism**

| Patients | $T_4$ (4.5–11.5 μg/dl) | Ratio $T_3U$ (0.8–1.2) | $T_3$ by RIA (110–190 ng/dl) |
|---|---|---|---|
| 1 | 19.7 | 1.33 | 450 |
| 2 | 10.4 | 1.22 | 430 |
| 3 | 17.4 | 1.00 | 405 |
| 4 | 15.2 | 1.02 | 320 |
| 5 | 19.4 | 1.25 | 415 |
| 6 | 13.5 | 1.25 | 430 |
| 7 | 14.9 | 0.7 | 221 |
| 8 | 16.6 | 1.06 | 280 |
| 9 | 20.8 | 1.10 | 357 |
| 10 | 17.4 | 0.85 | 380 |

$T_4$ = serum thyroxine level by radioimmunoassay (RIA); $T_3U$ = triiodothyronine resin sponge uptake; $T_3$ by RIA = triiodothyronine serum level by radioimmunoassay. Normal levels are given in parentheses.

sympathoadrenal system is probably not altered in these patients.[17]

To date, little has been reported concerning cardiac performance in patients with hyperthyroidism, especially during exercise.[18–20] This study evaluates cardiac peformance at rest and during upright exercise in 10 patients with untreated thyrotoxicosis.

## Methods

**Patient population:** The patient population consisted of 7 women and 3 men aged 23 to 59 years (mean ± SD 40 ± 10). The diagnosis of Graves disease with hyperthyroidism was confirmed by appropriate laboratory tests (Table I). The duration of symptoms was 3 to 6 months in all patients. No patient had noticeable weight loss. The rhythm was normal sinus in all patients. The only symptom in these patients was palpitations. Four patients (Patients 5, 6, 9, and 10) had been receiving small doses of propranolol (10 mg 4 times daily) for approximately 7 days; this was discontinued 1 day before the exercise studies. No patient had a known history of heart disease, specifically angina pectoris or dyspnea. The electrocardiographic results were normal in 8 patients but showed left ventricular hypertrophy in 2. The criteria for left ventricular hypertrophy were those of Romhilt and Estes[21] and were based upon a "point score" system. A minimal score of 6 points was needed to define left ventricular hypertrophy.

All patients underwent symptom-limited upright exercise testing on a bicycle ergometer (Quinton Instruments). The electrocardiograms (leads aVF and $V_5$) were continuously monitored, and blood pressure was measured every 2 minutes during exercise and recovery. The initial work load was 200 kpm/min and was increased by 100 kpm/min every 2 minutes until the endpoints of exercise, which in these patients were dyspnea (1 patient) and leg fatique (7 patients); the remaining 2 patients stopped the exercise because they achieved the target heart rate without symptoms.

Radionuclide ventriculograms at rest and during peak exercise were obtained with a computerized multicrystal gamma camera (Baird-Atomic System-77). The left ventricular ejection fraction, end-diastolic volume, end-systolic volume, stroke volume, and cardiac output were measured according to the method described previously.[22,23] Previous studies from this laboratory have shown excellent correlation between left ventricular ejection fraction, end-diastolic volume, and end-systolic volume measured with radionuclide ventriculography compared with similar measurements obtained by contrast angiography.[22]

The results in the study patients were compared with those obtained in 12 normal subjects who were evaluated for nonspecific chest pain and were found, upon cardiac catheterization, to have normal resting hemodynamics, normal left ventriculograms, and normal coronary angiograms. The age range in the normal subjects was 25 to 45 years (mean ± SD 38 ± 7).

**Statistical analysis:** The paired Student's $t$ test was used to compare differences in individual measurements at rest and during exercise in each group. Significance of differences between the groups was obtained using the unpaired $t$ test. A probability value of $<0.05$ was considered significant.

## Results

**Normal subjects:** The ejection fraction at rest was normal and increased during exercise by at least 5% in all subjects. During exercise, there was a significant increase in heart rate, systolic blood pressure, stroke volume, and cardiac output, but no significant change in diastolic blood pressure, end-diastolic volume, or end-systolic volume (Table II). The end-systolic volume in some normal subjects during exercise was greater than the end-systolic volume at rest. However, in these patients, the increase in end-diastolic volume was greater during exercise, resulting in a higher stroke volume and ejection fraction.

**TABLE II Data in Normal Subjects and Patients with Thyrotoxicosis**

| | Normal Subjects | | | Patients With Thyrotoxicosis | | | p Value: NL Versus Pts | |
|---|---|---|---|---|---|---|---|---|
| | R | Ex | p Value | R | Ex | p Value | R | Ex |
| HR | 80 ± 12 | 163 ± 7 | <0.001 | 91 ± 10 | 160 ± 16 | <0.001 | <0.05 | NS |
| SBP | 122 ± 20 | 168 ± 22 | <0.001 | 125 ± 15 | 169 ± 15 | <0.001 | NS | NS |
| DBP | 82 ± 11 | 88 ± 12 | NS | 75 ± 13 | 81 ± 14 | <0.05 | NS | NS |
| EF | 62 ± 6 | 75 ± 4 | <0.001 | 61 ± 10 | 68 ± 10 | <0.0 | NS | <0.05 |
| EDV | 153 ± 25 | 174 ± 37 | NS | 150 ± 49 | 159 ± 50 | NS | NS | NS |
| ESV | 58 ± 18 | 45 ± 19 | NS | 59 ± 26 | 51 ± 19 | NS | NS | NS |
| SV | 95 ± 14 | 120 ± 34 | <0.001 | 90 ± 26 | 108 ± 35 | NS | NS | NS |
| CO | 7.7 ± 1.1 | 21.1 ± 3.1 | <0.001 | 7.7 ± 2 | 17 ± 6 | <0.001 | NS | NS |
| Ex duration | ... | 11 ± 2 | ... | ... | 11.7 ± 1.2 | ... | ... | NS |
| BSA | 1.97 ± 0.16 | ... | ... | 1.78 ± 0.13 | ... | ... | <0.01 | ... |

BSA = body surface area ($m^2$); CO = cardiac output (liters/min); DBP = diastolic blood pressure; EDV = end-diastolic volume (ml); EF = left ventricular ejection fraction; ESV = end-systolic volume; Ex = exercise; HR = heart rate (beats/min); NL = normal; NS = not significant; Pts = patients; R = rest; SBP = systolic blood pressure; SV = stroke volume.

**TABLE III Data in Patients with Thyrotoxicosis**

| Pt | Age (yr) & Sex | BSA ($m^2$) | ECG | Medication | HR | BP | EF (%) | EDV | ESV | SV | CO |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 23M | 1.93 | NL | . . . | R 99 | 120/55 | 62 | 208 | 79 | 129 | 12.7 |
| | | | | | Ex 165 | 170/65 | 75 | 240 | 60 | 180 | 29.7 |
| 2 | 58F | 2.0 | NL | . . . | R 110 | 140/70 | 65 | 131 | 46 | 85 | 9.3 |
| | | | | | Ex 150 | 160/70 | 64 | 172 | 62 | 110 | 16.5 |
| 3 | 39F | 1.6 | NL | . . . | R 90 | 150/90 | 55 | 153 | 69 | 84 | 7.5 |
| | | | | | Ex 168 | 200/110 | 60 | 123 | 49 | 74 | 17.4 |
| 4 | 40M | 1.95 | LVH | . . . | R 87 | 110/60 | 58 | 132 | 55 | 77 | 6.6 |
| | | | | | Ex 164 | 170/70 | 64 | 204 | 73 | 130 | 21.3 |
| 5 | 47F | 1.67 | NL | P | R 80 | 110/65 | 55 | 213 | 96 | 117 | 9.3 |
| | | | | | Ex 164 | 160/70 | 67 | 190 | 62 | 127 | 20.8 |
| 6 | 31F | 1.72 | LVH | P | R 100 | 130/70 | 61 | 102 | 40 | 62 | 6.2 |
| | | | | | Ex 186 | 160/70 | 80 | 89 | 18 | 72 | 13.3 |
| 7 | 52F | 1.91 | NL | . . . | R 93 | 110/90 | 79 | 64 | 13 | 51 | 4.7 |
| | | | | | Ex 123 | 150/90 | 78 | 98 | 21 | 76 | 9.3 |
| 8 | 37F | 1.86 | NL | . . . | R 88 | 120/85 | 71 | 163 | 47 | 116 | 6.2 |
| | | | | | Ex 165 | 155/85 | 62 | 139 | 53 | 86 | 14.1 |
| 9 | 38M | 1.82 | NL | P | R 78 | 140/90 | 51 | 183 | 89 | 93 | 7.2 |
| | | | | | Ex 150 | 180/90 | 66 | 175 | 60 | 116 | 17.3 |
| 10 | 38F | 1.73 | NL | P | R 89 | 125/80 | 55 | * | * | * | * |
| | | | | | Ex 167 | 185/90 | 60 | 162 | 65 | 97 | 16.2 |

* Volumes at rest were not measured in this patient. BP = blood pressure (systolic and diastolic in mm Hg); BSA = body surface area ($m^2$); CO = cardiac output (liters/min); ECG = electrocardiogram; EDV = end-diastolic volume (ml); EF = left ventricular ejection fraction; ESV = end-systolic volume (ml); Ex = exercise; HR = heart rate (beat/min); LVH = left ventricular hypertrophy; NL = normal; P = propranolol; Pt = patient; R = rest; SV = stroke volume (ml); . . . = none.

**Patients with thyrotoxicosis:** Resting sinus tachycardia, as expected, was common. The systolic and diastolic blood pressure values were normal in all patients. The resting left ventricular ejection fraction and volumes were also normal. Four patients had high resting cardiac output levels (cardiac index ≥4.5 liters/min/$m^2$); in the remaining patients the cardiac output was normal (Table III).

During exercise, 7 patients had leg fatigue; 2 had no symptoms (Patients 8 and 10); Patient 9 had dyspnea. The exercise electrocardiographic results were normal in all patients.

The left ventricular ejection fraction during exercise was normal (≥60%) in all patients. Seven patients had a ≥5% increase in ejection fraction with exercise. In 2 patients, there was no change in ejection fraction with exercise (Patients 2 and 7); 1 patient (Case 8) had a decrease in ejection fraction with exercise. As a group, there were no significant changes in the end-diastolic and end-systolic volumes during exercise. Four patients had an increase in end-systolic volume with exercise (Patients 2, 4, 7, and 8). Three of the 4 patients also showed either no change or a decrease in ejection fraction with exercise; in the remaining patient, the ejection fraction increased with exercise (Table II).

**Correlation between normal subjects and patients with thyrotoxicosis:** At rest, there were no significant differences between the normal subjects and patients with thyrotoxicosis in systolic blood pressure, diastolic blood pressure, ejection fraction, end-diastolic volume, stroke volume, end-systolic volume, or cardiac output. The heart rate at rest was significantly higher in patients with thyrotoxicosis ($p < 0.05$) (Table II). During exercise, there were no significant differences in normal subjects and patients with thyrotoxicosis in heart rate, systolic blood pressure, diastolic blood pressure, end-diastolic volume, end-systolic volume, stroke volume, or exercise duration. The ejection fraction during exercise was significantly higher in normal subjects than in those with thyrotoxicosis ($p < 0.05$) (Table II).

## Discussion

Our study is the first to describe changes in global left ventricular function and volume during exercise in patients with untreated thyrotoxicosis. Our results indicate that some patients have an abnormal ejection fraction response to exercise, as defined by failure to increase the ejection fraction from rest to exercise by at least 5% or by an actual decrease in ejection fraction during exercise. This incidence of abnormal left ventricular response to exercise is much lower than that reported by Shafer and Bianco.[20] These investigators found that the ejection fraction response to exercise was abnormal in 7 of the 8 patients with thyrotoxicosis. The reasons for the differences between our results and those of Shafer and Bianco are unclear, but several mechanisms can be postulated. First, all patients studied by Shafer and Bianco were men; this is unusual, since thyrotoxicosis is more common in women, and therefore underlying heart disease in these patients cannot be excluded with certainty.

Second, it is possible that the degree of thyrotoxicosis of our patients differs from those of the other investigators' patients; this possibility, however, is extremely unlikely, since the serum levels of $T_4$ were not significantly different in the 2 sets of patients. Furthermore, the mean resting heart rate was almost identical in both studies.

Third, myocardial oxygen consumption ($M\dot{V}O_2$) during exercise may have differed in the 2 studies; systolic blood pressure was higher in the study of Schafer

and Bianco than in our study. However, the exercise heart rate was higher in our study, and so the double product should not differ in the 2 studies.

Fourth, the method of study was different in the 2 studies. Schafer and Bianco used supine exercise for their patients and measured ejection fraction by the gated equilibrium technique; we used upright exercise for our patients and measured ejection fraction by the first-pass method with a computerized multicrystal gamma camera.

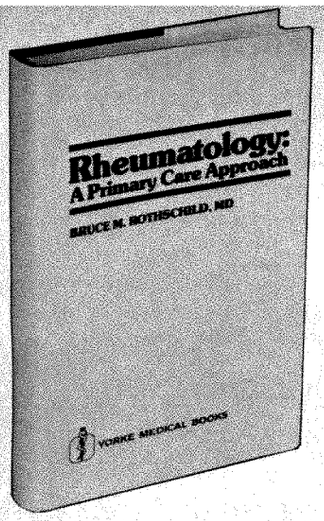
Finally, measurements of left-ventricular volumes were not reported by the other investigators; our results are shown in Tables II and III.

In our study, there was no significant change in end-diastolic and end-systolic volumes during exercise. Four of our 10 patients (including the 3 who had abnormal ejection fraction responses) had increases in the end-systolic volume with exercise. We previously showed that a slight increase in the end-systolic volume during exercise may occur even in normal subjects.[21] In these subjects, however, the end-diastolic volume increases to a greater extent during exercise, resulting in a higher stroke volume and ejection fraction. Our study also demonstrated no significant differences at rest in patients with thyrotoxicosis and normal subjects in systolic blood pressure, diastolic blood pressure, ejection fraction, end-diastolic volume, end-systolic volume, stroke volume, or cardiac output, whereas the resting heart rate, as expected, was higher in patients with thyrotoxicosis.

Similarly, during exercise, there were no significant differences between patients with thyrotoxicosis and normal subjects in heart rate, blood pressure, end-diastolic volume, end-systolic volume, stroke volume, and cardiac output, but the ejection fraction was lower in patients with thyrotoxicosis. The cardiac index was higher than 4.5 liters/m/m$^2$ in 5 of the 10 patients with thyrotoxicosis, but this finding was also seen in many of our normal subjects.

## References


1. **Symons C.** Thyroid heart disease. Br Heart J 1979;41:257–262.
2. **Zaimis E, Papadaki L, Ash ASF, Larbi E, Kakari S, Matthew M, Paradellis A.** Cardiovascular effects of thyroxine. Cardiovasc Res 1969;3:118–133.
3. **Taylor RR, Covell JW, Ross J Jr, Lewis R, McGill R.** Influence of the thyroid state on left ventricular tension velocity relations in the intact, sedated dog. J Clin Invest 1969;48:775–784.
4. **Amidi M, Leon DF, deGroot WJ, Kroetz FW, Leonard JJ.** Effect of the thyroid state on myocardial contractility and ventricular ejection rate in man. Circulation 1968;38:229–239.
5. **Parisi AF, Hamilton BP, Thomas CN, Mazzaferri EL.** The short cardiac preejection period; an index of thyrotoxicosis. Circulation 1974;49:900–904.
6. **Bussino RA, Spann JF, Pool PE, Braunwald E.** Influence of the thyroid state on the intrinsic contractile properties and the energy stores of the myocardium. J Clin Invest 1967;46:1669–1682.
7. **Hillis WS, Bremmer WF, Lawrie TDV, Thomson JA.** Systolic time intervals in thyroid disease. Clin Endocrinol 1975;4:617–627.
8. **Cohen J.** Role of endocrine factors in the pathogenesis of cardiac hypertrophy. Circ Res 1974;35 Suppl II:II-49–II-57.
9. **Skelton CL, Prindle KH, Epstein SE.** Regression of cardiac hypertrophy induced by chronic hyperthyroidism (abstr). Circulation 1972;46:Suppl II: II–46.
10. **deGroot WJ, Leonard JJ.** Hyperthyroidism as a high cardiac output state. Am Heart J 1970;79:265–275.
11. **Yazaki Y, Raben MS.** Effect of thyroid state on the enzymatic characteristics of cardiac myosin. Circ Res 1975;36:208–215.
12. **Sanford CF, Griffin EE, Wildenthal K.** Synthesis and degradation of myocardial protein during the development and regression of thyroxine-induced cardiac hypertrophy in rats. Circ Res 1978;43:688–694.
13. **Philipson KD, Edelman IS.** Thyroid hormone control of $Na^{+-}$ $K^{+-}$ ATPase and $K^{+-}$ dependent phosphatase in rat heart. Am J Physiol 1977;232: C196–201.
14. **Kunos G, Vermes-Kunos I, Nickerson M.** Effects of thyroid state on adrenoreceptor properties. Nature 1974;250:779–781.
15. **Grossman W, Robin NI, Johnson LW, Brooks H, Selenkow HA, Dexter L.** Effect of beta blockade on the peripheral manifestations of thyrotoxicosis. Ann Intern Med 1971;74:875–884.
16. **Howitt G, Rowlands DJ.** Beta-sympathetic blockade in hyperthyroidism. Lancet 1966;1:628–631.
17. **Bayliss RIS, Edwards OM.** Urinary excretion of free catecholamines in Graves' disease. Endocrinology 1971;49:167–170.
18. **Nixon JV, Anderson RJ, Cohen ML.** Alterations in left ventricular mass and performance in patients treated effectively for thyrotoxicosis. A comparative echocardiographic study. Am J Med 1979;67:268–276.
19. **Lewis BS, Ehrenfeld EN, Lewis N, Gotsman MS.** Echocardiographic left ventricular function in thyrotoxicosis. Am Heart J 1979;97:460–468.
20. **Shafer RB, Bianco JA.** Assessment of cardiac reserve in patients with hyperthyroidism. Chest 1980;78:269–273.
21. **Romhilt DW, Estes EH Jr.** A point score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 1968;75:752–758.
22. **Iskandrian AS, Hakki AH, Kane SA, Segal BL.** Quantitative radionuclide angiography in assessment of hemodynamic changes during upright exercise. Observations in normal subjects, patients with coronary artery disease and patients with aortic regurgitation. Am J Cardiol 1981;48: 239–246.
23. **Scholtz PM, Rerych SK, Moran JF, Newman GE, Douglas JM, Sabiston DS, Jones RH.** Quantitative radionuclide angiography. Cathet Cardiovasc Diagn 1980;6:265–284.




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Director, Division of Rheumatology, University Health Sciences, The Chicago Medical School Chief, Section of Rheumatology, V. A. Medical Center North Chicago, Illinois

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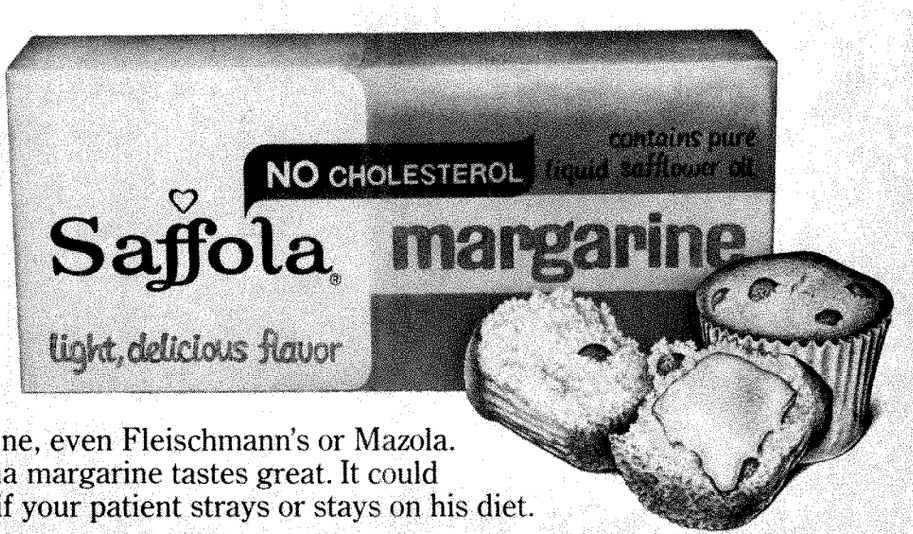
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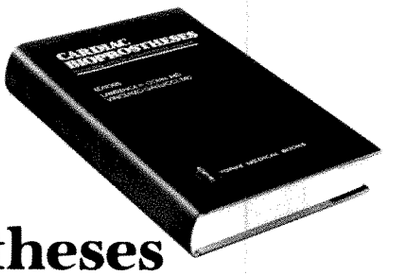

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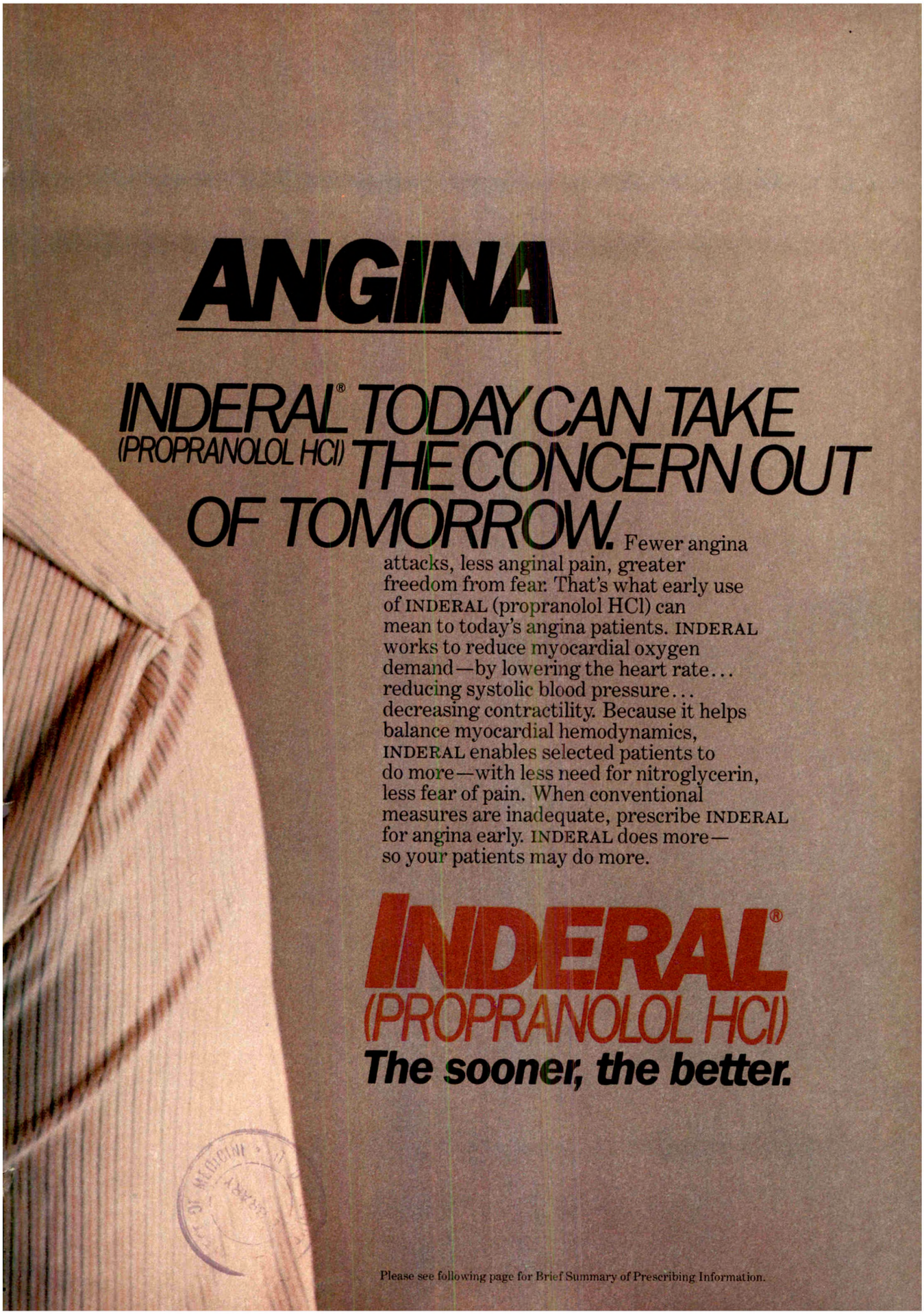
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A YORKE MEDICAL JOURNAL




ANGINA
INDERAL® (PROPRANOLOL HCl) TODAY CAN TAKE THE CONCERN OUT OF TOMORROW.
Fewer angina attacks, less anginal pain, greater freedom from fear. That's what early use of INDERAL (propranolol HCl) can mean to today's angina patients. INDERAL works to reduce myocardial oxygen demand—by lowering the heart rate... reducing systolic blood pressure... decreasing contractility. Because it helps balance myocardial hemodynamics, INDERAL enables selected patients to do more—with less need for nitroglycerin, less fear of pain. When conventional measures are inadequate, prescribe INDERAL for angina early. INDERAL does more—so your patients may do more.
INDERAL®
(PROPRANOLOL HCl)
The sooner, the better.
Please see following page for Brief Summary of Prescribing Information.

# INDERAL®
## (PROPRANOLOL HCl)

# THE MOST WIDELY PRESCRIBED BETA BLOCKER IN THE WORLD.




The appearance of these tablets is a trademark of Ayerst Laboratories

*BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
**Inderal®** (propranolol hydrochloride)

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

### CONTRAINDICATIONS

1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless it is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

### WARNINGS

CARDIAC FAILURE. In congestive heart failure, inhibition with beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients already receiving digitalis, propranolol may reduce the positive inotropic action of digitalis and may have an additive depressant effect on AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac failure has developed during propranolol therapy. At the first sign of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and observed closely. a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery. In case of emergency surgery, the effects of propranolol can be reversed by administration of beta-receptor agonists such as isoproterenol or levarterenol, but such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (e.g., CHRONIC BRONCHITIS, EMPHYSEMA), administer with caution, since propranolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA. Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY. Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

### PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

### ADVERSE REACTIONS

*Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat; laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

### HOW SUPPLIED

TABLETS

– Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains 10 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-91). Also in unit dose package of 100 (NDC 0046-0421-99).

– Each hexagonal-shaped, blue, scored tablet is embossed with an "I" and imprinted with "INDERAL 20," contains 20 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0422-81) and 1,000 (NDC 0046-0422-91). Also in unit dose package of 100 (NDC 0046-0422-99).

– Each hexagonal-shaped, green, scored tablet is embossed with an "I" and imprinted with "INDERAL 40," contains 40 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0424-81) and 1,000 (NDC 0046-0424-91). Also in unit dose package of 100 (NDC 0046-0424-99).

– Each hexagonal-shaped, yellow, scored tablet is embossed with an "I" and imprinted with "INDERAL 80," contains 80 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0428-81) and 1,000 (NDC 0046-0428-91). Also in unit dose package of 100 (NDC 0046-0428-99).

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Store at room temperature (approximately 25° C).

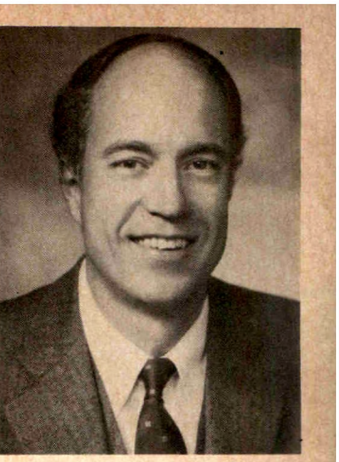
INJECTABLE

– Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

Store at room temperature (approximately 25° C).

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# Paper Accepted/Abstract Rejected or Vice Versa: Differences In the Grading of Abstracts and the Reviewing of Manuscripts

Through the years I often have been amazed that an abstract I considered excellent was rejected, and yet when the subject of that abstract was submitted later in manuscript form, it was rapidly accepted. The grading of abstracts and the reviewing of manuscripts are 2 entirely different processes.

I have had the privilege of serving on program committees of both The American Heart Association and The American College of Cardiology, and this responsibility included grading abstracts for presentation at the annual scientific sessions. An abstract from either society is graded similarly—by a score of 0 to 10, with a 10 representing the highest quality. Each abstract is graded by about 7 to 10 reviewers, and the final grade given is the average of the multiple grades. The most common grade given is a 7; very few abstracts receive grades <5. The average grade of abstracts accepted for presentation—either from the podium or by poster—is about 7.7. If the grader happens to be an author of an abstract, he or she is instructed to use the letter *P* for "prejudiced," and if the grader is "unqualified"—that is, does not have sufficient knowledge of the subject of the abstract—the letter *X* is used. Although a single line is provided for it, no explanation or justification for the grade is required. On one program committee of which I was a member, 50% of the abstracts were graded 1 by one committee member, whereas another member on the same committee registered a 7 or 8 on all abstracts he graded. Few graders give many 10's, and some rarely give a 9. Of course, the most useful grader is the one who clearly differentiates the good abstracts from the bad ones. In the 1960s, only the members of the program committee graded the abstracts for 1 of the 2 national cardiology societies, and that meant that each member graded a large number—about 300. During recent years both organizations have used non-committee member experts as graders, so that no grader is asked to review more than about 100 abstracts; the period of time allowed, however, remains short—about 2 weeks.

In contrast, when a reviewer recommends to an editor that he or she accept or reject a manuscript, that recommendation must be substantiated by criticisms or the lack of them. Although one could argue that because abstracts have far more graders than manuscripts have reviewers, the selection process for abstracts is a just one. I have no constructive suggestions for how to improve the abstract grading process. My enthusiasm, however, for abstracts is far weaker than that for manuscripts; in fact, my enthusiasm is roughly proportional to the amount of space occupied by a published abstract compared with that occupied by an average published manuscript.

Several years ago 3 of my abstracts were rejected for presentation at the annual meeting of one of the 2 cardiology societies, and all 3 were accepted without change of a single word for the annual meeting of the other society. I have about reached the point where for me abstracts simply provide a specified date for submission of an investigation, whereas original manuscripts have no deadline for submission.

An abstract should be viewed as a preliminary report on an investigation. (Incidentally, the use of abstracts as references should be avoided, except in unusual circumstances.) Thus, give me the manuscript—this is the final forum.

William C. Roberts

William C. Roberts, MD
Editor-in-Chief

# In Cardiac Edema*...




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## Serum $K^+$ and BUN should be checked periodically (see Warnings).

**Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.**

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

**Contraindications:** Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

**Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum $K^+$ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict $K^+$ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

**Precautions:** Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

**Adverse Reactions:** Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

**Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.**

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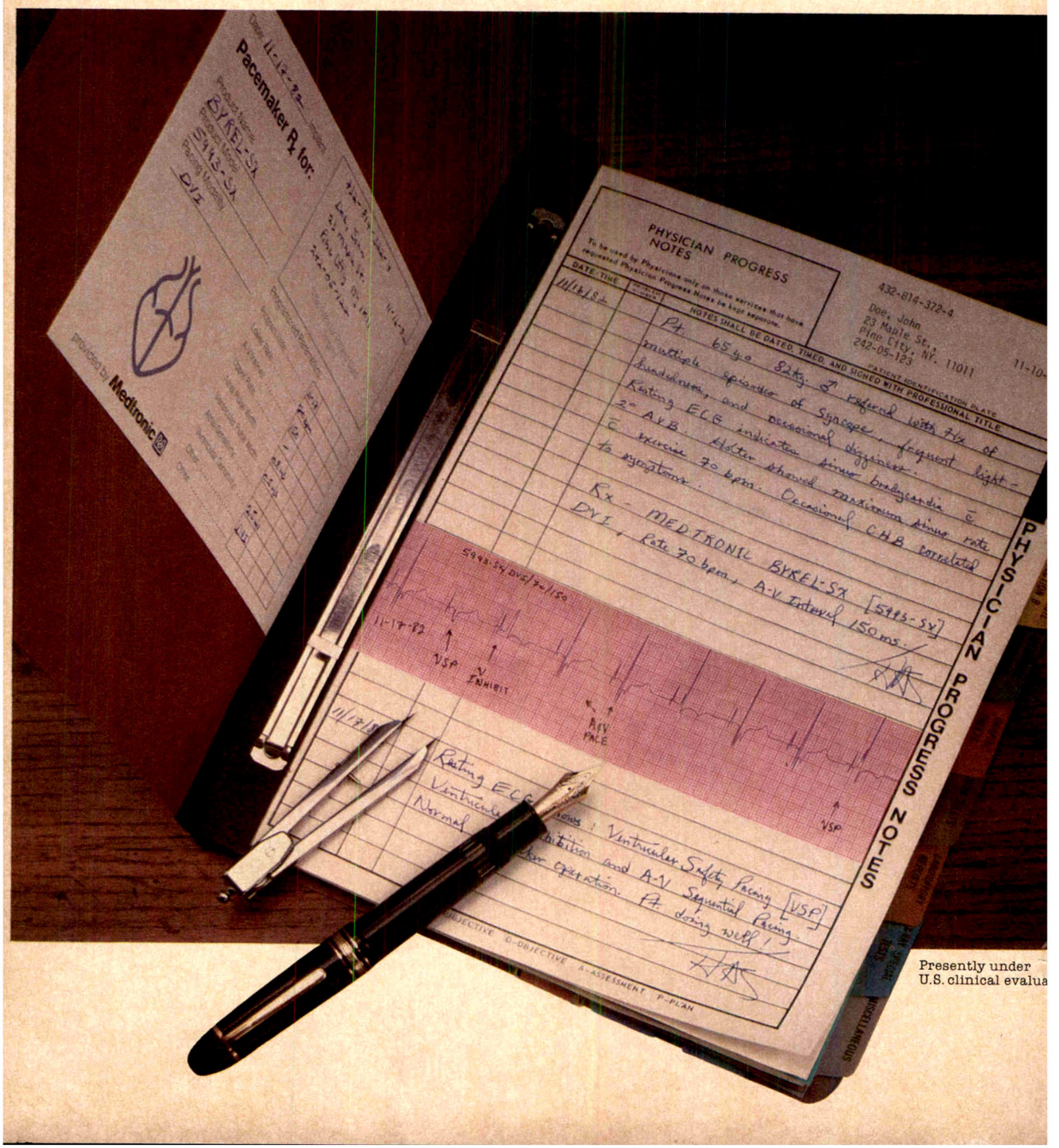
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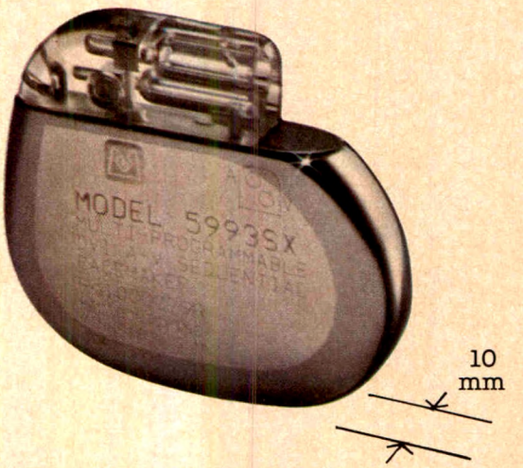
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Discover the Difference

## Byrel-SX Model 5993-SX Programmable Parameters

| | DVI | VVI |
|---|---|---|
| Rate | 40-120 bpm | 40-130 bpm |
| A-V Internal | 25-250 ms | NA |
| Atrial Pulse Width | 0.05, 0.1, 0.2...1.5 ms | NA |
| Ventricular Pulse Width | 0.05, 0.1, 0.2...1.5 ms | 0.05, 0.1, 0.2...1.5 ms |
| Ventricular Sensitivity | 2.5, 5.0 mv Asynchronous | 2.5, 5.0 mv Asynchronous |

**Power Source Depletion Characteristics**

**Initial Stage**

| | |
|---|---|
| Mode | as programmed |
| Voltage | 2.2 V |
| Magnet rate | 75 bpm |

**Secondary Stage**

| | |
|---|---|
| Mode | VVI at 65 bpm |
| Voltage | 2.0 V |

**INTENDED USE**

The Model 5993-SX universal A-V pulse generator has a wide range of application in patients requiring permanent cardiac pacing or to protect against arrhythmias related to the sequence of cardiac impulse propagation.

In the A-V sequential (DVI) mode, the Model 5993-SX has application in the following:

Sick Sinus Syndrome (sinus brady-cardia, sinus arrest, S-A block, and the brady-tachy syndrome).

A-V nodal reentrant tachycardias. (Short A-V interval settings may be useful in controlling reentrant tachy-cardias.)

Atrial and ventricular ectopic arrhythmias.

At any time, the Model 5993-SX can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry (e.g., atrial lead malfunction).

NOTE: The Medtronic* Model 5993-SX A-V pulse generator is under clinical investigation. The procedures for using this pulse generator, as well as its safety and efficacy, will be evaluated during this investigational study according to the Clinical Investigation Protocol. Therefore, the "Intended Use" section is based on Medtronic's experience with other physiologic pulse generators. No claims for safety and efficacy can be made for the Model 5993-SX pulse generator during its clinical investigation. Patients should be advised that the Model 5993-SX generator is under clinical investigation.

**CONTRAINDICATIONS**

There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician. In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation of flutter.

**WARNINGS**

Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site. Electrosurgical units should never be used in the vicinity of unipolar pulse generators because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

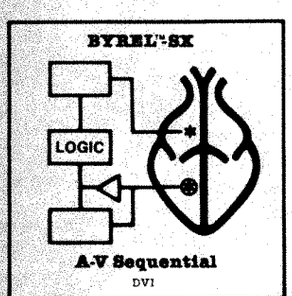
Positioning a magnet or the programmer over the pulse generator makes it subject to programming. Do not use electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programmer has been positioned over the pulse generator.

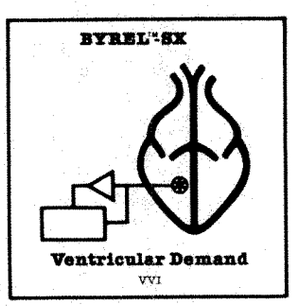
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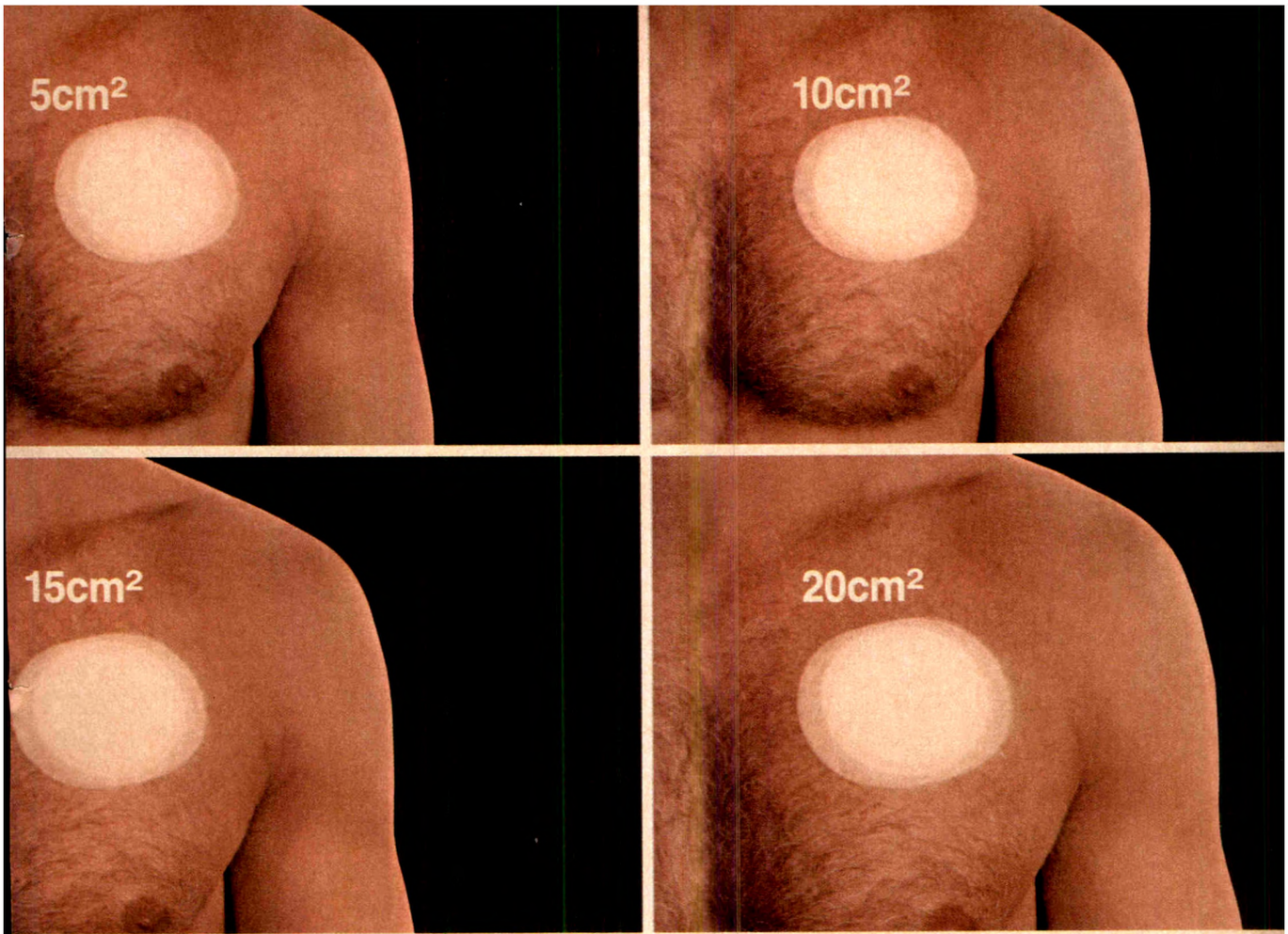
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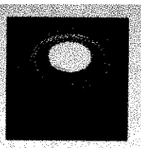
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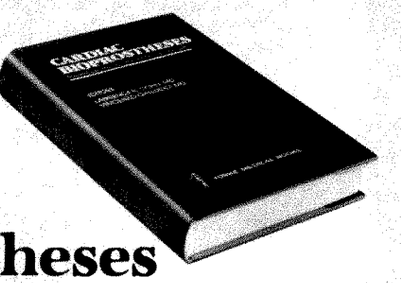
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**Proceedings of the Second International Symposium**
**Rome, Italy, May 17-19, 1982**

**edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD**
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**Vincenzo Gallucci, MD,** is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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**353 Effect of Coronary Artery Bypass Grafting on Subsequent Hospitalization**

WILLIAM M. HAMILTON, KARL E. HAMMERMEISTER, TIMOTHY A. DeROUEN, MAY S. ZIA, and HAROLD T. DODGE

Rates of hospitalization during follow-up for a matched pair cohort of medically and surgically treated patients were compared. There was a 26% reduction in cardiovascular hospitalizations in the surgically compared with the medically treated patients, due to a significant reduction in hospitalization rates for myocardial infarction and other cardiovascular reasons. There was no significant difference between the 2 treatment groups in hospitalization rates for chest pain not due to myocardial infarction or for myocardial infarction including perioperative infarctions. Acute myocardial infarction accounted for only 8% of all cardiovascular hospitalizations and was not related to the number of stenotic vessels in medically treated patients.

**361 Can Noninvasive Exercise Test Criteria Identify Patients With Left Main or 3-Vessel Coronary Disease After a First Myocardial Infarction?**

RANDOLPH E. PATTERSON, STEVEN F. HOROWITZ, CALVIN ENG, JOSE MELLER, STANLEY J. GOLDSMITH, AUGUSTO D. PICHARD, DORIS A. HALGASH, MICHAEL V. HERMAN, and RICHARD GORLIN

This study attempts to determine whether exercise treadmill testing with clinical, electrocardiographic, and thallium-201 myocardial perfusion imaging data can identify which patients have left main or 3-vessel (anatomically high risk) coronary disease after their first myocardial infarction. A thallium defect outside the vascular distribution of the infarct was the most reliable criterion for distinguishing anatomically high risk coronary disease. Failure to achieve 85% of predicted exercise heart rate was a useful criterion in patients not taking propranolol. Exercise electrocardiography could not distinguish anatomically high risk coronary disease after infarction. Cardiac catheterization is not required to exclude 3-vessel or left main coronary disease after infarction in patients with (1) absence of thallium-201 defects outside the vascular distribution of the infarction, and (2) 85% of the predicted peak exercise heart rate.

**373 Papillary Muscle Rupture Complicating Acute Myocardial Infarction: Analysis of 17 Patients**

RICK A. NISHIMURA, HARTZELL V. SCHAFF, CLARENCE SHUB, BERNARD J. GERSH, WILLIAM D. EDWARDS, and ABDUL J. TAJIK

Papillary muscle rupture is a rare but life-threatening complication of acute myocardial infarction. The records of 17 patients with this diagnosis were reviewed; 9 patients had the diagnosis confirmed at autopsy, and 8 underwent operation after papillary muscle rupture had been diagnosed. The site of myocardial infarction was inferolateral in 15 and anterior in 2; a mean of 6 days elapsed after myocardial infarction before rupture occurred. Five of 11 patients with pulmonary congestion alone died suddenly after stabilization; 5 of 6 patients with pulmonary congestion and hypotension died. Single-vessel coronary artery disease was present in 7 of 14 patients; autopsy evaluation revealed a small subendocardial myocardial infarction in half of the patients. The unpredictable clinical deterioration and the limited extent of coronary atherosclerosis suggest that early surgical intervention should be undertaken for papillary muscle rupture after acute myocardial infarction.

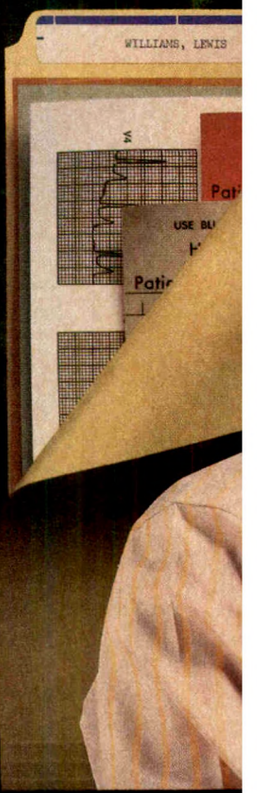
**378 Comparative Rates of Resolution of QRS Changes After Operative and Nonoperative Acute Myocardial Infarcts**

DAVID E. ALBERT, ROBERT M. CALIFF, DAVID A. LeCOCQ, RAY A. McKINNIS, RAYMOND E. IDEKER, and GALEN S. WAGNER

In this study a QRS scoring system which estimates myocardial infarct size was used to compare the evolution of the electrocardiogram in patients after operative and nonoperative myocardial infarction. Both groups showed similar peak QRS scores during the acute phase. However, QRS scores decreased more rapidly in the operative group than in the nonoperative group over the subsequent 2 months (43% versus 19%). After this period the

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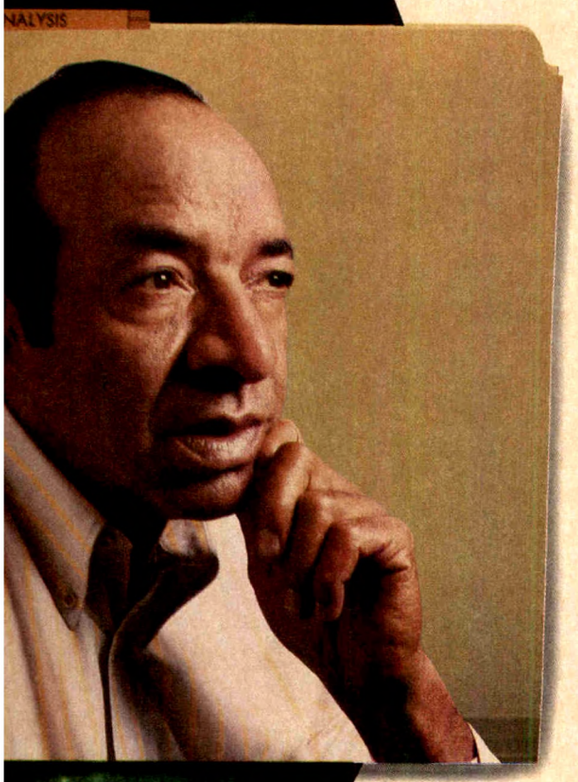

## may reveal the cause of his hypertension...

In their study of the humoral mechanisms involved in hypertension, researchers are focusing not only on the kidneys and adrenal glands but on other glandular bodies as well.

Recently, a new aldosterone-stimulating factor (ASF) has been isolated from normal human urine.* Through immunofluorescence, ASF—a glycoprotein with a number of similarities to ACTH and angiotensin II—has been traced to the pituitary gland. By helping to raise plasma levels of aldosterone, which in turn leads to increased renal sodium retention, ASF presumably contributes to hypertension. The importance of its role must still be determined—and eventually will be, as researchers continue to look "beneath the surface."

*Sen S *et al: Hypertension 3*(Suppl 1):81-86, May-Jun 1981. By permission of the American Heart Association, Inc.

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## as well as the cause of his excessive anxiety

When the hypertensive patient also has anxiety which may cause him to resist, or even ignore, his medical regimen, discreet probing often provides sufficient information about possible underlying causes to help you deal with the situation. At times, however, neither counseling nor reassurance seems to work. The patient remains tense, apprehensive and—perhaps most damaging of all—noncompliant.

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Another important advantage: Valium has been used with most primary cardiac medications, including cardiac glycosides, diuretics and vasodilators. Side effects more serious than drowsiness, fatigue and ataxia are rare and seldom severe. Patients should, of course, be cautioned against drinking alcoholic beverages or driving while taking Valium. Periodic reassessment of the need for psychotropic medication is also recommended.

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## diazepam/Roche

2-mg, 5-mg, 10-mg scored tablets

## A primary choice for anxiety associated with hypertension

Please see summary of product information on the next page.

ROCHE®

# VALIUM®
## diazepam/Roche

**Before prescribing, please consult complete product information, a summary of which follows:**
**Indications:** Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).
The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.
**Contraindicated:** Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.
**Warnings:** Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

**Precautions:** If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.
**Side Effects:** Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.
**Dosage:** Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
**How Supplied:** For oral administration, Valium scored tablets — 2 mg, white; 5 mg, yellow; 10 mg, blue — bottles of 100* and 500;* Prescription Paks of 50, available in trays of 10;* Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25,† and in boxes containing 10 strips of 10.*

*Supplied by Roche Products Inc., Manati, Puerto Rico 00701
†Supplied by Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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Manati, Puerto Rico 00701

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rates of regression were similar in both groups. By 18 months the total decrease in the QRS score was 62% in the operative group and 37% in the nonoperative group. These results could mean that factors other than acute infarction are responsible for the perioperative QRS changes or that the infarct healing process may differ in the 2 clinical settings.

**382 Evaluation of a QRS Scoring System for Estimating Myocardial Infarct Size. III. Correlation With Quantitative Anatomic Findings for Inferior Infarcts**

STEVEN F. ROARK, RAYMOND E. IDEKER, GALEN S. WAGNER, DANIEL R. ALONSO, SANFORD P. BISHOP, COLIN M. BLOOR, DEAN A. BRAMLET, JESSE E. EDWARDS, JOHN T. FALLON, GEOFFREY J. GOTTLIEB, DONALD B. HACKEL, HARRY R. PHILLIPS, KEITH A. REIMER, WILLIAM J. ROGERS, WAYNE K. RUTH, ROBERT M. SAVAGE, RICHARD D. WHITE, and RONALD H. SELVESTER

A QRS scoring system for estimating the size of myocardial infarcts was evaluated by quantitative autopsy correlation in patients with single infarcts in the inferior third of the left ventricle. The study was limited to patients whose electrocardiogram did not indicate left or right ventricular hypertrophy, left or right bundle branch block, or left anterior or posterior fascicular block. Thirty-one patients from 6 medical centers met these criteria. In the electrocardiogram of 28 (90%) of the 31 patients, lead aVF exhibited a Q wave of at least 30 ms. The correlation coefficient between the total QRS score and the percent infarction of the left ventricle was 0.74. In patients without confounding factors in the electrocardiogram and with single infarcts, the electrocardiogram provides a marker for infarcts in the inferior third of the left ventricle and a quantitative QRS scoring system provides an estimate of infarct size.

**390 Segmental Right Ventricular Function After Acute Myocardial Infarction: Two-Dimensional Echocardiographic Study in 63 Patients**

JOSE LOPEZ-SENDON, MIGUEL ANGEL GARCIA-FERNANDEZ, ISABEL COMA-CANELLA, MAR MORENO YANGÜELA, and FERMIN BANUELOS

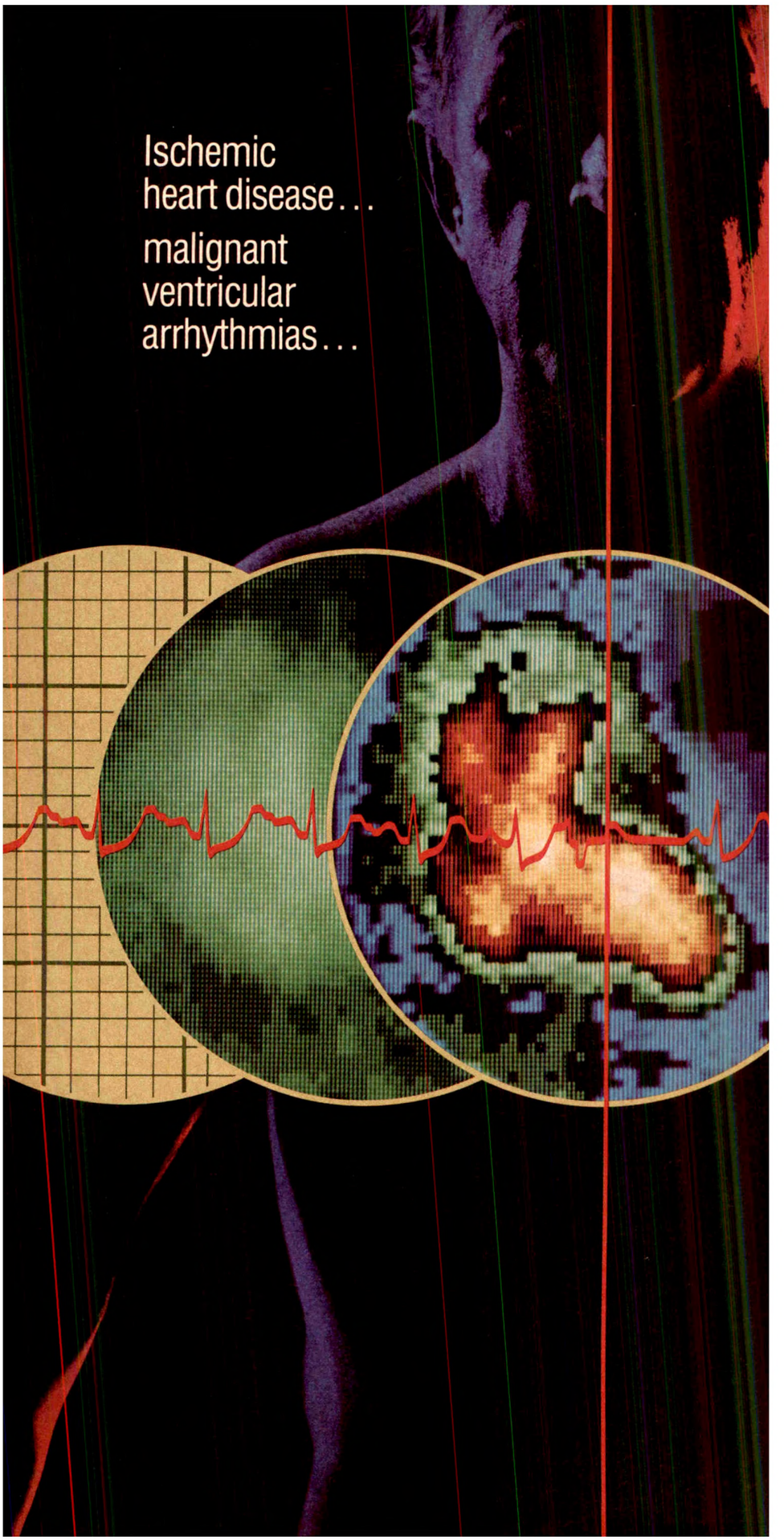
Right ventricular (RV) segmental contraction was studied in 63 patients with acute myocardial infarction (MI), using 2-dimensional (2-D) echocardiography. Group A included 32 patients with ischemic RV dysfunction: 19 had a disproportionate increase in right atrial pressure at the time of the examination (Group AI) and in 13 patients, right atrial pressure was normal when the echocardiogram was obtained (Group AII). Group B included 31 patients without ischemic RV dysfunction. Akinesia or dyskinesia of the RV wall was found in 30 patients: 19 from Group AI, 8 from Group AII, and 3 from Group B. Asynergy could be identified in all segments of the RV wall including the outflow tract, RV apex, and anterior wall, but was more frequently found in the posterior wall (29 patients), best seen in the transversal subcostal short-axis view. A significant difference was found either in the frequency of wall motion abnormalities or in the number of segments with asynergy among the 3 groups ($p < 0.001$). However, asynergy of the RV wall may be present in some patients with normal right heart hemodynamic function, suggesting that asynergy may be more sensitive than hemodynamic function in the diagnosis of acute RV infarction. Paradoxical septal motion was found in 8 patients, all in Group AI, and all had a right atrial pressure equal to or greater than pulmonary capillary pressure.

**397 Variable Threshold Exertional Angina in Patients With Transient Vasospastic Myocardial Ischemia. Repeat Exercise Test Results and Therapeutic Implications**

STEFANO DE SERVI, GIUSEPPE SPECCHIA, COLOMBA FALCONE, ANTONELLO GAVAZZI, ANTONIO MUSSINI, LUIGI ANGOLI, EZIO BRAMUCCI, DIEGO ARDISSINO, LAURA VACCARI, JORGE SALERNO, and PIERO BOBBA

Twelve patients with vasospastic angina at rest presented with a variable threshold of angina during exercise. In these patients 3 exercise tests, performed in the morning on different days, yielded different results because chest pain and ischemic electrocardiographic changes occurred at different work loads with a wide range of heart rate-systolic pressure product. Two patients, in whom great cardiac vein flow was measured during exercise before and after nifedipine, after the drug tolerated heavier work loads with a more marked increase in flow during exercise. Variable threshold exertional angina can be objectively demonstrated by repeated exercise tests in patients with vasospastic angina. Variability of the angina threshold may be due to a functional mechanism that causes myocardial ischemia in addition to increased myocardial metabolic requirements provoked by exercise.

Continued on Page A21


Ischemic
heart disease...
malignant
ventricular
arrhythmias...

# ZEROING IN ON THE CANDIDATE AT RISK

Frequent and complex forms of PVCs sharply increase the risk of sudden cardiac death (SCD) in patients with ischemic heart disease, especially in the presence of left ventricular dysfunction.[1,2]



To reduce the risk of potentially fatal arrhythmias in such patients

# QUINAGLUTE® 324 mg DURA-TABS®

## (quinidine gluconate)

- If initially tolerated, can usually be taken successfully over long periods.[3]
- Demonstrated by programmed ventricular stimulation to be effective in accepted "standard" doses.[4]
- BID or TID dosage helps improve compliance while providing 24-hour antiarrhythmic activity.
- "As a rule, GI toxicity associated with quinidine gluconate is less frequent and less severe than that associated with quinidine sulfate."[5]

References: **1.** Lown B, Podrid PJ, Graboys TB, et al: *Curr Probl Cardiol* 4:13-14, 1980. **2.** Schulze RA Jr, Strauss HW, Pitt B: *Am J Med* 62:192-199, 1977. **3.** Pine MB, Aronow WS: *Ration Drug Ther* 14:1-5, 1980. **4.** Kastor JA, Horowitz LN, Harken AH, et al: *N Engl J Med* 304: 1004-1020, 1981. **5.** Podrid PJ: *Patient Care* 15:100-132, 1981.

Please turn page for brief summary of prescribing information.

BERLEX Laboratories, Inc., Cedar Knolls, New Jersey 07927

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**QUINAGLUTE® (quinidine gluconate) DURA-TABS®**

**INDICATIONS AND USAGE:** Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:

**1. Ventricular arrhythmias:** Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).

**2. Junctional (nodal) arrhythmias:** A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).

**CONTRAINDICATIONS:** 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.

**WARNINGS:** 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.

3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.

7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

**PRECAUTIONS: General:** The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.

**Drug Interactions:**

| *Drug* | *Effect* |
|---|---|
| Quinidine with anticholinergic drugs | Additive vagolytic effect |
| Quinidine with cholinergic drugs | Antagonism of cholinergic effects |
| Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics | Alkalinization of urine resulting in decreased excretion of quinidine |
| Quinidine with coumarin anticoagulants | Reduction of clotting factor concentrations |
| Quinidine with tubocurare, succinylcholine and decamethonium | Potentiation of neuromuscular blockade |
| Quinidine with phenothiazines and reserpine | Additive cardiac depressive effects |
| Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin) | Decreased plasma half-life of quinidine |
| Quinidine with digoxin | Increased plasma concentrations of digoxin (see WARNINGS) |

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.

**Pregnancy:** *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

**Nursing Mothers:** Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.

**Pediatric Use:** There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.

**ADVERSE REACTIONS:** Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.

Less frequently encountered adverse reactions:

**Cardiovascular:** Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.

**Hematologic:** Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.

**Central Nervous System:** Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.

**Dermatologic:** Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.

**Hypersensitivity Reactions:** Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.

*See package insert for full information.*

**BERLEX Laboratories, Inc., Cedar Knolls, New Jersey 07927**


## CARDIAC ANGIOGRAPHY 1983

The department of radiology of Harvard Medical School in cooperation with the Council on Cardiovascular Radiology of the American Heart Association will sponsor its annual cardiac angiography course, "Cardiac Angiography 1983: Diagnostic and Therapeutic Coronary Arteriography", May 23–26, 1983 at the Marriott-Long Wharf, Boston, Mass. The program will consist of formal lectures in the morning, followed by panel discussions and small group workshops in the afternoons. Workshops will focus on cine techniques, intracoronary streptokinase, cardioactive drugs, interpretation of coronary angiograms, digital cardiac imaging, coronary angioplasty as well as other topics. Harvard Medical School faculty include Drs. Abrams, Block, Cohn, Collins, DeSanctis, Levin, Paulin, Pohost, and others. Guest faculty include Drs. Bulkley, Higgins, Kennedy, and Myler. The fee is $390 for physicians, $285 for residents, fellows and RTs. The course is approved for 26 Category I credits.

For further information contact: Jo-Anne Latino, Coordinator of Continuing Education, Brigham and Women's Hospital, Department of Radiology, 75 Francis Street, Boston, Massachusetts 02115.

## CARDIOLOGIST—ELECTROPHYSIOLOGIST

CREIGHTON UNIVERSITY MEDICAL CENTER is offering a position for a cardiologist who has special interest and sufficient training in clinical electrophysiology to direct the Electrophysiology Laboratory. Present 11 man faculty group conducts a busy clinical, research and teaching program and desires to expand and improve the Electrophysiology Laboratory. This is a fulltime academic position with salary and academic rank commensurate with the level of training and experience.

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**CARDIOLOGIST WANTED** to associate with another sub-specialist with busy clinical practice. Midwestern town of 40,000 near large metropolitan area. Invasive and non-invasive skills necessary. Excellent salary, benefits and practice opportunity with eventual partnership. Reply with C.V., to Box 250, The American Journal of Cardiology, 875 Third Ave., New York, N. Y. 10022.

# CONTENTS


**403 Cardiovascular Disease in the Very Elderly. Analysis of 40 Necropsy Patients Aged 90 Years or Over**

BRUCE F. WALLER and WILLIAM C. ROBERTS

Clinical and necropsy observations are described in 40 patients (29 women) aged 90 years and older. At necropsy, 39 had 1 or more major cardiac abnormalities, the most common being calcific deposits in the major epicardial coronary arteries in 37 (92%). In 28 patients (70%), 1 or more of the 4 major coronary arteries was narrowed 76 to 100% in cross-sectional area (XSA) by atherosclerotic plaques, an average of 1.9/4.0 per patient. Of the 12 patients with clinical events compatible with myocardial ischemia (angina pectoris or myocardial infarction), the average was 2.2/4 and in the other 28 patients, 1.0/4.0. In 36 patients, a histologic section was examined from each 5-mm long segment from each of the 4 major coronary arteries. Of the 1,789 segments, 6 (>1%) were narrowed 96 to 100% in XSA by plaques; 147 (8%), 76 to 95%; 339 (19%), 51 to 75%; 930 (52%), 26 to 50%; and 367 (21%), 0 to 25%. The average amount of XSA narrowing for each of the 1,789 segments was about 42%. Of 10 patients with clinical evidence of myocardial ischemia, the average amount of narrowing per segment was about 55%, and in the 26 patients without clinical ischemia it was about 38%. Of the 40 patients, 18 (45%) had left ventricular transmural foci of fibrosis or necrosis, or both.

**422 Hemodynamic Effects of a New Antiarrhythmic Agent, Flecainide (R-818), in Coronary Heart Disease**

VICTOR LEGRAND, MICHEL VANDORMAEL, PIERRE COLLIGNON, and HENRI E. KULBERTUS

Flecainide acetate, a class I antiarrhythmic agent, was administered intravenously to 10 patients with coronary artery disease. It increased the P-R, QRS, and Q-T duration. Negative inotropic effects consisting of an increase of pulmonary wedge pressure and a decrease in stroke index, stroke work index, left ventricular ejection rate, and dP/dt were noted. No significant changes in mean aortic pressure or systemic or pulmonary vascular resistance were observed. Left ventriculography performed after drug administration revealed an increase in systolic volume as well as a decrease in ejection fraction and mean velocity of circumferential fiber shortening. The drug was well tolerated and the hemodynamic changes appeared moderate.

**427 Pindolol and Propranolol in Patients With Angina Pectoris and Normal or Near-Normal Ventricular Function. Lack of Influence of Intrinsic Sympathomimetic Activity on Global and Segmental Left Ventricular Function Assessed by Radionuclide Ventriculography**

DANTE E. MANYARI, WILLIAM J. KOSTRUK, S. GEORGE CARRUTHERS, DONALD J. JOHNSTON, and PAUL PURVES

The role of intrinsic sympathomimetic activity on left ventricular function during antianginal therapy with beta-blocking agents was evaluated in 23 patients with chronic exercise-induced angina pectoris. During 3 randomly allocated treatment periods (propranolol, a drug without intrinsic sympathomimetic activity; pindolol, a drug with intrinsic sympathomimetic activity; and control), left ventricular function was evaluated at rest and during supine exercise with radionuclide ventriculography. Both propranolol and pindolol exhibited similar effects on global and regional left ventricular function; neither decreased ejection fraction or wall motion at rest, while both prevented a decrease in ejection fraction and the development of wall motion abnormalities with exercise.

**434 Determination of the Angiographic Appearance of Coronary Vessels: The Importance of Supplying and Recipient Arteries**

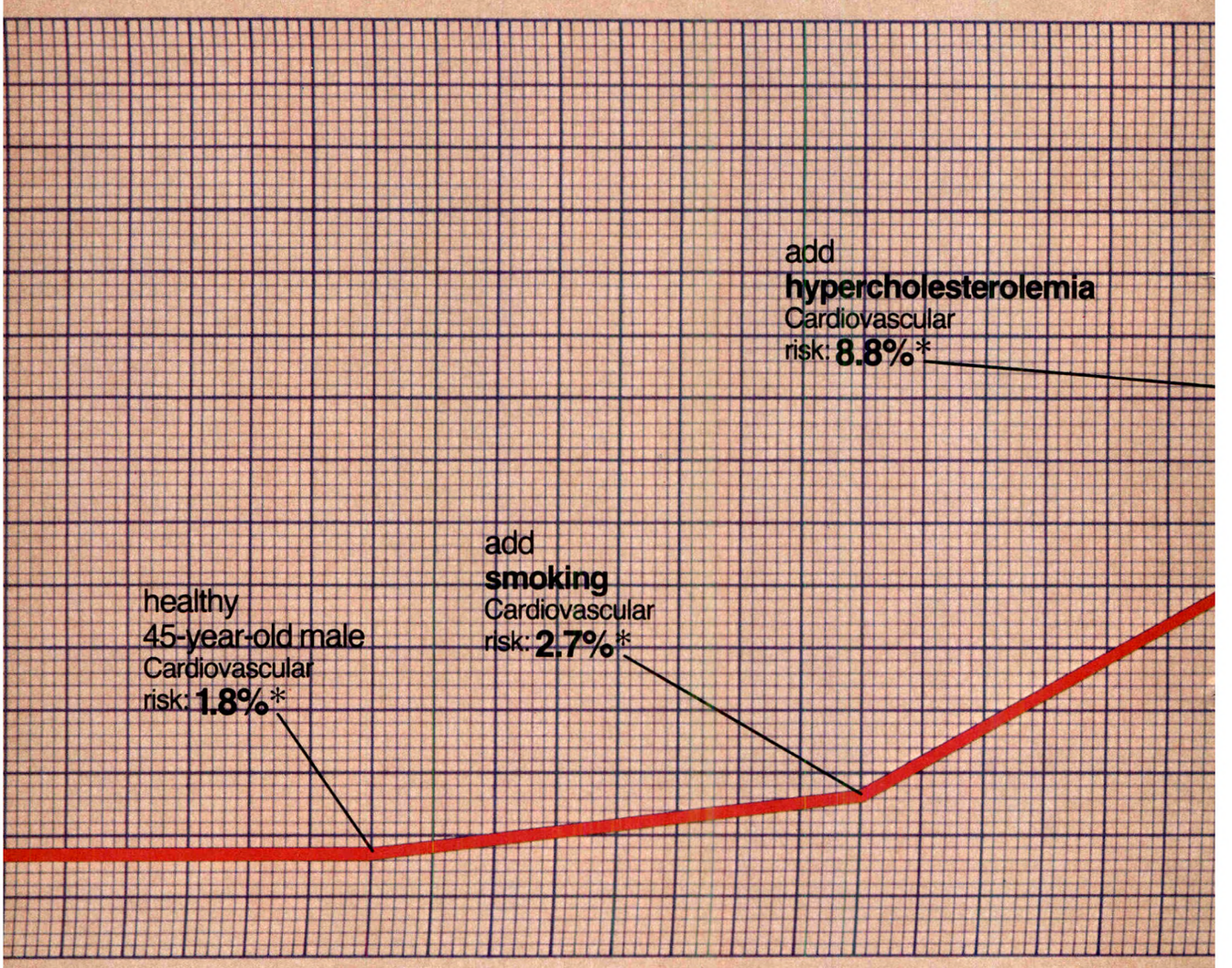
HARVEY L. GOLDBERG, JONATHAN GOLDSTEIN, JEFFREY S. BORER, MICHAEL B. COLLINS, JEFFREY W. MOSES, and GEORGE ELLIS, *With the technical assistance of* RICHARD QUIROZ

To determine the relation between the angiographic appearance of the coronary arteries and coronary collateral vessels, 121 coronary angiograms were reviewed. The coronary arteries were graded on a 5 point scale (<75%, ≥75% to 89%, ≥90% to 99%, and total occlusion); collateral vessels were graded on a 3 point scale (absent, poor, or good). Stenosis of the recipient artery was an important determinant of collateral frequency and angiographic grade; as the grade of stenosis increased, the likelihood of demonstrability of collateral vessels and the probability that such vessels were "good" increased. Collateral grade also was influenced by the extent of stenosis of the artery supplying that collateral vessel; "good" collateral vessels were more likely to arise from arteries without important stenoses, and poor collateral vessels generally arose from more severely stenotic arteries. The probability that a totally occluded artery received collateral vessels was reduced to the extent that stenoses were present in all potential sources of collateral supply. Thus, the angiographic appearance of the recipient and supplying coronary arteries is a major determinant of the angiographic appearance of coronary collateral vessels.


Continued on Page A25

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# In hypertensive patients:

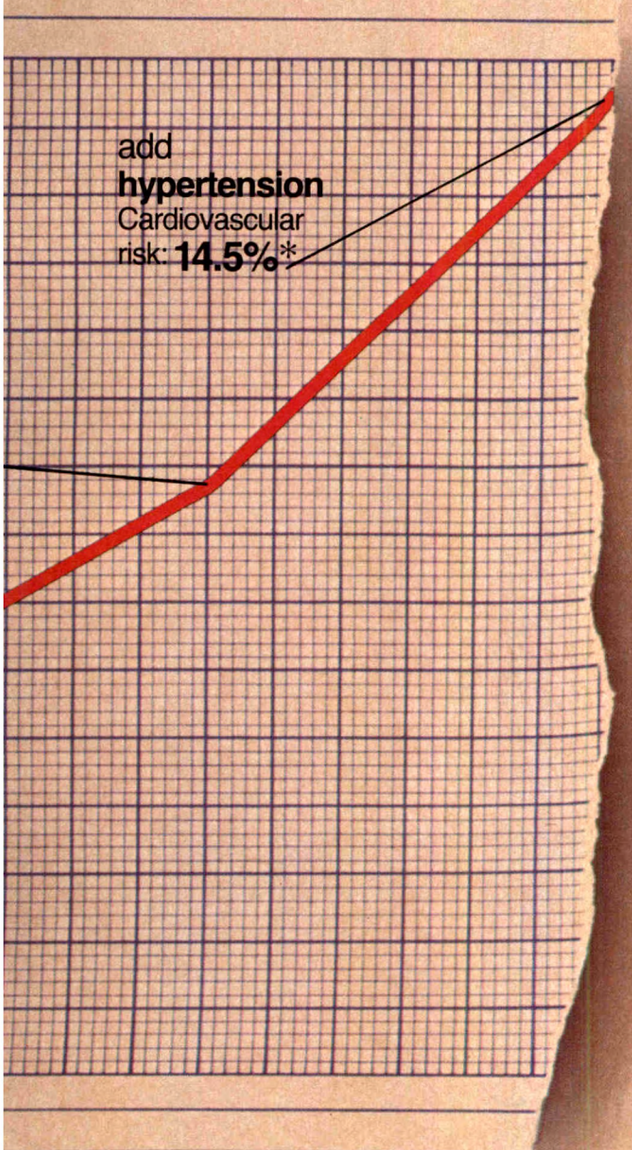



Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

# Consider the Risks




- When selecting antihypertensive therapy, clinical consideration should be given to the effects of the specific drug on coronary risk factors. Blood pressure control should be achieved without adversely affecting blood lipids.

## Minipress Effectively Controls Hypertension Without Adverse Effect on Blood Lipids†

- Minipress effectively treats hypertension. Patients have benefited from the effectiveness of Minipress in over 5 years of clinical use in this country.[1-5]
- Minipress has been shown not to have an adverse effect on blood lipids, according to The Oslo Study and other reports.[6-9] Because Minipress lowers high blood pressure and does not produce lipid changes which are potentially atherogenic, it provides your patient with a net reduction in risk.

†Minipress is not indicated for the treatment of hyperlipidemia.

*Please see Minipress brief summary on following page.*

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(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

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# Minipress® (prazosin HCl) Capsules 1mg, 2mg, 5mg

**B.I.D. Dosage Convenience**

**BRIEF SUMMARY**
**MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use***
**INDICATIONS:** MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.
**WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.**
If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.
Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.
More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.
***Usage in Pregnancy:*** Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.
***Usage in Children:*** No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.
**ADVERSE REACTIONS:** The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.
The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)
Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular: edema, dyspnea, syncope, tachycardia.
Central Nervous System: nervousness, vertigo, depression, paresthesia.
Dermatologic: rash, pruritus, alopecia, lichen planus.
Genitourinary: urinary frequency, incontinence, impotence, priapism.
EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.
Other: diaphoresis.
Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.
In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.
**DOSAGE AND ADMINISTRATION:** The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:
***Initial Dose:*** 1 mg two or three times a day. (See Warnings.)
***Maintenance Dose:*** Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.
***Use With Other Drugs:*** When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.
**HOW SUPPLIED:** MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).
*More detailed information available on request.*

**References:** 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet*: 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.

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**440 Identification of Septal Ischemia During Exercise by Q-Wave Analysis: Correlation With Coronary Angiography**

MICHAEL A. FAMULARO, YOGESH PALIWAL, ROBERT REDD, and MYRVIN H. ELLESTAD

Changes in the precordial septal Q wave with exercise have been shown to correlate with ischemia. This study evaluates the concept that exercise-induced changes in the septal Q wave reflect the contractual state of the septum. An increase in Q-wave amplitude is associated with good contraction, whereas a decrease indicates ischemia and reduced function. Twenty-nine patients with single-vessel disease with >50% diameter reduction were compared with 12 whose coronary arteries were demonstrated normal on angiography. Of the 13 with left anterior descending disease, 8 had a decrease in Q-wave amplitude and 5 had no change. No patient with left anterior descending disease increased the magnitude of the septal Q amplitude, whereas 9 (75%) of the 12 patients with normal coronary arteries showed this change. No patient with normal coronary arteries with isolated right or circumflex disease had a loss of septal Q-wave amplitude. Thus, a decrease in septal Q-wave amplitude with exercise has a good sensitivity and a very high specificity for significant left anterior descending disease. An increase in the septal amplitude indicates normal septal contraction and usually good flow in the left anterior descending coronary artery.

**444 Surgery for Coronary Heart Disease Due to Mucocutaneous Lymph Node Syndrome (Kawasaki Disease). Report of 6 Patients**

SOICHIRO KITAMURA, KANJI KAWACHI, RYOICHI HARIMA, TETSUO SAKAKIBARA, HAJIME HIROSE, and YASUNARU KAWASHIMA

Early and late surgical results in 6 patients with coronary heart disease secondary to mucocutaneous lymph node syndrome (Kawasaki disease) are presented. They had severe coronary artery narrowings, obstructions, and aneurysms with or without mitral regurgitation. Previous myocardial infarction was documented in 5 patients. Aortocoronary bypass grafting utilizing the autologous saphenous vein was performed in 5 patients; in the remaining patient, mitral valve replacement was carried out. There were operative or late deaths. A long-term bypass graft patency was demonstrated in patients aged 26, 17, and 10 years with resulting clinical, angiographic, and/or scintigraphic improvements. However, the graft that had been patent in a 4-year-old boy was found completely obstructed 3 years after surgery without any symptomatic changes. The formation of rich collateral channels was found. The risk of saphenous vein graft closure may be high in young growing children. In older children or adolescents, however, coronary vein bypass grafting for this specific inflammatory coronary artery lesion has been effective with long-term graft patency. Severe mitral regurgitation is also an indication for surgery, but poor left ventricular function associated with mitral regurgitation, probably secondary to myocarditis, persists after surgery and may give rise to future problems.

**449 The Changing "Natural History" of Symptomatic Coronary Artery Disease: Basis Versus Bias**

LEE GOLDMAN, GILBERT H. MUDGE, Jr., and E. FRANCIS COOK

An uncritical reading of recent "natural history" studies would suggest far greater improvements in the survival of symptomatic coronary patients than has been demonstrated by national mortality statistics. However, attempts to compare patients from different studies and different eras may greatly overestimate the true improvement in natural history because of at least 3 biases in the selection of cases from the spectrum of diseased patients. Because of lead-time bias, patients who are diagnosed earlier live longer regardless of whether interventions are efficacious. Because of referral bias, current patients may have symptoms or anatomy that place them at a different stage of severity than patients who were chosen for earlier studies. Because of incidence-prevalence bias, prevalence studies will be over-represented with survivors of previous incidence cohorts who have slower-progressing disease. The authors suggest that all natural history studies be carefully scrutinized for such biases before they are compared with each other.

## CONGESTIVE HEART FAILURE

**455 Intermittent, Continuous Outpatient Dobutamine Infusion in the Management of Congestive Heart Failure**

MARK M. APPLEFELD, KATHRYN A. NEWMAN, WILLIAM R. GROVE, FREDERICK J. SUTTON, DAVID S. ROFFMAN, WILLIAM P. REED, and STEVEN E. LINBERG

Continuous dobutamine infusions were given twice weekly by a portable infusion pump-chronic venous access catheter system to 3 outpatients with heart failure. Left ventricular function and congestive failure improved with this therapy in each patient. The only complications during 58 cumulative weeks of treatment were 3 mild infections around the catheter exit site. This form of therapy shows promise for the management of refractory congestive heart failure.


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## SYSTEMIC HYPERTENSION

**459 R-Wave Amplitude Change During Aerobic Exercise in Hypertensive Adolescents After Treatment**

BONITA FALKNER, DAVID T. LOWENTHAL, MELTON B. AFFRIME, and BARBARA HAMSTRA

The purpose of this study was to determine whether the blunted reduction in R-wave amplitude during progressive aerobic exercise observed in hypertensive adolescents could be altered by pharmacologic therapy to reduce blood pressure. Twenty-nine hypertensive adolescents were randomly assigned to either diuretic therapy (hydrocholorothiazide) or a centrally acting agent (clonidine). Exercise stress testing was performed before therapy and after 16 weeks of therapy. Therapy that lowered blood pressure also resulted in a change in R-wave response. In both treatment groups the change in R-wave amplitude during exercise corresponded to the R-wave response pattern observed in normotensive control subjects. These observations indicate that the altered R-wave response to exercise observed in young patients with hypertension is reversible. These findings suggest that the R-wave response before treatment may be related to a relatively higher vascular resistance.

**464 Increased Plasma Concentrations of Prostacyclin in Metabolite 6-Keto-$PGF_{1\alpha}$ in Essential Hypertension. Influence of Therapy With Labetalol**

LOUIS ROY, JAWAHAR MEHTA, and PAULETTE MEHTA, *With the technical assistance of* NANCY OSTROWSKI, CHRISTINE HORALEK, and GEORGIA KELLEY

The concentrations of 6-keto-$PGF_{1\alpha}$ and thromboxane $B_2$, stable metabolites of prostacyclin and thromboxane $A_2$, respectively, were measured in patients with essential hypertension. Plasma 6-keto-$PGF_{1\alpha}$ levels were markedly increased in the placebo phase, while thromboxane $B_2$ levels were normal. Intravenous labetalol lowered the blood pressure but did not reduce 6-keto-$PGF_{1\alpha}$ levels. Therapy with labetalol for 6 weeks decreased 6-keto-$PGF_{1\alpha}$ concentrations. Thromboxane $B_2$ levels were unaffected by intravenous or oral therapy. Increased plasma levels of 6-keto-$PGF_{1\alpha}$ in patients with untreated hypertension suggests that enhanced prostacyclin activity may be a protective mechanism to prevent organ damage. As blood pressure is controlled, prostacyclin activity declines as this increase is no longer needed.

**468 Analysis of Ventricular Emptying and Filling Indexes During Acute Increases in Arterial Pressure**

ROBERT A. SLUTSKY, G. B. JOHN MANCINI, KENNETH H. GERBER, HOWARD C. DITTRICH, and CHARLES B. HIGGINS

During periods of increased systemic arterial pressure, the ejection fraction, ejection rate, and filling rate behaved similarly in normal subjects and patients with previous myocardial infarction. Global indexes of mid-systole, holosystole, and diastole appeared of similar discriminatory value in differentiating normal subjects from patients with infarction.

## VALVULAR HEART DISEASE

**476 Serial Changes in Left Ventricular Function After Correction of Chronic Aortic Regurgitation. Dependence on Early Changes in Preload and Subsequent Regression of Hypertrophy**

JOHN D. CARROLL, WILLIAM H. GAASCH, MICHAEL ZILE, and HERBERT J. LEVINE

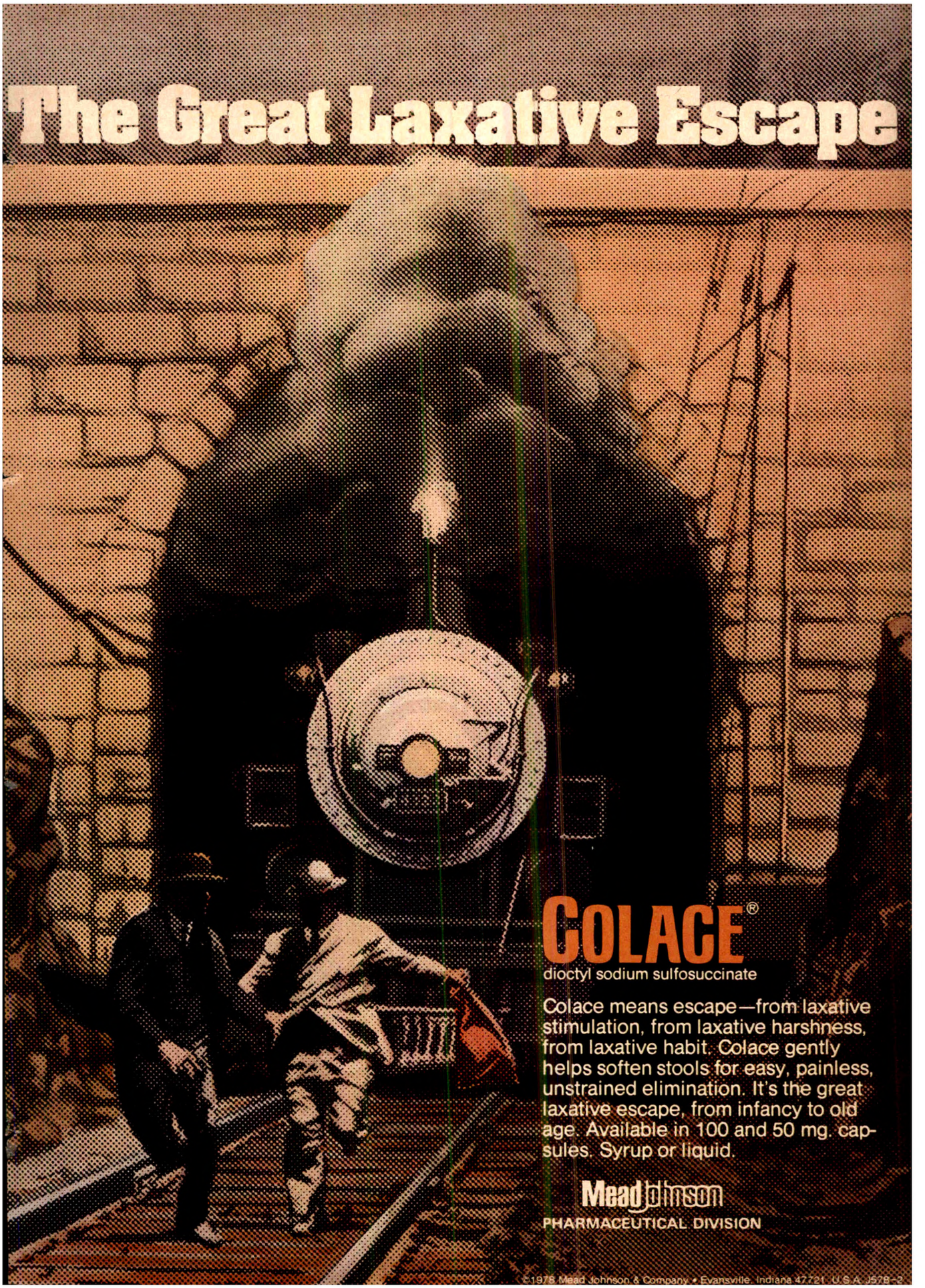
The early postoperative left ventricular dysfunction seen in many patients after correction of chronic aortic regurgitation is usually a temporary finding due to an acute reduction in left ventricular preload. The gradual improvement in ventricular function which occurs over the subsequent 6 to 9 months is partly related to the regression of hypertrophy. Persistent postoperative left ventricular enlargement and persistent hypertrophy are associated with persistent left ventricular dysfunction. In most patients left ventricular volume, mass, and function are not stable during the first postoperative year, and for this reason optimal assessment of ventricular function requires serial studies.

**483 Radionuclide Ventriculographic Study of Adaptations to Exercise in Aortic Regurgitation**

RICHARD M. STEINGART, CORINE YEE, LAWRENCE WEINSTEIN, and JAMES SCHEUER

Twenty patients with clinically isolated aortic regurgitation underwent supine rest and exercise-gated radionuclide ventriculography. The regurgitant index, a measure of the severity of regurgitation, was $3.46 \pm 1.25$ at rest and decreased to $2.6 \pm 0.8$ with exercise ($p < 0.001$). The greater the regurgitant index at rest, the greater the decrease with exercise. The wide variations in end-diastolic count and stroke count responses to exercise were explained in part by the decreasing regurgitant index. The data support the findings in previous catheterization studies and confirm that gated radionuclide ventriculography is a useful tool for monitoring adaptations to exercise in aortic regurgitation.


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**489 Indexes of Intravascular Hemolysis, Quantification of Coagulation Factors, and Platelet Survival in Patients With Porcine Heterograft Valves**

MARK E. THOMPSON, JESSICA H. LEWIS, FREDERICK L. PORKOLAB, UTE HASIBA, and JOEL A. SPERO, *With the technical assistance of* JOHN WILSON and MICHAEL SNYDER

Ten patients with porcine heterograft valves who were not receiving anticoagulant agents were evaluated to determine effect of the valves on red blood cell survival, platelet activation and consumption, and chromium-51 platelet survival time. There was no evidence of significant intravascular hemolysis. The coagulation profile and the results of platelet function studies were normal. No statistically significant difference was observed between the platelet survival time calculated for the 10 unanticoagulated patients with porcine heterograft valves (half-life 3.2 ± 0.6 days) and the 11 normal control subjects (half-life 3.6 ± 0.6 days) ($p > 0.2$). The normal platelet survival time determined in patients with porcine heterograft valves is consistent with clinical experience indicating this device is associated with a low incidence of systemic embolization.

**492 Rheumatic Tricuspid Valve Disease: Two-Dimensional Echocardiographic, Hemodynamic, and Angiographic Correlations**

STEVEN J. DANIELS, GARY S. MINTZ, and MORRIS N. KOTLER

The authors studied 372 patients with rheumatic heart disease using 2-dimensional echocardiography; 23 (6%) had 2-dimensional echo evidence of tricuspid valve involvement. Nineteen patient with 2-dimensional echo tricuspid valve involvement underwent cardiac catheterization; only 4 patients had tricuspid stenosis. Twelve patients with 2-dimensional echo involvement had right ventriculography; 9 patients had predominant and significant tricuspid regurgitation. Thirty-one patients with no 2-dimensional echo involvement had right ventriculography; 11 had significant tricuspid regurgitation.

**497 Calcium Phosphorus Metabolism in Dialysis Patients With and Without Mitral Anular Calcium. Analysis of 30 Patients**

PASQUALE F. NESTICO, NICHOLAS L. DePACE, MORRIS N. KOTLER, LESLIE I. ROSE, JOSEPH H. BREZIN, CHARLES SWARTZ, GARY S. MINTZ, and ALLAN B. SCHWARTZ

In chronic dialysis patients mitral anular calcification (MAC) is frequently detected by M-mode echocardiography. In order to study calcium phosphorus metabolism in such patients, the biochemical findings in 10 dialysis patients with MAC were compared with those in 20 patients without MAC. Higher serum phosphorus levels 5.41 ± 0.82 mg/dl and calcium phosphorus products 49.7 ± 9.0 were found in MAC patients than in patients without MAC (phosphorus 4.09 ± 1.05 mg/dl, and calcium phosphorus product 34.46 ± 10.8). Both groups had increased parathyroid hormone levels, and there was no difference in the 2 groups with regard to age, supine predialysis systolic and diastolic blood pressure, and duration of dialysis. Thus, mitral anular calcification in dialysis patients is associated with disturbed calcium phosphorus metabolism and is independent of the level of parathyroid hormone.

## MYOCARDIAL HEART DISEASE

**501 Quantitative Morphologic Findings of the Myocardium in Idiopathic Dilated Cardiomyopathy**

FRANZ SCHWARZ, GERHARD MALL, HORST ZEBE, JOHANNES BLICKLE, HARALD DERKS, JOACHIM MANTHEY, and WOLFGANG KÜBLER

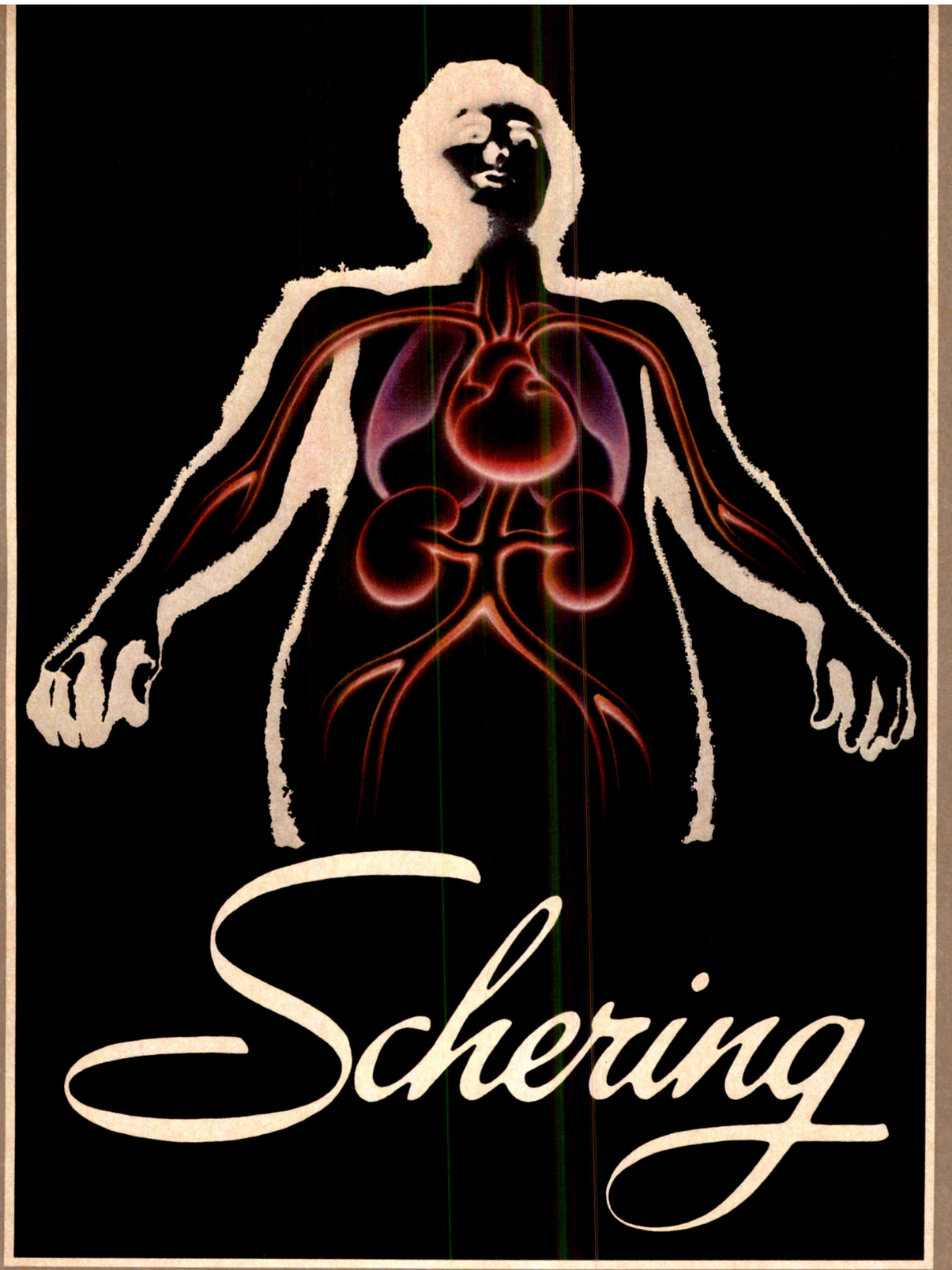
Left ventricular endomyocardial catheter biopsies were obtained from 73 patients. All patients had normal coronary arteriograms but abnormal electrocardiograms. Twenty-six patients had normal left ventricular function and 47 had contractile dysfunction. Myocardial fiber diameter, the volume fraction of interstitial fibrosis, and the intracellular volume fraction of myofibrils were determined from light microscopic morphometry, and these results were confirmed by electron microscopy. The coefficient of variation was 6% for determination of fiber diameter, 43% for interstitial fibrosis, and 3% for volume fraction of myofibrils. Fiber diameter and fibrosis showed a significant negative correlation and the volume fraction of myofibrils a significant positive correlation with the left ventricular ejection fraction. Thus, a reduction in the volume fraction of myofibrils and an increase in fibrosis are morphologic correlates of left ventricular dysfunction in patients with idiopathic dilated cardiomyopathy.

**507 Significance of Ventricular Tachycardia in Idiopathic Dilated Cardiomyopathy: Observations in 35 Patients**

SHOEI K. HUANG, JOSEPH V. MESSER, and PABLO DENES

Thirty-five patients with idiopathic dilated cardiomyopathy were studied in order to (1) evaluate the significance of ventricular tachycardia (VT), and (2) correlate the presence of ventricular arrhythmias with the hemodynamic findings. All patients had right and left heart catheterization and coronary angiography. Holter monitoring was done in all patients. Frequent ventricular premature beats were observed in 23 patients (83%). Twenty-one pa-


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tients (60%) had nonsustained VT consisting of 3 to 46 beats (8 ± 4.7) with rates of 75 to 210 beats/min. No difference was found between patients with and without VT with regard to clinical or electrocardiographic findings or hemodynamic measurements. During follow-up study (mean 34.1 ± 16.6 months), 4 patients died. Two deaths were sudden (1 with and the other without previous VT); the other 2 patients died from intractable congestive heart failure and sepsis. It is concluded that (1) the incidence of ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy is very high, (2) VT is common and usually occurs in the nonsustained form, and (3) there is no correlation between VT and the clinical and hemodynamic findings.

## ARRHYTHMIAS AND CONDUCTION DISTURBANCES

**513 Transesophageal Pacing for Prognostic Evaluation of Preexcitation Syndrome and Assessment of Protective Therapy**

GIUSEPPE CRITELLI, GINO GRASSI, FRANCESCO PERTICONE, FERNANDO COLTORTI, VITTORIO MONDA, and MARIO CONDORELLI

Decremental atrial pacing and elective induction of atrial fibrillation were performed using an esophageal lead in 5 patients with Wolff-Parkinson-White syndrome, before and after amiodarone therapy. In the control state, the mean cycle length with 1:1 conduction over accessory pathway was 232 ms. The average of the shortest R-R interval during atrial fibrillation was 198 ms and the mean ventricular rate was 196 beats/min. After amiodarone therapy, the shortest cycle length with 1:1 conduction increased in all patients, with a mean of 370 ms. During atrial fibrillation no preexcited beat was present in 2 patients, while the minimum preexcited R-R interval in the other 3 patients was 290, 240, and 370 ms, with the ventricular rate decreasing in all patients.

**519 Electrophysiologic Studies Before and After Myocardial Revascularization in Patients With Life-Threatening Ventricular Arrhythmias**

HASAN GARAN, JEREMY N. RUSKIN, JOHN P. DiMARCO, WAYNE M. DERKAC, CARY W. AKINS, WILLARD M. DAGGETT, W. GERALD AUSTEN, and MORTIMER J. BUCKLEY

Programmed cardiac stimulation was performed in 17 patients with severe proximal coronary artery disease and left ventricular ejection fractions >30% undergoing coronary artery bypass graft surgery after prehospital ventricular fibrillation (VF) or ventricular tachycardia (VT). Before surgery and off antiarrhythmic drugs, programmed cardiac stimulation induced VF in 4 patients and VT (≥5 beats) in 11 patients. When studied with programmed cardiac stimulation again an average of 19 days after coronary artery bypass graft surgery, 10 patients had no inducible VT or VF off all antiarrhythmic drugs, and 6 had induced VT. One patient had spontaneous VT. An effective antiarrhythmic regimen that suppressed inducible and spontaneous VT was defined by serial tests in 4 patients; 3 patients continued to manifest inducible VT with all drugs tested. All but 1 patient, in whom postoperative VT could not be suppressed, are free of arrhythmias after a mean follow-up period of 23 months (range 6 to 53).

**525 Electrophysiologic Mechanism of Exercise-Induced Sustained Ventricular Tachycardia**

RUEY J. SUNG, EDWARD N. SHEN, FRED MORADY, MELVIN M. SCHEINMAN, DAVID HESS, and ELIAS H. BOTVINICK

This report describes clinical and electrophysiologic findings in 12 patients in whom sustained ventricular tachycardia (VT) developed during treadmill exercise testing. Electrophysiologic studies provoked paroxysms of sustained VT identical to those observed during treadmill exercise testing in 10 patients. Seven patients had VT suggestive of a reentrant mechanism, as the VT could be initiated with programmed ventricular extrastimulation or terminated by overdrive ventricular pacing. The remaining 3 patients had VT suggestive of catecholamine-sensitive abnormal automaticity. In the latter 3 patients, VT could not be initiated with programmed electrical stimulation but could be provoked by intravenous isoproterenol infusion; furthermore, VT could not be terminated with overdrive ventricular pacing but could be abolished by discontinuing isoproterenol infusion. These observations suggest that the mechanism of exercise-induced VT varies among patients; it can be caused by either reentry or catecholamine-sensitive abnormal automaticity.

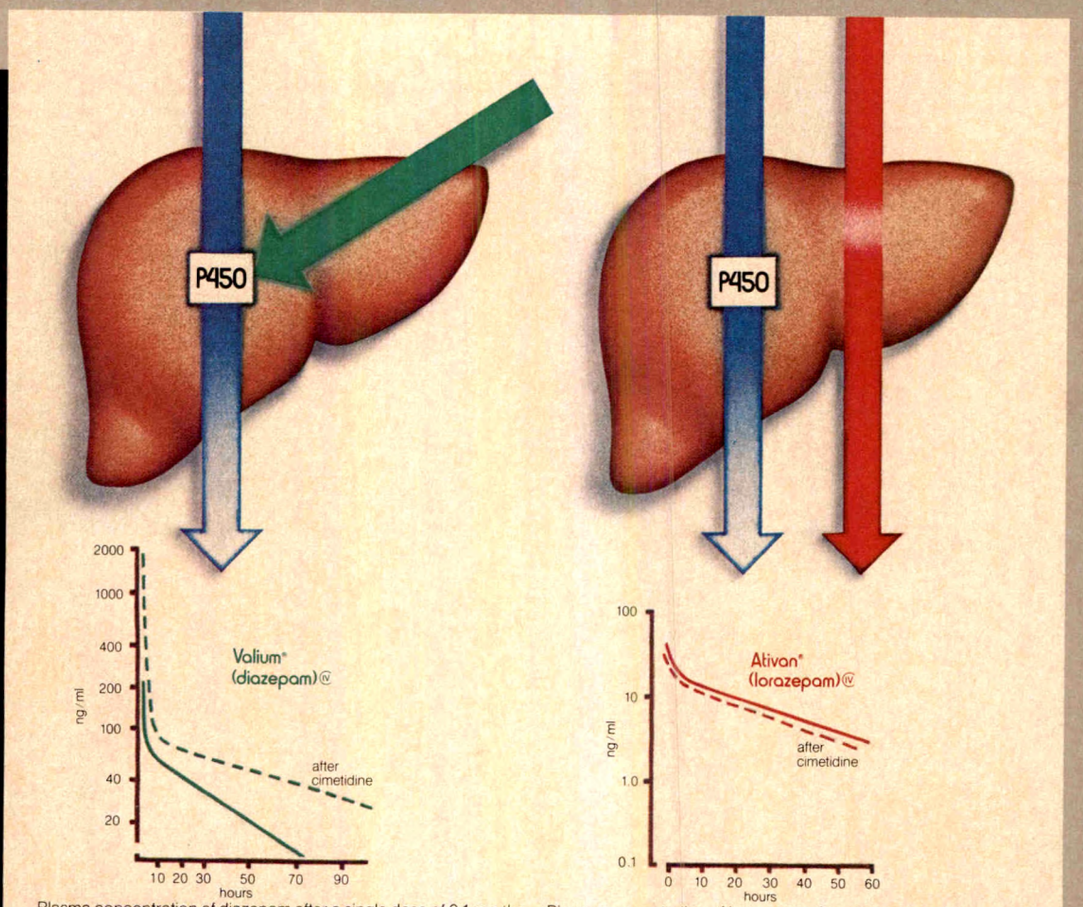
**531 Programmed Electrical Stimulation of the Heart in Coronary Artery Disease**

PETER R. KOWEY, EDWARD D. FOLLAND, ALFRED F. PARISI, and BERNARD LOWN

Patients who have had ventricular tachycardia or fibrillation frequently undergo electrophysiologic evaluation to permit the selection of appropriate therapy. However, these techniques have not been systematically applied to patients with coronary disease and no history of ventricular tachyarrhythmias. This study reports the results

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Plasma concentration of lorazepam after single dose of 2 mg IV in 8 normal subjects before (—) and after (---) 7 days of treatment with cimetidine, 300 mg orally qid. (Adapted from Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980.)

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**Brief Summary of Prescribing Information.**

**Indications and Usage:** Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

**Contraindications:** Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

**Warnings:** Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

**Precautions:** In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

**Adverse Reactions,** if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

**Overdosage:** In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

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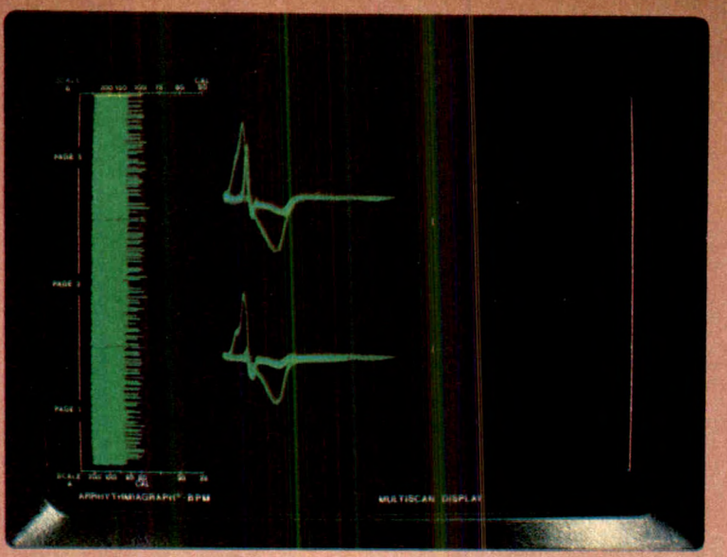
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of extrastimulation in 32 patients. Fourteen of the patients manifested ≥3 extraventricular responses to ≥3 right ventricular stimuli delivered during ventricular pacing. Twelve (86%) of these 14 had evidence of left ventricular dysfunction. The remaining 18 patients had ≤2 responses, and only 4 (22%) had ventricular dysfunction. Proximal 3-vessel coronary disease was more common in patients with ≥3 responses. Only 5 patients demonstrated complex arrhythmia during exercise testing or ambulatory monitoring. The induction of ventricular responses during extrastimulation may serve as an independent marker of electrical instability in the coronary population and is much more common in patients with ventricular dysfunction.

## CONGENITAL HEART DISEASE

**537 Juxtaductal Aortic Coarctation. Analysis of 84 Patients Studied Hemodynamically, Angiographically, and Morphologically After Age 1 Year**

D. LUKE GLANCY, ANDREW G. MORROW, ALLAN L. SIMON, and WILLIAM C. ROBERTS

Clinical, hemodynamic, angiographic, operative, and pathoanatomic features of juxtaductal aortic coarctation were correlated in 84 patients aged >1 year. Associated cardiovascular malformations occurred in 36 (43%). Aortic valve disease, patent ductus arteriosus, mitral valve disease, and ventricular septal defect, alone or in combination, occurred in 34. Systolic blood pressures were significantly elevated *for age* in 80% of all patients and in 90% of the 70 patients operated on. Of the latter, 3 (4%) died, and each had complex associated malformations. Blood pressure decreased after operation in most patients, but remained significantly increased for age late postoperatively in 25%. Detailed histologic studies of 72 coarctation specimens disclosed the luminal narrowing to be caused primarily by invagination of the elastic media of the posterior wall of aorta toward the ductus or ligamentum. Intimal jet lesions often caused further narrowing. The diameters of the aortic lumens correlated directly with the diameters measured angiographically and inversely with the prevalence of radiographically visible rib notching, the magnitude of collateral circulation seen angiographically, and, for luminal diameters ≥1.5 mm, the mean pressure gradient across the coarctation. The data suggest that with luminal diameters <1.5 mm, most blood reaches the descending aorta by collateral vessels.

**552 Hemodynamics and Intracardiac Conduction After Operative Repair of Tetralogy of Fallot**

DOLORES TAMER, GRACE S. WOLFF, PEDRO FERRER, ARTHUR S. PICKOFF, ALFONSO CASTA, ASHOK V. MEHTA, OTTO GARCIA, and ARTHUR GELBAND

Postoperative cardiac catheterization and electrophysiologic studies were done in 47 children 1 to 13 years after surgery for tetralogy of Fallot. Fifteen had arrhythmias, and 8 of these had ventricular extrasystoles. Abnormalities of intracardiac conduction were found in children with and without arrhythmia and were not related to residual hemodynamics. The prognostic significance of the arrhythmias and the conduction abnormalities will require further follow-up studies.

**557 Terminal Cardiac Electrical Activity in Pediatric Patients**

CHRISTINE KULL WALSH and EHUD KRONGRAD

To determine terminal cardiac electrical activity in children, 100 hospitalized pediatric patients were studied during the death process. The terminal cardiac electrical activity was bradycardic arrest throughout the death process in 88% of newborns, 67% of infants, and 64% of children. Although bradycardic arrest was still most common, the incidence of ventricular tachyarrhythmias increased in patients who were beyond the neonatal period, who weighed >2.23 kg, who had congenital heart disease, or who received cardiopulmonary resuscitation. No definite association could be established between arterial blood gases, electrolyte values, and type of terminal cardiac electrical activity. These clinical observations support electrophysiologic data suggesting that the development of ventricular fibrillation may be related to cardiac mass and the developing autonomic nervous system, and therefore that it may be less likely to occur in smaller hearts.

**562 Percutaneous Transluminal Angioplasty of Congenital Coarctation of the Aorta**

DONALD R. SPERLING, THOMAS J. DORSEY, MARSHALL ROWEN, and ALAN B. GAZZANIGA

Two cases in which congenital coarctation of the aorta was dilated using the Gruntzig technique are reported. The patients were aged 3 weeks and 11 months, and the gradients were reduced from 50 to 6 mm Hg and from 23 to 7 mm Hg. Surgery was postponed and symptoms abated in the 3-week-old infant. The older patient's pulses have remained palpable and blood pressures have remained equal for 8 months.

Continued on Page A39

# ISOPTIN® (verapamil HCl/Knoll) TABLETS OR NIFEDIPINE?

## Given these facts, which would you choose?

In angina of effort, Isoptin "...was more effective and better tolerated than nifedipine..."

B Subramanian, et al, *Am J Cardiol*, 1982[1]

In angina of effort, Isoptin and nifedipine "...were equally effective...but side effects were more common with nifedipine."

JR Dawson, et al, *Br Heart J*, 1981[2]

In angina at rest, Isoptin and nifedipine "...are of similar efficacy...However, adverse effects occurred more frequently with nifedipine..."

MD Winniford, et al, *Am J Cardiol*, 1982[3]

Please see last page of this advertisement for brief summary of prescribing information.

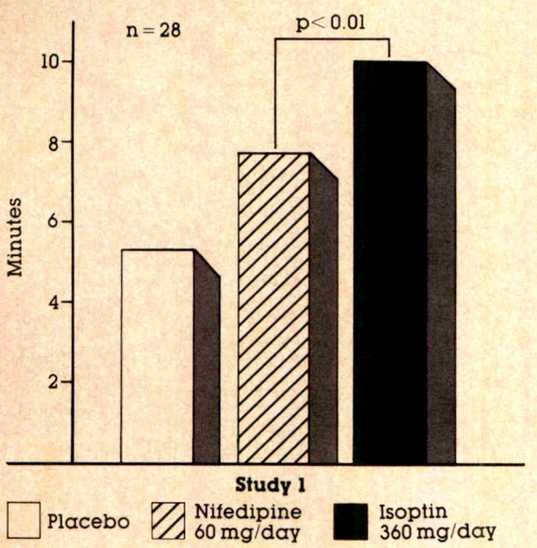
# ISOPTIN® (verapamil HCl/Knoll) TABLETS OR NIFEDIPINE?

Over 20 years and 18 million patient years of experience make Isoptin the most thoroughly studied of the calcium channel blockers. Is it any wonder that Isoptin — not nifedipine or diltiazem — is indicated for first-line therapy of all forms of angina pectoris?

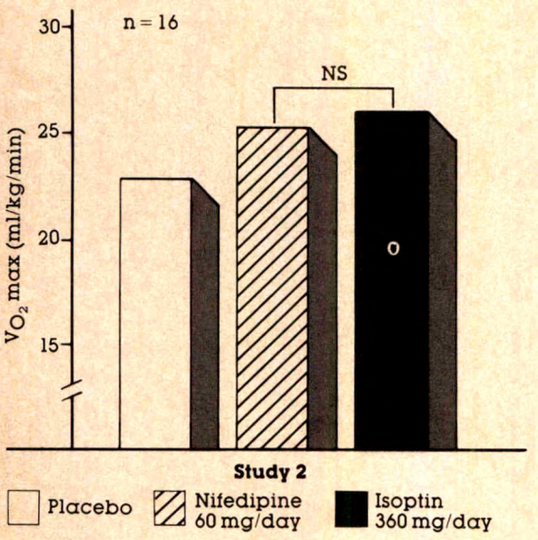
Before making your choice, consider the following clinical results. And consider the long history of safety and efficacy that makes Isoptin one of the most widely prescribed calcium channel blockers in the world.

# Isoptin was equal or superior in efficacy in angina of effort

Mean Maximal Exercise Time
**ISOPTIN MORE EFFECTIVE**[1]

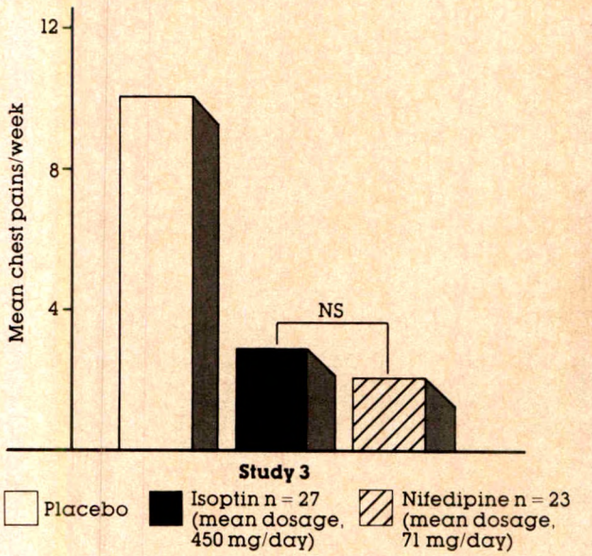



Mean Maximal Work Capacity
**ISOPTIN AS EFFECTIVE**[2]




# Isoptin was equal in efficacy in angina at rest

Angina Frequency
**ISOPTIN AS EFFECTIVE**[3]




# In all forms of angina, Isoptin caused fewer side effects

**Study 1:** "Few adverse reactions were noted with verapamil (Isoptin); none were serious, and none required discontinuation ... In contrast, 7 of the 32 patients developed side effects during nifedipine therapy serious enough to require its withdrawal..."[1]

**Study 2:** "...side effects with nifedipine occur frequently...In contrast, verapamil (Isoptin) was relatively free from side effects apart from constipation..."[2]

**Study 3:** "...adverse reactions limited the amount of nifedipine that could be administered; in contrast, side effects during verapamil (Isoptin) administration were relatively minor and did not alter the dosage."[3]

Please see next page for brief summary of prescribing information.

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Isoptin is contraindicated in severe left ventricular dysfunction, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), and second- or third-degree AV block.

# ISOPTIN®

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**Contraindications:** Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before ISOPTIN is used. ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild, and controlled by decrease in ISOPTIN dose). Occasional elevations of liver enzymes have been reported; patients receiving ISOPTIN should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g., W-P-W or L-G-L syndromes) may develop a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema, and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with ISOPTIN. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patient carefully monitored. ISOPTIN may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C*: There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in 80 mg and 120 mg sugar-coated tablets.
July 1982 2068

**References: 1.** Subramanian B, Bowles MJ, Khurmi NS, et al: Rationale for the choice of calcium antagonists in chronic stable angina. An objective double blind placebo-controlled comparison of nifedipine and verapamil. *Am J Cardiol* 50:1173-1179, 1982. **2.** Dawson JR, Whitaker NHG, Sutton GC: Calcium antagonist drugs in chronic stable angina: *Comparison of verapamil and nifedipine. Br Heart J* 46:508-512, 1981. **3.** Winniford MD, Johnson SM, Mauritson DR, et al: Verapamil therapy for Prinzmetal's variant angina. Comparison with placebo and nifedipine. *Am J Cardiol* 50:913-918, 1982.

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## MISCELLANEOUS TOPICS


**565 Subepicardial Adipose Tissue Producing Echocardiographic Appearance of Pericardial Effusion. Documentation by Computed Tomography and Necropsy**

JEFFREY M. ISNER, BARBARA L. CARTER, WILLIAM C. ROBERTS, and MARK S. BANKOFF

Computed tomographic imaging and necropsy examination were used to study the basis for an isolated anterior echo-free space in 3 patients and a combination anteroposterior echo-free space in 2 patients. In all 5 patients the echo-free spaces were determined to represent subepicardial adipose tissue. In 2 patients with cardiac neoplasms, the echo-free space caused by fat was interposed between the overlying neoplasm and the underlying myocardium. These findings confirm that subepicardial fat is the basis for the finding of an isolated anterior echo-free space as well as for echocardiograms previously reported as being falsely positive for pericardial effusion in patients with a cardiac neoplasm.

**570 Exercise-Induced Cardiac Dysfunction in Sickle Cell Anemia. A Radionuclide Study**

WESLEY COVITZ, CASIMIR EUBIG, IAN C. BALFOUR, RAJINDER JERATH, BRUCE S. ALPERT, WILLIAM B. STRONG, and ROBERT H. DuRANT, *With the technical assistance of* BONNIE G. HADDEN

The objective of this study was to characterize the abnormalities of cardiac function that result in poor exercise performance in adolescents with sickle cell anemia. Cardiac performance was studied by radionuclide angiography at rest and during exercise in 22 patients and 12 control subjects. At maximal exercise, the heart rate, ejection fraction, and percent increase in cardiac output were significantly lower than normal. Four subjects had an abnormal ejection fraction response in association with electrocardiographic signs of ischemia. The cardiac output response was related to the severity of anemia. A decrease in left ventricular end-diastolic volume at maximal exercise was noted in the sickle cell patients and was associated with a reduced cardiac output response. Exercise intolerance appears, therefore, to be due to the demands put on the circulation by the anemia itself; however, the ability of the heart to cope is reduced as abnormalities of systolic and diastolic function develop.


## METHODS


**576 Variability of Digitized Echocardiography: Size, Source, and Means of Reduction**

CHARLES POLLICK, PETER J. FITZGERALD, and RICHARD L. POPP

The technical and biologic variability of digitized M-mode echocardiographic measurements of the left ventricle was assessed. Technical variability was small, with correlation coefficients of 0.70 to 1.00 between and within observers. Biologic variability was large, with expected normal differences between 2 measurements (95% confidence limits) of 11 to 55%, and 37 to 106% for standard dimensions and rates of change, respectively. By averaging measurements of 5 beats from each of 2 days, the expected normal differences are reduced to 6 to 32%, and 23 to 63% for standard dimensions and rates of change. This study emphasizes the large biologic variability and rates of change of digitized left ventricular measurements. Normal variation between studies can be reduced and real physiologic or pathologic changes perceived best if many beats from more than 1 day are measured.

**583 Left Ventricular Isovolumic Pressure Decay and Diastolic Mechanics After Postextrasystolic Potentiation and During Exercise**

JOHN D. CARROLL, RENÉ WIDMER, OTTO M. HESS, HEINZ O. HIRZEL, and HANS P. KRAYENBUEHL

Left ventricular contraction, relaxation, and diastolic mechanics were examined in man after postextrasystolic potentiation and contrasted with dynamic exercise. Twelve patients had extrasystoles induced during left ventricular cineangiography (PES Group). Six patients with no or minimal cardiovascular disease underwent exercise (Exercise Group). From high-fidelity pressure curves the time constant of relaxation, a theoretical baseline for isovolumic pressure decay, and the lowest diastolic pressure were determined. Frame-by-frame analysis was used to quantitate filling and to construct diastolic pressure-volume relations. It is concluded that postextrasystolic potentiation, like dynamic exercise, enhances shortening and augments restoring forces by producing a smaller end-systolic chamber. Yet postextrasystolic potentiation prolongs relaxation. Diastolic mechanics are not subsequently altered, suggesting that enhanced restoring forces counterbalance the slower inactivation. With exercise diastolic filling is enhanced, with both more rapid pressure decay and increased restoring forces.


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# CONTENTS


## EXPERIMENTAL STUDIES

591 **Comparison of the Antithrombotic Action of Calcium Antagonist Drugs With Dipyridamole in Dogs**

CHARLES W. PUMPHREY, VALENTIN FUSTER, MRINAL K. DEWANJEE, JAMES H. CHESEBRO, RONALD E. VLIETSTRA, and MICHAEL P. KAYE, *With the technical assistance of* JOHN RITTER and JAMES ROSEMARK

Because platelet activation involves a flux of calcium into the cytoplasm, calcium antagonist drugs such as verapamil and nifedipine may have value as platelet inhibitor drugs. Thus, the antithrombotic effects of these drugs in preventing indium-111–labeled platelet deposition and thrombus formation in bilateral polytetrafluoroethylene femorofemoral artery grafts in mongrel dogs were compared with those of dipyridamole, an established platelet inhibitor drug, and isotonic saline solution. Verapamil, nifedipine, and dipyridamole significantly reduced indium-111–labeled platelet deposition and the weight of thrombus in the grafts after 3 hours of blood flow compared with saline infusion. The calcium antagonist drugs are as effective as dipyridamole in preventing thrombus formation through inhibition of platelet deposition in this model but require further study in humans.

596 **Influence of Intracoronary Platelet Aggregation on Ventricular Electrical Properties During Partial Coronary Artery Stenosis**

PETER R. KOWEY, RICHARD L. VERRIER, BERNARD LOWN, and ROBERT I. HANDIN

Clinical studies have suggested that drugs which inhibit platelet function may protect against sudden death after myocardial infarction. That intracoronary platelet aggregation causes cardiac arrhythmia, however, has not been proven. Induction of coronary stenoses in dogs resulted in cyclical flow reductions, previously demonstrated to be associated with endothelial formation of platelet aggregates. These reductions were accompanied by a significant lowering of the vulnerable period threshold. Prostacyclin and indomethacin each caused a decrease in the frequency and intensity of the coronary flow reductions and returned the ventricular fibrillation threshold to control levels. The mechanism of flow reduction appears to be mechanical blockade of the vessel lumen by platelet thrombi. These results suggest that intracoronary platelet aggregation contributes to electrical instability and may predispose to ventricular tachyarrhythmias. A model is thus available for further work on the role of antiplatelet drugs in the prevention of sudden cardiac death.

## EDITORIAL

603 **Congestive Heart Failure: A Propitious Time for Intensified Research**

EUGENE BRAUNWALD, MICHAEL M. MOCK, and JOHN T. WATSON

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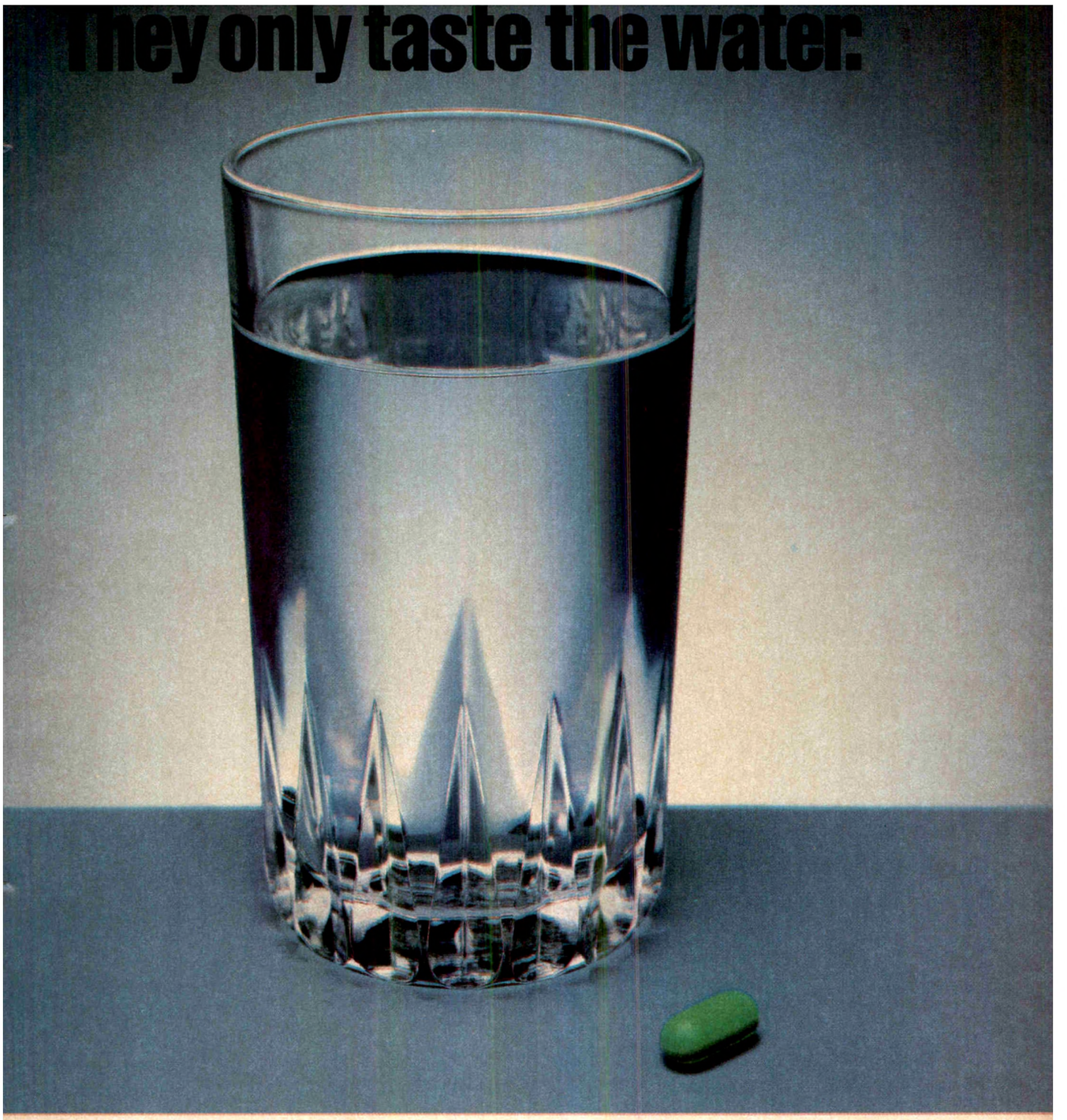
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BRUNO V. MANNO, IOANNIS P. PANIDIS, MORRIS N. KOTLER, GARY S. MINTZ and JOHN ROSS




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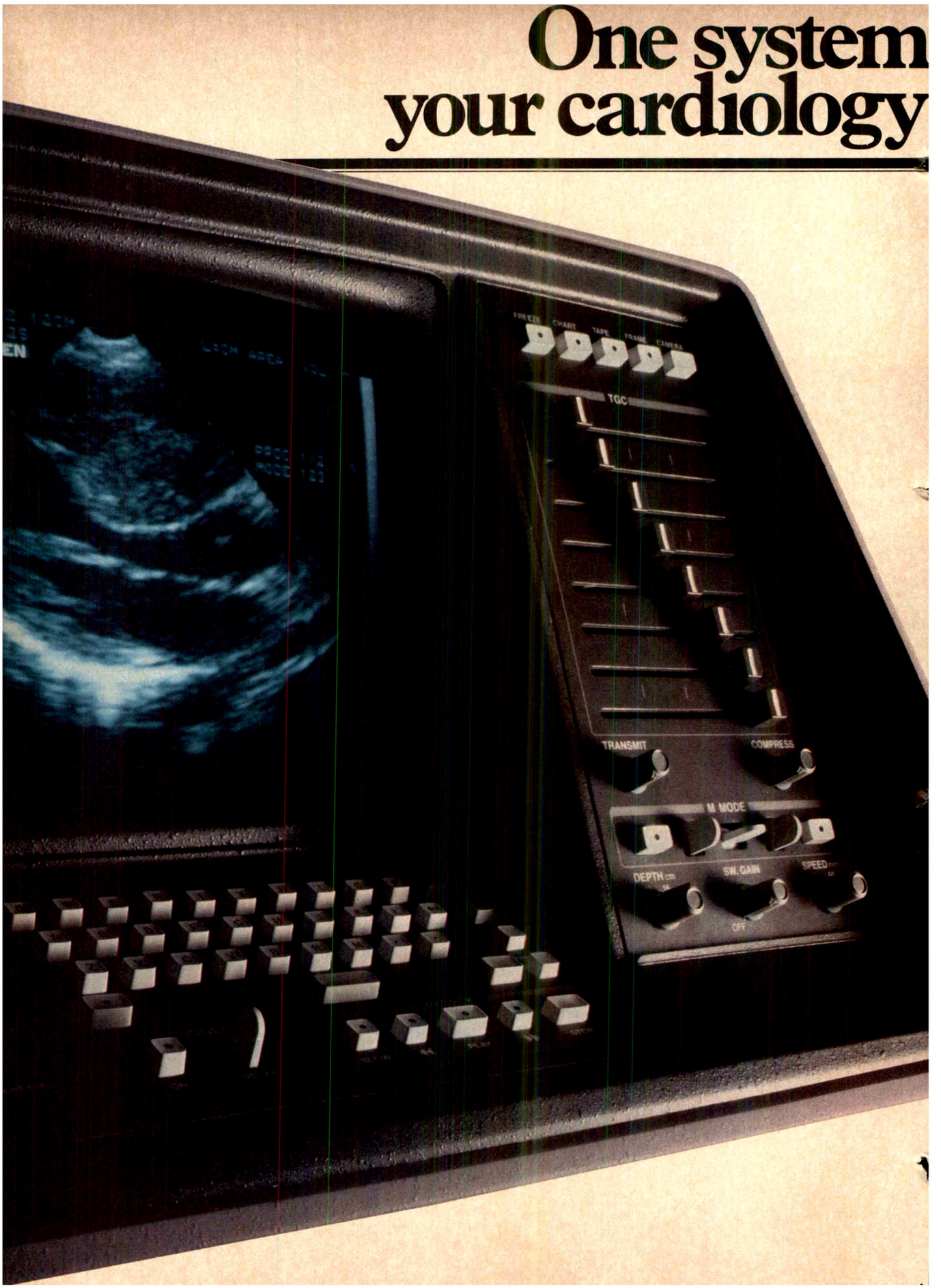
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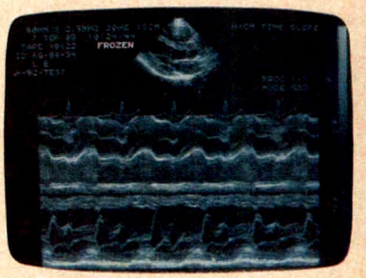
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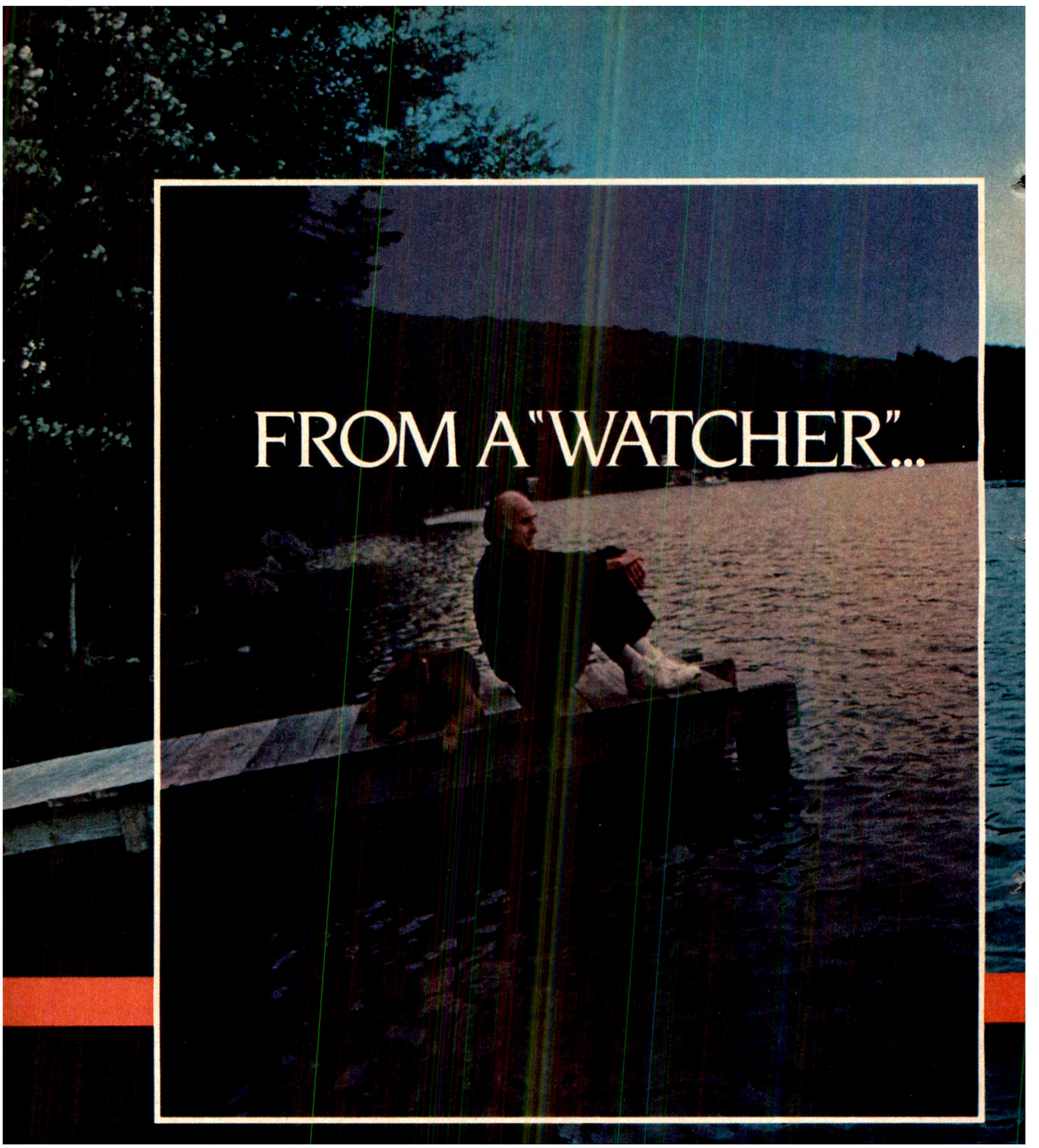
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*Procardia is indicated for the management of:

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# PROCARDIA®
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For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because Procardia decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration is suggested. Close observation is especially recommended for patients taking medication known to lower blood pressure.

## *–Offers a favorable safety profile*

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.


**References:**

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Eng J Med* 302:1269-1273, June 5, 1980.
3. De Ponti C, De Biase AM, Pirelli S, et al: Effects of nifedipine, acebutolol, and their association on exercise tolerance in patients with effort angina. *Cardiology* 68 (suppl 2): 195-199, 1981.


**BRIEF SUMMARY**
**PROCARDIA® CAPSULES** For Oral Use
(nifedipine)

**INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA** (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

**II. Chronic Stable Angina (Classical Effort-Associated Angina):** PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

**CONTRAINDICATIONS:** Known hypersensitivity reaction to PROCARDIA.

**WARNINGS: Excessive Hypotension:** Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out.

**Increased Angina:** Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

**Beta Blocker Withdrawal:** Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

**Congestive Heart Failure:** Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

**PRECAUTIONS: General: Hypotension:** Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

**Peripheral edema:** Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

**Drug interactions:** Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

**ADVERSE REACTIONS:** The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

**Laboratory Tests:** Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

**HOW SUPPLIED:** Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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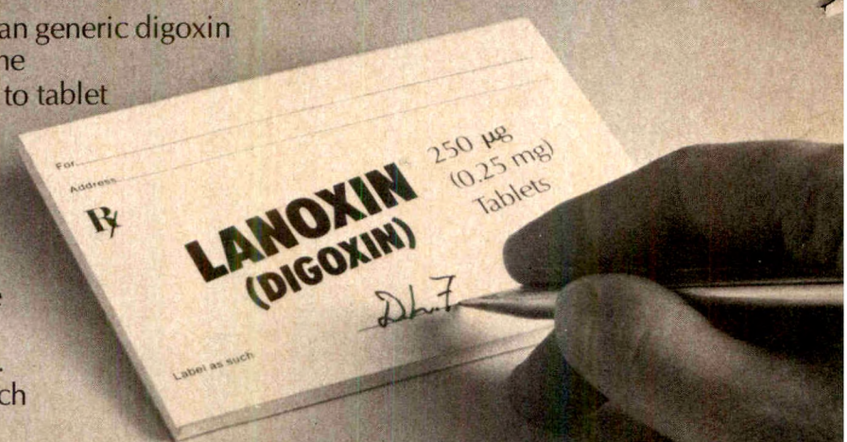
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CORONARY HEART DISEASE

# Effect of Coronary Artery Bypass Grafting on Subsequent Hospitalization

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**The rates of hospitalization during follow-up for a matched pair cohort of medically and surgically treated patients from the Angiography Registry of Seattle Heart Watch were compared. Medically and surgically treated patients were matched according to extent of disease, left ventricular ejection fraction, age, and 3 other survival rate-related characteristics. There was a 26% reduction in cardiovascular hospitalizations in the surgically treated patients (19%/year) compared with the medically treated patients (26%/year). This was due to a significant reduction in hospitalization rate for myocardial infarction (surgically treated patients 1.1%/year, medically treated patients 2.6%/year), and for other cardiovascular reasons (surgically treated patients 12.5%/year, medically treated patients 15.7%/year). No significant (p = 0.146) reduction occurred in hospitalization rate for chest pain not due to myocardial infarction (surgically treated patients 5.6%/year, medically treated patients 7.7%/year). When the perioperative infarctions are included for the surgical cohort, the overall myocardial infarction rate is not significantly different (p = 0.173) between the 2 treatment groups (surgically treated patients 1.9%/year, medically treated patients 2.6%/year). Acute myocardial infarction was an uncommon reason for hospitalization, accounting for only 8% (55 of 685) of all cardiovascular hospitalizations, and was not related to the number of stenotic vessels in medically treated patients.**

There is now reasonable evidence to document the efficacy of coronary artery bypass grafting in prolonging survival (left main disease[1] and 3-vessel disease[2]) and in relieving symptoms of severe angina.[3,4] However, the efficacy of coronary artery bypass surgery in reducing other measures of morbidity such as frequency of hospitalization has not been previously reported. The purpose of this report is to compare the rates of hospitalization during follow-up of a well-characterized, nonrandomized, matched pair cohort of medically and surgically treated patients with coronary artery disease from the Angiography Registry of Seattle Heart Watch.

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## Methods

The Angiography Registry of Seattle Heart Watch was a cooperative; community-wide registry of patients undergoing coronary arteriography for suspected coronary disease. Treatment (medical or surgical) assignment was made on a nonrandom basis by the patient's physician(s). The surgical cohort consists of patients who were operated upon between 1968 and 1974 inclusively, and represents 94% (1,870 of 1,985) of all patients undergoing direct myocardial revascularization

during this period in Seattle. From the 1,870 surgically and 746 medically treated patients initially entered into Seattle Heart Watch, 287 pairs were selected by matching 1 surgical with 1 medical patient according to 7 variables determined previously by multivariate analyses to be predictive of survival.[5] These variables are ejection fraction, ventricular arrhythmia on electrocardiography, age, heart murmur, left main coronary artery stenosis ≥50%, number of vessels with stenosis(es) ≥70%, and diuretic use. Ninety-seven percent (279 of 287) of operated patients had angina; in 44% (126 of 287) this was thought to be unstable. Both the mean number of grafts and the mean number of stenotic vessels (≥70%) per patient were 1.7. Of the 99 operated patients undergoing repeat arteriography, an average of 6 months postoperatively, 56% (55 of 99) had all grafts patent; 34% (34 of 99) at least 1 patent graft, but 1 or more occluded grafts; and 10% (10 of 99) had total occlusion of all grafts. Myocardial protection techniques were those commonly used during this period (1968 to 1974). Systemic, topical hypothermia, or both, were used in 79% (226 of 287), but 21% (61 of 287) were operated at normothermia.

Follow-up for death and hospitalization was by mailed questionnaire at 6-month intervals. Mean follow-up was 6.1 years for medically treated patients and 6.2 years for surgically treated patients. Follow-up has been complete in 92% (263 of 287) of medically treated patients and in 97% (277 of 287) of surgically treated patients. Death occurred in 22% (62 of 287) of the medically treated patients, but only 11% (21 of 287) of the surgically treated patients. Reasons for hospitalization were classified as nonfatal myocardial infarction, chest pain not due to myocardial infarction (includes unstable angina), other cardiovascular causes, and noncardiovascular disease. Diagnoses included among other cardiovascular causes were atherosclerotic heart disease, rhythm disorders, congestive heart failure, embolization, defibrillation, pacemaker implantation, and repeat cardiac catheterization. Hospitalizations culminating in death are not included in this report, so as to not overlap with our other analyses on survival rates.[6-9]

If a patient reported he had been hospitalized for myocardial infarction, heart attack, or symptoms thereof, confirmation of myocardial infarction was obtained from the patient's physician. To ascertain the accuracy of classification of reason for hospitalization into myocardial infarction or chest pain (not myocardial infarction) categories, one of the investigators (KEH) reviewed the discharge summaries, serum enzyme data, and electrocardiograms on 29 randomly selected hospitalizations in these categories. A diagnosis of myocardial infarction was confirmed if any 2 of the following 3 were present: (1) history of prolonged ischemic pain, (2) typical serum enzyme increase and decrease, and (3) appearance of new Q waves on the electrocardiogram. This review agreed with the coded diagnosis in 83% (24 of 29). The electrocardiograms of all patients coded as having a perioperative infarction by their physician were reviewed by one of the investigators (KEH). A diagnosis of perioperative infarction was confirmed if, within 1 week after surgery, there were new Q waves ≥0.02 second in duration or if existing Q waves had widened by ≥0.02 second.

Rates of hospitalization were determined by dividing the number of events (hospitalizations) experienced by the total number of person-years of follow-up time for individual patients and for groups.

Determinations of differences between hospitalization rates for medically versus surgically treated patients used the Wilcoxon signed rank test[10] on paired differences in patient rates. Actuarial curves were constructed to compare time with first hospitalization. Zero time is taken as the date of coronary arteriography for medically treated patients and the date of surgery for surgically treated patients.

## Results

There were no significant differences between the 2 treatment groups in frequency of unstable angina, cardiomegaly, left ventricular hypertrophy on electrocardiography, resting S-T segment depression or elevation, mitral regurgitation, $S_3$ gallop, use of digitalis, or left ventricular end-diastolic pressure, as well as the 7 matching variables. However, some differences in baseline characteristics between medically and surgically treated patients were observed. More surgical

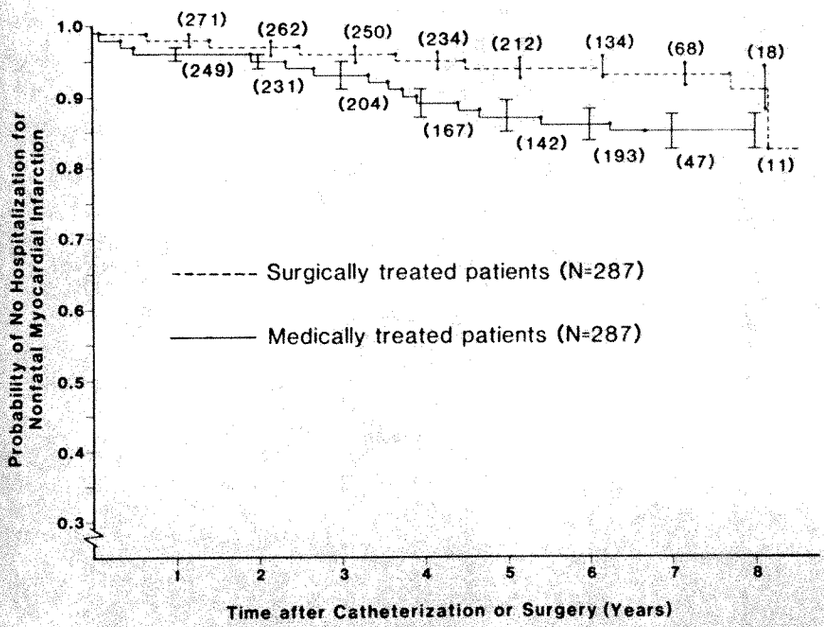



**FIGURE 1.** Actuarial display of time to first hospitalization for nonfatal myocardial infarction (excluding perioperative myocardial infarctions) for medically and surgically treated patients. The numbers in parentheses are the number of patients at risk at each year of follow-up. The **vertical bars** represent 1 standard error.

**TABLE I Number and Rate of Hospitalizations for Myocardial Infarction Per 1,000 Patient-Years of Follow-Up (Perioperative Infarction Not Included)**

| | Medically Treated Patients | | | Surgically Treated Patients | | | |
|---|---|---|---|---|---|---|---|
| Group | n | Hosp | Rate | n | Hosp | Rate | p |
| 1 Vessel | 140 | 19 | 25 | 140 | 11 | 14 | 0.128 |
| 2 Vessel | 97 | 10 | 22 | 97 | 7 | 12 | 0.215 |
| 3 Vessel | 50 | 8 | 30 | 50 | 0 | 0 | 0.012 |
| All patients | 287 | 37 | 26 | 287 | 18 | 11 | 0.004 |

Hosp = number of hospitalizations; n = number of patients in each subgroup; p = significance of difference in hospitalization rates between medically and surgically treated patients.

**TABLE II Number and Rate (Per 1,000 Patient-Years of Follow-Up) of Hospitalizations for Myocardial Infarction (Including Perioperative Myocardial Infarction)**

| | Medically Treated Patients | | | Surgically Treated Patients | | | |
|---|---|---|---|---|---|---|---|
| Group | n | Hosp | Rate | n | Hosp | Rate | p |
| 1 Vessel | 140 | 19 | 25 | 140 | 17 | 21 | 0.705 |
| 2 Vessel | 97 | 10 | 22 | 97 | 11 | 19 | 0.557 |
| 3 Vessel | 50 | 8 | 30 | 50 | 2 | 9 | 0.059 |
| All patients | 287 | 37 | 26 | 287 | 30 | 14 | 0.173 |

Abbreviations as in Table I.

patients were in functional class III or IV (175 of 287, 61%) compared with medically treated patients (92 of 287, 32%; $p < 0.01$). This difference in functional class was consistent with the exercise results; mean functional aerobic impairment (percent decrement from age, sex, and activity status predicted maximal oxygen uptake) was 39 ± 24% for surgically treated patients and 33 ± 24% for medically treated patients ($p < 0.05$). On the other hand, the medically treated patients had a higher frequency of prior myocardial infarction (148 of 287, 52% compared with 113 of 287, 39%; $p < 0.01$). This probably accounted for the slightly larger end-diastolic volume in medically treated patients (75 ± 26 ml/m$^2$) compared with surgically treated patients (68 ± 22 ml/m$^2$; $p < 0.01$).

Table I compares the rates of hospitalization for myocardial infarction during follow-up of medically and surgically treated patients. The rate of hospitalization for myocardial infarction during follow-up in surgically treated patients (1.1%/year) is less than half that of medically treated patients (2.6%/year); the subgroup with the largest difference was comprised of patients

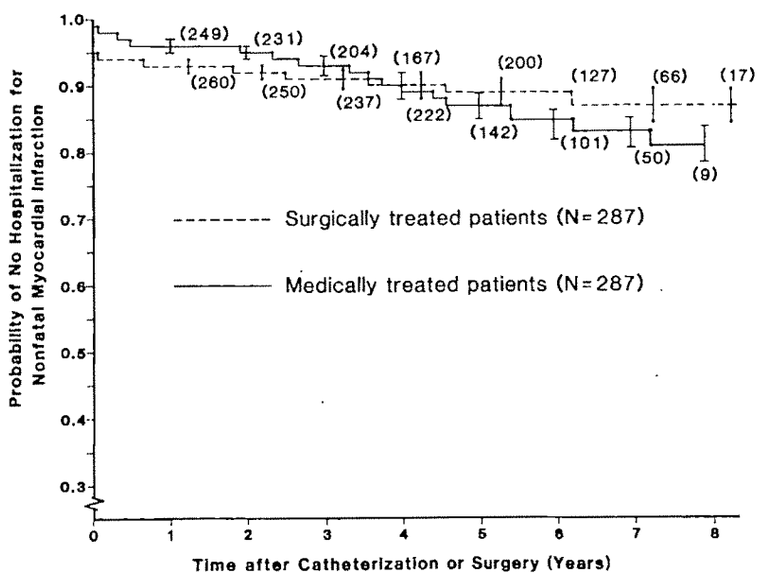



**FIGURE 2.** Actuarial display of time to first nonfatal myocardial infarction including perioperative myocardial infarctions.

**TABLE III Number and Rate of Hospitalizations for Chest Pain (Not Myocardial Infarction) Per 1,000 Patient-Years of Follow-Up**

| | Medically Treated Patients | | | Surgically Treated Patients | | | |
|---|---|---|---|---|---|---|---|
| Group | n | Hosp | Rate | n | Hosp | Rate | p |
| 1 Vessel | 140 | 68 | 90 | 140 | 61 | 75 | 0.426 |
| 2 Vessel | 97 | 29 | 64 | 97 | 25 | 44 | 0.600 |
| 3 Vessel | 50 | 14 | 60 | 50 | 4 | 17 | 0.069 |
| All patients | 287 | 111 | 77 | 287 | 90 | 56 | 0.146 |

Abbreviations as in Table I.

**TABLE IV Number and Rate of Hospitalizations for Other Cardiovascular Reasons Per 1,000 Patient-Years of Follow-Up**

| | Medically Treated Patients | | | Surgically Treated Patients | | | |
|---|---|---|---|---|---|---|---|
| Group | n | Hosp | Rate | n | Hosp | Rate | p |
| 1 Vessel | 140 | 115 | 152 | 140 | 112 | 138 | 0.203 |
| 2 Vessel | 97 | 79 | 173 | 97 | 47 | 82.2 | 0.001 |
| 3 Vessel | 50 | 33 | 142 | 50 | 43 | 183 | 0.978 |
| All patients | 287 | 227 | 157 | 287 | 202 | 125 | 0.004 |

Abbreviations as in Table I.

**TABLE V Distribution of "Other Cardiovascular" Hospitalizations by Reason and Treatment**

| Reason | Medically Treated Patients | Surgically Treated Patients |
|---|---|---|
| ASCVD | 44 | 40 |
| Rhythm disturbance | 29 | 14 |
| Surgery (cardiac) | 40 | 9 |
| CHF | 13 | 5 |
| Stroke | 14 | 6 |
| Peripheral vascular disease | 15 | 19 |
| Embolism | 1 | 6 |
| Defibrillation | 1 | 0 |
| Pacemaker | 7 | 1 |
| Cardiac catheterization | 63 | 93 |
| Other | 0 | 9 |
| Total | 227 | 202 |

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure.

with 3-vessel coronary disease. Figure 1 is an actuarial display of time to first hospitalization for myocardial infarction showing that at 5 years approximately 14% of medically treated patients, but only 5% of surgically treated patients, will have been hospitalized at least once for myocardial infarction.

The preceding analysis did not include perioperative infarctions (12 of 287, 4.2%) in the surgically treated patients. The analysis shown in Table II includes the data in Table I with the addition of these 12 surgical perioperative infarctions. There is now no significant difference ($p = 0.173$) in total myocardial infarction rate between medically (2.6%/year) and surgically (1.9%/year) treated patients for the total cohort or any subgroup. Figure 2 shows the actuarial curves of time to first myocardial infarction (perioperative infarctions included), again indicating no difference between treatment groups.

The numbers and rates of hospitalization for chest pain not due to myocardial infarction for medically and surgically treated patients are shown in Table III. While the differences in the rates are not significant, there is a trend toward a lower rate of hospitalization for surgically treated patients both for the total cohort (5.6%/year versus 7.7%/year; $p = 0.146$) and for patients with 3-vessel disease (6.0%/year versus 1.7%/year; $p = 0.069$).

Table IV shows that the rate of hospitalization for other cardiovascular reasons is significantly lower ($p = 0.004$) in surgically treated patients (12.5%/year) compared with medically treated patients (15.7%/year). When patients are divided into subgroups according to number of stenotic vessels, patients with 2-vessel disease show a highly significant difference ($p = 0.001$). Table V shows the frequency of hospitalization by each specific diagnosis included under "other" cardiovascular reasons; fewer hospitalizations occurred in surgically treated patients even though they were hospitalized more frequently for cardiac catheterizations, some of which were undoubtedly investigational.

Table VI lists the rates of hospitalization for all cardiovascular reasons during follow-up (perioperative myocardial infarctions were excluded). There is a highly significant ($p < 0.001$) difference overall in favor of surgical therapy, due primarily to the differences in the 2-vessel disease subgroup. Linearized annual hospitalization rates are 25.9% for medically treated patients and 19.1% for surgically treated patients, which is 26% fewer total cardiovascular hospitalizations for surgically treated patients. Figure 3 is an actuarial display of time to first hospitalization for any cardiovascular reason

**TABLE VI Number and Rate of All Cardiovascular Hospitalizations (Excluding Perioperative Myocardial Infarction) Per 1,000 Patient-Years of Follow-Up**

| | Medically Treated Patients | | | Surgically Treated Patients | | | |
|---|---|---|---|---|---|---|---|
| Group | n | Hosp | Rate | n | Hosp | Rate | p |
| 1 Vessel | 140 | 202 | 267 | 140 | 184 | 226 | 0.034 |
| 2 Vessel | 97 | 118 | 259 | 97 | 79 | 138 | 0.003 |
| 3 Vessel | 50 | 55 | 237 | 50 | 47 | 200 | 0.343 |
| All patients | 287 | 375 | 259 | 287 | 310 | 191 | <0.001 |

Abbreviations as in Table I.

**TABLE VII Number of Patients With None, 1, and Multiple Cardiovascular Hospitalizations During Follow-Up**

| Hospitalizations/ Patient | Medically Treated Patients | Surgically Treated Patients |
|---|---|---|
| 0 | 118 | 143 |
| 1 | 71 | 75 |
| 2 | 49 | 34 |
| 3 | 24 | 16 |
| 4 | 12 | 6 |
| >4 | 13 | 13 |

comparing medically and surgically treated patients. Half of the medically treated patients had 1 or more hospitalizations for cardiovascular disease within 3 years of angiography, while it took 5 years before 50% of surgically treated patients had been hospitalized at least once after surgery.

In Table VII, the numbers of patients with none, 1, or more than 1 cardiovascular disease hospitalization are shown. No cardiovascular hospitalizations were observed in 41% (118 of 287) of medically treated patients and 50% (143 of 287) of surgically treated patients, while multiple hospitalizations occurred in 34% (98 of 287) of medically treated patients and 24% (69 of 287) of surgically treated patients.

Table VIII and Figure 4 show no significant differences in rate of hospitalization for noncardiovascular reasons between medically and surgically treated patients or between patients with 1-, 2-, or 3-vessel disease. Hospitalization for noncardiovascular reasons accounts for 34% (357 of 1,042) of all hospitalizations.

## Discussion

A 26% reduction in cardiovascular hospitalization was observed in surgically treated compared with medically treated patients with coronary disease in our matched pair cohort. This was due to significant reductions in hospitalization among patients treated surgically for myocardial infarction and other cardiovascular reasons and a trend toward a reduced rate for chest pain.

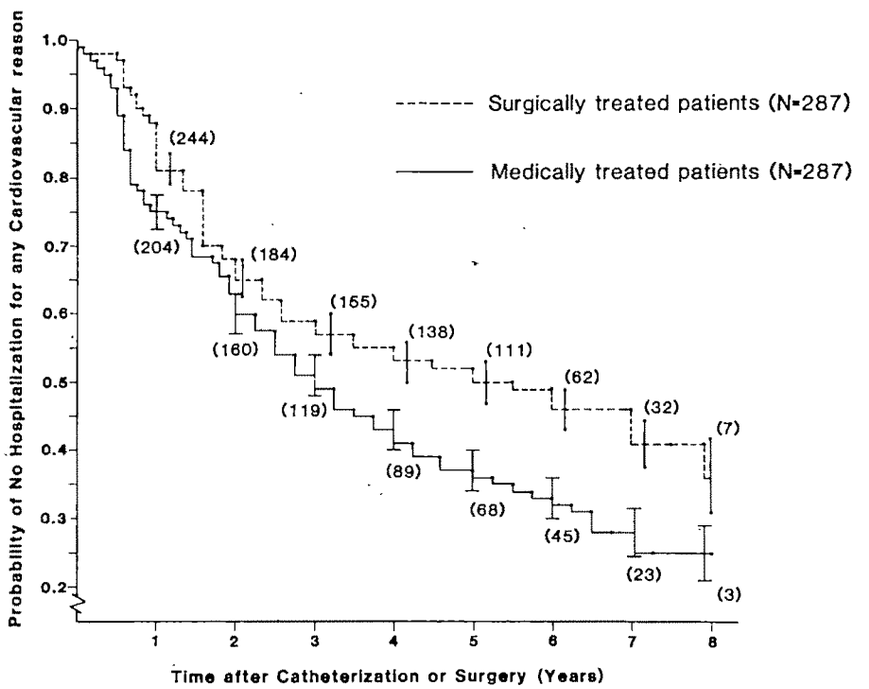



**FIGURE 3.** Actuarial display of time to first hospitalization for any cardiovascular reason.

However, when the perioperative myocardial infarctions are also counted, there is not a statistically significant difference in infarction rates between the 2 treatment groups.

The comparison of nonfatal coronary event rates between medically and surgically treated coronary disease patients is complicated by a number of problems. First is the detection of the event. Our data include only events associated with hospitalization. Thus, myocardial infarctions not resulting in hospitalization (for example, "silent infarction") are not included, because routine electrocardiograms were not obtained on our patients.

In the Framingham study 23% (73 of 319) of first myocardial infarctions between 1950 and 1970 were "unrecognized," that is, did not result in medical attention with a correct diagnosis, but were detected on a study electrocardiogram.[11] The proportion of undetected infarctions in Seattle Heart Watch is likely to be lower than that for Framingham study of 10 to 30 years earlier, given the widespread public education about coronary heart disease, the relative medical sophistication of the Seattle community, and the ready availability of a superb, rapid-response, emergency medical care system (Medic I). Regardless, we know of no reason to believe that undetected infarction would occur more frequently in 1 treatment group than the other. The rate of nonfatal myocardial infarction reported here for medically treated patients (2.6%/year) is identical to that reported by Harris et al[12] from the Duke data bank (2.6%/year). Both studies show that nonfatal infarction occurs about half as frequently as death. Total myocardial infarction rates are also underestimated by the limitation to nonfatal events. We chose to do this both because we did not want these analyses overlapping with our survival analyses,[5-9] and because of the difficulty of diagnosing myocardial infarction in patients who die soon after onset of acute symptoms; 49% (46 of 93) of the deaths in the matched pair cohort occurred within 24 hours of the onset of acute symptoms.

Second is the problem of accuracy of diagnosis. Follow-up of our patients was by a questionnaire mailed to the patient. If the patient reported a reason for hospitalization that was suggestive of acute infarction, confirmation was sought from the patient's physician, but primary data (electrocardiographic and enzyme changes) were not included in the data file. However, a careful review of detailed data (discharge summary, serial serum enzyme values, and serial electrocardiograms) on a random sample of 29 hospitalizations coded as chest pain (not infarction) or myocardial infarction indicated 83% (24 of 29) correct diagnoses.

Third is the problem presented by the unequal loss of patients from both treatment groups. Twice as many medically treated patients (62) died as surgically treated patients (31). Furthermore, 16% (47 of 287) of the initially medically treated patients crossed over to surgical therapy during follow-up because of unacceptable symptoms. While both of these events were treated as "patient lost-to-follow-up" in the data analyses, it is likely that these patients were at higher risk for hospitalization, myocardial infarction, or both, than the patients who remained in the medical cohort. This problem, for which there is no entirely satisfactory solution, is likely to bias the results against surgical therapy.

Fourth, we are comparing 2 forms of therapy that have clearly evolved and improved since the entry of these patients into Seattle Heart Watch. Both operative mortality and perioperative infarction rates have fallen by ≥50%—due in large part to improved myocardial protection.[13,14] Medical therapy has undoubtedly improved as well, but this change is less easily quantified. Yet, it is impossible to assess relatively infrequently occurring events such as death or hospitalization without long-term follow-up, which implies outmoded initial therapy (the "catch-22" of long-term coronary disease studies).

Finally, there is a problem peculiar to nonrandomized observational studies: the 2 treatment groups are not identical. We have documented this in our patients

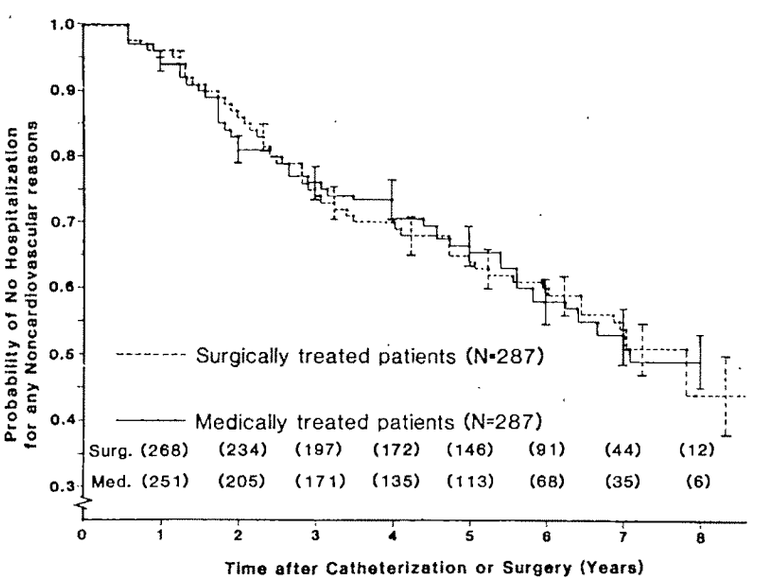



**FIGURE 4.** Actuarial display of time to first hospitalization for any noncardiovascular reason.

**TABLE VIII Number and Rate of All Noncardiovascular Hospitalizations Per 1,000 Patient-Years of Follow-Up**

| | Medically Treated Patients | | | Surgically Treated Patients | | | |
|---|---|---|---|---|---|---|---|
| Group | n | Hosp | Rate | n | Hosp | Rate | p |
| 1 Vessel | 140 | 86 | 114 | 140 | 89 | 109 | 0.402 |
| 2 Vessel | 97 | 54 | 118 | 97 | 73 | 128 | 0.528 |
| 3 Vessel | 50 | 24 | 103 | 50 | 31 | 132 | 0.869 |
| All patients | 287 | 164 | 113 | 287 | 193 | 119 | 0.96 |

Abbreviations as in Table I.

despite matching on 7 different baseline characteristics. However, it is not clear in which direction the observed differences in baseline characteristics would influence the outcome variables. It might well be that the greater symptomatic status of the surgically treated patients at entry has an effect opposite to the slightly poorer left ventricular function and greater frequency of prior myocardial infarction in the medically treated patients. The virtually identical rates of hospitalization for noncardiovascular reasons indicate that the general health status of the 2 treatment cohorts was similar.

We would predict the various biases discussed above to either act equally in both treatment groups (incomplete detection of myocardial infarction, <100% accurate diagnosis of myocardial infarction, unequal distribution of baseline characteristics) or to bias the results against surgical therapy (excessive loss of medically treated patients at risk and recent improvements in surgical techniques). Thus, we would attribute the reduction in hospitalization rate for all cardiovascular reasons as being most likely due to surgical therapy. The reduction is not dramatic (26%), but may be influenced by a higher frequency of postoperative catheterization (93 of 287, 32%) then than now.

Whether myocardial infarction can be prevented by coronary bypass surgery has been a question of great interest. The 2 large randomized trials on stable angina[2,15] have not reported data on this question, perhaps because of the methodologic problems discussed above. Two small single-institution randomized trials comparing medical with surgical therapy of stable angina pectoris have not shown any difference in myocardial infarction rates,[3,16] as was the case with an observational nonrandomized study of patients with disease confined to the proximal left anterior descending coronary artery.[17] The number of patients in these 3 studies probably was not large enough to be reasonably certain of detecting a treatment difference, if such difference did actually exist—for example, an acceptably low type II or beta error.[18] In patients presenting with unstable angina, neither the small single-institution randomized trial from Portland,[19] nor the much larger National Heart, Lung, and Blood Institute sponsored multicenter randomized trial[20] have shown a reduction in myocardial infarction rates with surgery. The perioperative infarction rate in the latter study, however, was high (24 of 141, 17%), possibly because the protocol was designed to test the effect of immediate surgery (with no medical "cooling off" period) against conventional medical therapy. Our data on hospitalization rates for myocardial infarction do not provide a convincing answer to the question. While the hospitalization rate for myocardial infarction during follow-up in the surgically treated patients (1.1%/year) was less than half that of the medically treated patients (2.6%/year, $p = 0.004$), the inclusion of the perioperative infarctions eliminates the statistically significant difference, even though there continues to be a trend favoring surgical therapy (1.9%/year compared with 2.6%/year). We look forward to data from the 3 large, randomized trials of medical versus surgical therapy (the European Coronary Surgery Study,[2] the Veterans Administration Cooperative Study,[15] and the National Heart, Lung, and Blood Institute-sponsored coronary artery surgery study[21]), which will hopefully shed light on this important question.

Our data provide 2 interesting insights into the occurrence of hospitalization for myocardial infarction in patients with documented coronary disease. First, it is an uncommon cause of hospitalization, accounting for only 8% (55 of 685) of all cardiovascular hospitalizations, with the percentage being fairly similar for medical (9.9%; 37 of 375) and surgical (5.8%; 18 of 310) cohorts. Hospitalization for chest pain (not myocardial infarction) was, by far, the most frequent cause of hospitalization, accounting for 29% (201 of 685) of all cardiovascular hospitalizations. Second, there does not appear to be an increased likelihood of being hospitalized for myocardial infarction with increasing extent of coronary disease. Among medically treated patients, there is only a slight increase in the hospitalization rate for infarction in patients with 3-vessel disease (3.0%/year) compared with patients with 1-vessel disease (2.5%/year). In fact, in the surgical cohort, a gradient in the opposite direction is seen (0%/year in 3-vessel disease patients; 1.4%/year in 1-vessel disease patients). This is in striking contrast to the relation between extent of disease and mortality, where there is about a 3-fold increase in mortality in patients with 3-vessel disease compared with 1-vessel disease.[5,22] There is, of course, no a priori reason why variables predictive of death should be the same as those predictive of nonfatal infarction. In another report from Duke, the probability of developing a nonfatal infarction over 5 years appears to be about equal between medically treated patients with 1-, 2-, or 3-vessel disease.[23]

Great emphasis should not be placed on the fact that there was a statistically significant reduction in hospitalization for other cardiovascular reasons, but not for chest pain (not infarction). The proportionate reduction

in hospitalization rate among surgically treated patients was similar for the 2 categories (21% reduction in hospitalization for other cardiovascular reasons, 27% reduction in hospitalization for chest pain). The likely reason for the lack of statistical significance ($p = 0.146$) in the chest pain category is the fewer number of end points (hospitalizations). There is still the question of why we did not observe a greater reduction in chest pain hospitalizations in the surgically treated patients, as most studies have shown elimination or marked reduction of angina in most operated patients. It is likely that hospitalization for nonischemic chest pain (postoperative pain, musculoskeletal pain, pericarditis) was more common in surgically treated than in medically treated patients. Our data base does not allow separation of these various entities.

Comparison of nonmorbid events between medically and surgically treated coronary disease patients is a complex task with many factors influencing the conclusions. Our data show a 26% reduction in hospitalization rate for all cardiovascular reasons in the surgical cohort, with a similar proportionate reduction in hospitalization for chest pain (not infarction) and other cardiac reasons. This reduction is likely due to surgical therapy and not confounding factors. While we observed a trend toward a reduction in myocardial infarction with surgical therapy, further studies are needed before the effect of myocardial revascularization on subsequent infarction is clear.

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## References

1. **Takaro T, Hultgren H, Lipton MJ, Detre KM, participants of the study group.** The VA Cooperative Randomized Study of Surgery for Coronary Arterial Disease. II. Subgroup with significant left main lesions. Circulation 1976; 54:Suppl III:III-107–III-117.
2. European Coronary Surgery Study Group. Second Interim Report. Prospective randomized study of coronary artery bypass surgery in stable angina pectoris. Lancet 1980;2:491–495.
3. **Mathur VS, Guinn GA.** Prospective randomized study of the surgical therapy of stable angina. Cardiovasc Clin 1977;8:131–144.
4. **Peduzzi P, Hultgren HN.** The effect of medical vs. surgical treatment on symptoms in stable angina pectoris. The Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. Circulation 1979;60:888–900.
5. **Hammermeister KE, DeRouen TA, Dodge HT.** Variables predictive of survival in patients with coronary disease. Selection by univariate and multivariate analyses from the clinical, electrocardiographic, exercise, arteriographic, and quantitative anglographic evaluations. Circulation 1979;59:421–430.
6. **Hammermeister KE, DeRouen TA, Murray JA, Dodge HT.** *Effect of* aortocoronary saphenous vein bypass grafting on death and sudden death. Comparison of nonrandomized medically and surgically treated cohorts with comparable coronary disease and left ventricular function. Am J Cardiol 1977;39:925–934.
7. **Hammermeister KE, DeRouen TA, Dodge HT.** Evidence from a nonrandomized study that coronary surgery prolongs survival in patients with two-vessel coronary disease. Circulation 1979;59:430–435.
8. **Hammermeister KE, DeRouen TA, Dodge HT.** Effect of coronary surgery on survival in asymptomatic and minimally symptomatic patients. Circulation 1980;62:Suppl I:I-98–I-102.
9. **DeRouen TA, Hammermeister KE, Dodge HT.** Comparison of effects on survival after coronary artery surgery in subgroups of patients from Seattle Heart Watch. Circulation 1981;65:537–545.
10. **Wilcoxon F.** Individual comparisons by ranking methods. Biometrics 1945;1:80.
11. **Kannel WB, Sorlie P, McNamara PM.** Prognosis after initial myocardial infarction: The Framingham Study. Am J Cardiol 1979;44:53–59.
12. **Harris PJ, Harrell FE, Lee KL, Rosati RA.** Nonfatal myocardial infarction in medically treated patients with coronary artery disease. Am J Cardiol 1980;46:937–942.
13. **Tyras DH, Barner HB, Kaiser GC, Codd JE, Laks H, Pennington DG, Willman VL.** Long-term results of myocardial revascularization. Am J Cardiol 1979;44:1290–1296.
14. **Berger RL, Davis KB, Kaiser GC, Foster ED, Hammond GL, Tong TG, Kennedy JW, Sheffield T, Ringqvist I, Wiens RD, Chaitman BR, Mock M.** Preservation of myocardium during coronary bypass grafting. Circulation 1981;64:Suppl II:I-61–I-66.
15. **Murphy ML, Hultgren HN, Detre K, Thomsen J, Takaro T.** Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration Cooperative Study. N Engl J Med 1977;297: 621–627.
16. **Kloster FE, Kremkau EL, Ritzman LW, Rahimtoola SH, Rösch J, Kanarek PH.** Coronary bypass for stable angina. A prospective randomized study. N Engl J Med 1979;300:149–157.
17. **Kouchoukos NT, Oberman A, Russell RO Jr, Jones WB.** Surgical versus medical treatment of occlusive disease confined to the left anterior descending coronary artery. Am J Cardiol 1975;35:836–842.
18. **Freiman JA, Chalmers TC, Smith H Jr, Kuebler RR.** The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. N Engl J Med 1978;299:690–694.
19. **Neill WA, Ritzman LW, Okies JE, Anderson RP, Selden R.** Medical vs. surgical therapy for acute coronary insufficiency. Cardiovasc Clin 1977; 8:179–187.
20. National Cooperative Study Group to compare surgical and medical therapy. Unstable angina pectoris. II. In-hospital experience and initial followup results in patients with one, two, and three vessel disease. Am J Cardiol 1978;42:839–848.
21. Principal investigators of CASS and their associates. The National Heart, Lung, and Blood Institute Coronary Artery Surgery Study (CASS). Circulation 1981;63:Suppl I:I-1–I-81.
22. **Bruschke AVG, Proudfit WL, Sones FM Jr.** Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5–9 years: arteriographic considerations. Circulation 1973;47:1147–1153.
23. **Harris PJ, Lee KL, Harrell FE, Behar VS, Rosati RA.** Outcome in medically treated coronary artery disease. Ischemic events: nonfatal infarction and death. Circulation 1980;62:718–726.

# Can Noninvasive Exercise Test Criteria Identify Patients With Left Main or 3-Vessel Coronary Disease After a First Myocardial Infarction?

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**This study attempts to determine whether exercise treadmill testing with clinical, electrocardiographic, and thallium-201 myocardial perfusion imaging data can identify which patients have left main or 3-vessel (anatomically high-risk) coronary artery disease (CAD) after their first transmural myocardial infarct (MI). Twelve exercise test criteria for high-risk disease were compared in 40 patients referred for cardiac catheterization; 34 had a history of chest pain and 17 had angiographically defined high-risk CAD. A thallium image defect outside the vascular distribution of the MI was the most reliable criterion to distinguish patients with high-risk CAD ($p = 0.00052$ for Fisher's exact test of discrimination). Thallium imaging was somewhat more sensitive (92 versus 65%, $p = 0.108$) when patients with negative thallium imaging criteria who failed to achieve 85% of the age-predicted maximal heart rate were excluded. Failure to achieve 85% of predicted heart rate was by itself a useful criterion for detecting high-risk CAD ($p = 0.017$), especially in patients not taking propranolol ($p = 0.004$). Development of positive S-T segment depression at <70% predicted heart rate also discriminated left main or 3-vessel disease from less extensive CAD ($p = 0.016$). Other criteria failed to discriminate significantly between high-risk and less extensive CAD in patients after their first MI ($p > 0.05$). S-T segment depression ($p = 0.199$) or chest pain ($p = 0.577$) during exercise testing were particularly unreliable. Further, none of the criteria for high-risk CAD were influenced by irreversible left ventricular dysfunction.**

**It is concluded that patients with thallium imaging defects outside the region of the infarct, decreasing blood pressure during exercise, failure to achieve 85% of predicted heart rate, or S-T depression at <70% of predicted heart rate have a high probability of having left main or 3-vessel disease. Patients without these criteria have a very low probability of having high-risk CAD and probably do not need coronary angiography for the purpose of excluding these high-risk coronary lesions after a first MI.**

The annual mortality rate after a first transmural MI averages 5%/year but varies widely for different groups of patients.[1-4] The prognosis after MI depends on the size of the MI and resulting left ventricular dysfunction[3,5,6] and on the extent of CAD jeopardizing the noninfarcted myocardium.[7,8] Most clinical indicators of a poor prognosis after a first MI primarily reflect the extent of irreversible myocardial damage.[9,10] Anginal chest pain after infarct suggests but does not prove the patient has multivessel CAD—chest pain is absent in many patients with extensive CAD.[1,2,11] Exercise electrocardiography has been reported as helping to identify subgroups of patients at greater risk of death after MI.[12-14] Although positive S-T segment responses to exercise identify patients with multivessel CAD moderately well,[15-19] it is not clear whether a positive exercise electrocardiogram identifies patients with a poor prognosis due to large infarcts (irreversible) or due to extensive CAD (potentially reversible by surgery). The usefulness of exercise electrocardiography in the presence of MI may be limited by the MI itself.[20,21] The many false-negative and false-positive results in anginal histories and exercise electrocardiograms after a first MI lend support to the proposal that coronary angiography should be recommended to every young and otherwise healthy patient after a first MI.[22] Adoption

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of this policy for the 600,000 patients who have infarcts each year would greatly increase the number of patients undergoing cardiac catheterization, with its risks, inconvenience, and expense, which might be considered by many to be excessive.[23–25] Thus, it would be useful to have a reliable noninvasive test to detect multivessel disease. Thallium-201 myocardial imaging has proven useful in diagnosing the presence of CAD, but its value in distinguishing multivessel disease is controversial[26–30] and may be influenced by the presence of the infarct defect per se.[1,7]

This study examines whether exercise treadmill testing with clinical, electrocardiographic, and thallium imaging data can identify patients in whom left main or 3-vessel disease adversely influences the prognosis. The continuing controversy concerning the effects of coronary artery bypass graft surgery on prognosis suggests a need to identify specifically those patients with left main or 3-vessel disease who may benefit most from surgery.[1,2,31,32]

## Methods

**Patient selection:** We analyzed results in 150 consecutive patients who had been referred by their private physicians for cardiac catheterization, exercise treadmill testing with electrocardiography, and thallium imaging. From this group we identified the 40 patients who had had a transmural MI within the preceding 3 to 24 months. MI was confirmed by history, pathologic Q waves on resting electrocardiogram in all patients, and asynergic regional contraction patterns on contrast left ventricular angiography (36 of 40 patients). Chest pain syndromes were present in 34 patients after MI and were believed to be typical of angina pectoris in 29. Only 4 patients were women; the age range was 26 to 64 years (mean ± standard deviation 51.3 ± 7.5). Patients with 2 or more MIs were excluded.

**Cardiac catheterization:** Each patient had left ventricular and coronary angiography by the Sones[33] or Judkins[34] technique. Two angiographers analyzed all angiograms independently and without knowledge of the other data about the patient, as described previously.[35,36] Significant CAD was defined as ≥50% narrowing of luminal diameter seen in 2 or more views, or ≥70% narrowing in only 1 view. Nitroglycerin was administered before coronary angiography in all patients, and no patient had significant valvular or cardiomyopathic heart disease.

**Exercise treadmill test with electrocardiography:** All patients had an exercise test performed within 2 months of cardiac catheterization; there were no clinical episodes suggesting new MI or intermediate coronary syndrome between the time of exercise testing and catheterization. Exercise testing was performed within 3 to 24 months of the patient's first infarct, using the Bruce protocol.[37] Each patient continued exercise until the occurrence of limiting symptoms, a blood pressure decrease >5 mm Hg, or flat or downsloping S-T segment depression ≥2.0 mm below control values, 0.08 second after the J point. A 12-lead electrocardiogram was recorded before, during, and after exercise. If the S-T segment shifted more than 1.0 mm from the baseline or from a resting abnormality, then the electrocardiogram was also read as positive during exercise. The electrocardiogram was considered uninterpretable if S-T depression >1.0 mm occurred in a patient receiving digitalis or in the presence of an intraventricular conduction delay or left ventricular hypertrophy. Exercise electrocardiography was considered equivocal with S-T elevation or upsloping S-T segment depression >1.0 mm but <2 mm, 0.08 second after the J point. Arterial blood pressure was monitored by cuff sphygmomanometer every 2 to 3 minutes before, during, and after exercise.

**Thallium-201 myocardial perfusion imaging (Fig. 1 and 2):** As described previously,[34,35] 1.5 to 2.0 mCi of thallium-201 was injected intravenously during exercise when symptoms suggested that the patient was near the limits of his or her tolerance for exercise. Each patient exercised for an additional 30 to 120 seconds at the same or reduced work load to allow thallium tissue distribution during the period of maximal coronary blood flow. Each patient was imaged 5 to 10 minutes after exercise for the "exercise image" and 3 to 4 hours later for the "delayed rest image."[38] Images were recorded with the patient in a supine position in the 45° left anterior oblique, anterior, and left lateral views to a total of 500,000 counts/image.

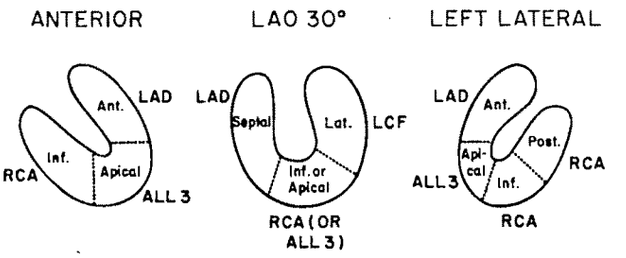



FIGURE 1. Nomenclature for segments of left ventricle seen on the thallium-201 perfusion image. These diagrams indicate the correspondence between particular coronary arteries and the myocardial image in each view. Note that the apical region did not correspond to the distribution of any 1 specific artery. Ant = anterior; Inf = inferior; LAD = left anterior descending coronary artery; LCF = left circumflex coronary artery; RCA = right coronary artery.

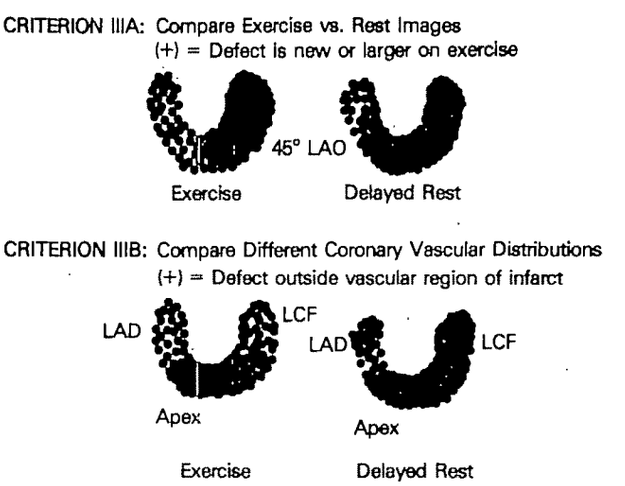



FIGURE 2. Two thallium-201-imaging criteria, A and B, for high-risk CAD involving the left main trunk or 3 vessels after myocardial infarction. Criterion IIIA compares exercise (**left**) and delayed rest (**right**) images and is considered positive (+) when an exercise defect disappears or decreases in size or severity on the delayed rest image (as shown for the septal defect here). Criterion IIIB compares different coronary vascular distributions using the scheme in Figure 1 and is considered positive when there is a defect in a vascular region outside the infarct region as shown for the septal, left anterior descending, and lateral wall-circumflex defects here. Ant = anterior; Inf = inferior; LAD = left anterior descending coronary artery; LCF = left circumflex coronary artery; RCA = right coronary artery.

We set a 20% window centered on the photopeak of thallium, using an Ohio Nuclear model 120 portable gamma camera with a high-sensitivity, parallel-hole collimator. Each image was recorded on Kodak SO-179 transparency film in both unprocessed and contrast-enhanced forms. Contrast enhancement was performed on the video display of the Ohio Nuclear Series 150 Data System by an observer without knowledge of the patient's history or other test data. Each image was read by 2 observers who did not know other data about the patient; interobserver agreement was 95% for positive or negative thallium image reading and 88% for defining which regions were abnormal. Results were drawn from readings after resolution of differences.

**Noninvasive criteria to identify patients with left main or 3-vessel CAD (Table I):** During the exercise test symptoms, heart rates, blood pressures, electrocardiograms, and thallium images were classified according to the criteria shown in Table I. The location of the transmural infarct was established by the pathologic Q waves of the electrocardiogram and confirmed by regional asynergy on the contrast left ventriculogram. We used criteria which correlate abnormalities of thallium images and the exercise response of the S-T segment of the electrocardiogram with the anatomic site of myocardial ischemia.[39,40] Although these correlations may be imperfect, we designated the following correspondence between electrocardiogram and coronary vascular distributions, in accordance with previous studies: leads II, III, and aVF, right coronary artery; I, aVL, $V_{5,6}$, circumflex artery; $V_1$ to $V_4$, left anterior descending artery.[39,40] Consistent with previous correlations of thallium images with cardiac catheterization data,[41] we designated the correspondence between thallium image regions, walls of the left ventricle, and coronary vascular distributions as illustrated in Figure 1. It should be noted that the apical portion of the left ventricle was not used to localize the coronary artery involved because it is difficult to assign this region to the vascular distribution of 1 coronary artery.[42] Two thallium-201 criteria to predict anatomically high-risk CAD after infarction are shown in Figure 2 (criterion IIIC was adapted from IIIB).

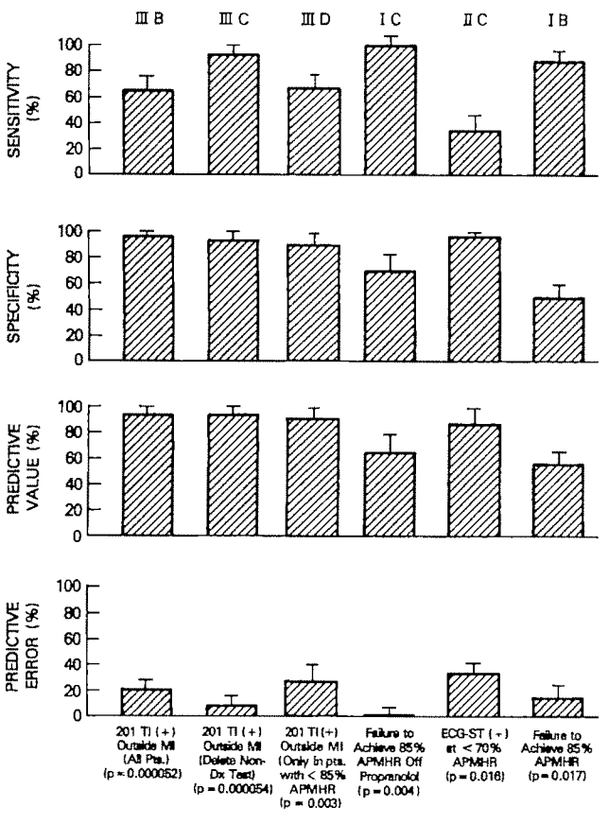



**FIGURE 3.** Exercise test criteria which successfully discriminate high-risk CAD after MI. The criteria are listed in order of the p value from Fisher's exact test for their ability to discriminate anatomically high-risk disease from less extensive disease, from the lowest p value on the **left** to the highest p values on the **right.** The p value is shown under the bar graph representing each criterion. The panels show sensitivity, specificity, predictive value, and predictive error. The population prevalence of high-risk disease was 43%. APMHR = age-predicted maximal heart rate; Dx = diagnostic; ECG-ST = electrocardiographic S-T; Pts. = patients; Tl = thallium.

**Analysis of data:** Coronary angiography determined each patient's anatomic extent of CAD. Patients with left main or 3-vessel disease were classified for the purpose of this study as a high-risk subgroup of the population of patients after their first MI.[1,7,8] Each criterion in Table I was tested in each patient to determine whether the particular findings on exercise testing were present or absent. For each criterion, the result in each patient was defined as follows: true positive (TP) = a patient with left main or 3-vessel disease (that is, high-risk subgroup), and noninvasive criterion positive; true negative (TN) = noninvasive criterion negative in a patient without high-risk CAD; false negative (FN) = noninvasive criterion negative in a patient with high-risk CAD; and false positive (FP) = noninvasive criterion positive in a patient without high-risk CAD.[43,44]

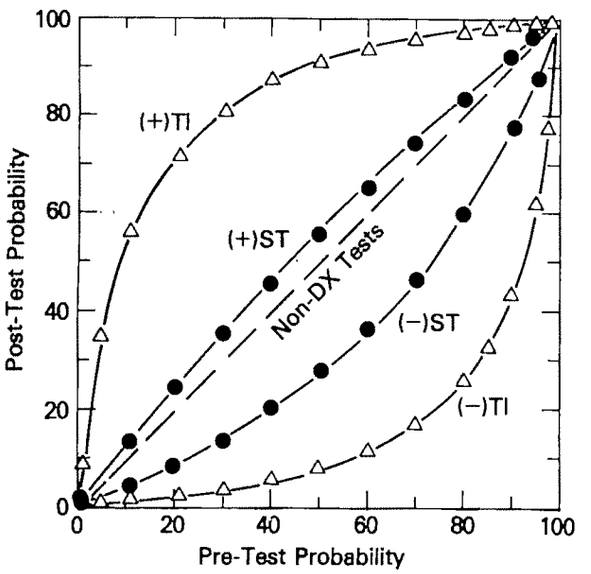
In order to characterize fully all aspects of the ability of each criterion to identify high-risk subgroups of CAD, we calculated the following proportions as percentages: sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); predictive error = FN/(FN + TN); predictive value = TP/(TP + FP). We estimated the standard deviation of each proportion (Pr) as $[(Pr)(1 - Pr)/n]^{1/2}$, where n is the number of observations as indi-

**TABLE I Exercise Treadmill Test Criteria to Identify Left Main Trunk or 3-Vessel CAD in Patients After Their First MI***

I. Clinical and hemodynamic criteria during exercise test
  A. Development of chest pain
  B. Failure to achieve 85% of age-predicted maximal heart rate (considering all patients)
  C. Failure to achieve 85% maximal heart rate (drop patients taking propranolol)
  D. Decreased blood pressure during exercise
II. Electrocardiographic criteria during exercise test
  A. Positive S-T segment response (all patients)
  B. Positive S-T response (drop patients with nondiagnostic tests)*
  C. Positive S-T segment response at heart rate <70% maximal heart rate
  D. Positive S-T segment response in lead not involved by infarct
III. Thallium-201 myocardial perfusion imaging criteria
  A. Defect on exercise image which disappears or improves on delayed rest image
  B. Any defect located in a vascular distribution outside the infarct (all patients)
  C. Defect outside infarct (drop patients with nondiagnostic tests)
  D. Defect outside infarct (considering only patients who failed to achieved 85% maximal heart rate)

* Criteria for diagnostic tests are to exclude patients with (A) electrocardiographic S-T segment response positive in a patient taking digitalis or with conduction defect, or with 1.0 mm S-T depression which is upsloping, or with S-T elevation; also, negative S-T response, but <85% maximal heart rate; (B) thallium-201 imaging normal in regions not involved by infarct, but <85% of the predicted maximal heart rate is achieved.

cated in Figure 3.[45] We tested the ability of each criterion to discriminate between the anatomically high-risk group and other patients by Fisher's exact test, the chi-square test with Yates' continuity correction, and a modification of the z statistic to compute confidence intervals.[45] We report the results of Fisher's exact test except where noted specifically. We used the chi-square test with Yates' correction for small numbers since the expected values were <5 in some tests. The modified z statistic was calculated to account for correlated proportions.[45] Results of these 3 statistical tests were similar. The p values were somewhat lower for the modified z statistic; for only 1 criterion did differences become significant ($p < 0.05$) by the modified z statistic but not by other tests. This 1 difference is indicated in the results. The z statistic does not account for small numbers and, thus, probably overestimates the significance of differences in small populations.[45]




| Criterion | Code | Sensitivity | Specificity | Non-DX |
|---|---|---|---|---|
| $^{201}$Tl(+) Outside MI (DX only) | △ | 92% | 92% | 16 |
| ECG-ST ↓ (DX only) | ● | 90% | 29% | 13 |

**FIGURE 4.** Influence of population prevalence (pretest probability) of anatomically high-risk disease on thallium (Tl) exercise imaging and exercise electrocardiographic S-T (ECG-ST) predictions after MI, using Bayes' theorem. Considering the number of patients, these curves represent clinical trends rather than precise calculations of the probability of high-risk CAD for a particular patient. If thallium-201 imaging is positive (+) outside the infarct region, the probability (posttest) that the patient has 3-vessel or left main coronary disease remains high over a wide range of pretest probabilities, as shown by the **top left curve.** If thallium-201 imaging is negative outside the vascular distribution of the infarct and heart rate is >85% of the age-predicted maximum, the probability (posttest) of anatomically high-risk disease is very low over a wide range of pretest likelihoods, as shown by the **lower right curve.** The curves calculated from Bayes' theorem show that the posttest probability of anatomically high-risk disease is higher when the pretest probability (or prevalence) is higher. The curves indicate that a positive thallium-201 image outside the infarct is more reliable than a positive exercise S-T response as an indicator of anatomically high-risk disease, and that a negative S-T response is less reliable than a negative thallium-201 image outside the infarct to exclude 3-vessel or left main coronary disease after a first MI. DX = diagnostic result.

More sophisticated statistical tests of multivariate analysis might have indicated some improvement in the predictive power of some exercise test criteria, and Tables II and III provide data for such analysis. We did not adopt this statistical approach because our goal was to assess the clinical usefulness of different exercise test criteria. The more sophisticated statistical tests using multivariate analysis might have indicated statistical significance in situations where clinical significance would be lacking. Thus, we ranked exercise test criteria in ascending order of their p values for discriminating anatomically high-risk disease, using Fisher's exact test. The rank order was the same using either chi-square or the modified z statistic.

We tested differences between group means by Student's $t$ test for unpaired variables.[45] We calculated the linear regression equations and correlation coefficients. One-way analysis of variance was used to test whether slopes of these regression lines differed significantly from zero.[45] A p value <0.05 was required for statistical significance.

We estimated the influence of different population prevalence rates (or pretest probabilities) of the high-risk subgroup CAD on the predictive value and predictive error of these noninvasive criteria by application of Bayes' theorem. We calculated the probability of high-risk CAD with a given result of the noninvasive criterion, using the values of sensitivity and specificity of each criterion found in our population as follows[44,46–48]: if the criterion is negative, then the probability of high-risk disease (predictive error) = [(100 − sensitivity %) (prevalence %)]/[(100 − sensitivity %) (prevalence %) + (specificity %) (100 − prevalence)]. If the criterion is positive, then the probability of high-risk CAD (predictive value) = [(sensitivity %) (prevalence %)]/[(sensitivity %) (prevalence %) + (100 − specificity %) (100 − prevalence %)].

These calculations in 40 patients seem justifiable because of the clinical implications of different population groups. Clearly, Figure 4 does not represent an exact calculation of the probability of left main or 3-vessel coronary disease in every patient, but it does indicate the influence of population prevalence of high-risk disease on the predictions by these criteria.

## Results

**Cardiac catheterization:** In the 40 patients with previously documented transmural MI, coronary angiography revealed disease involving 1 coronary vessel in 13, 2 vessels in 8, and 3 vessels in 17. Three of the 17 patients with 3-vessel disease also had left main coronary stenosis, and 2 patients had normal coronary angiograms. Left ventricular ejection fraction in patients with 3-vessel or left main disease (high-risk subgroup) was 51.2 ± 21.9% (mean ± standard deviation), which did not differ significantly from the patients with less extensive CAD, 56.2 ± 24.4%. The proportion of patients with ejection fraction <40% also was not significantly greater in patients in the high-risk subgroup (1 of 17) than in patients with less extensive CAD (1 of 23). Asynergic contraction was identified on the left ventriculogram in 36 of 40 patients; the location agreed with the pathologic Q waves on the electrocardiogram in 35 patients, and with the defects on delayed rest thallium imaging in 34 patients.

**Clinical and hemodynamic exercise test criteria (1A to 1D) (Tables II and III):** Development of chest pain during the exercise test did not distinguish patients with high-risk CAD from those with less extensive CAD

**TABLE II Patients With 3-Vessel or Left Main CAD, or Both**

| | I: Clinical | | | | II: Exercise Electrocardiography | | | | III: Exercise/Delayed Rest Thallium-201 Imaging | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | A | B | C | D | A | B | C | D | A | B | C | D |
| 1 | N | P | P | N | P | P | N | P | N | N | ... | N |
| 2 | N | P | P | N | P | P | N | N | P | P | P | P |
| 3 | N | P | ... | P | P | P | P | P | P | N | ... | N |
| 4 | N | P | ... | N | N | ... | N | N | P | P | P | P |
| 5 | P | P | P | N | P* | ... | N | N | N | P | P | P |
| 6 | N | P | ... | N | N | ... | N | N | P | N | ... | N |
| 7 | N | N | ... | N | P | P | N | P | N | N | N | ... |
| 8 | N | P | P | N | P | P | P | P | P | P | P | P |
| 9 | P | P | ... | N | P | P | P | N | N | P | P | P |
| 10 | P | P | ... | N | P | P | P | P | N | N | ... | N |
| 11 | N | P | P | P | N | ... | N | N | N | P | P | P |
| 12 | N | P | ... | N | P* | ... | P* | P* | N | P | P | P |
| 13 | N | P | P | N | P* | ... | N | N | N | N | ... | N |
| 14 | P | P | ... | N | N | N | N | N | P | P | P | P |
| 15 | N | P | P | N | P | P | N | N | P | P | P | P |
| 16 | N | N | ... | P | N | ... | N | N | P | P | P | ... |
| 17 | N | P | ... | N | P | P | P | N | N | P | P | P |
| P | 4 | 15 | 7 | 3 | 12 | 9 | 6 | 6 | 8 | 11 | 11 | 10 |
| N | 13 | 2 | 0 | 14 | 5 | 1 | 11 | 11 | 9 | 6 | 1 | 5 |
| NDx | ... | ... | 10 | ... | ... | 7 | ... | ... | ... | ... | 5 | 2 |

* Positive electrocardiographic S-T in patient receiving digitalis.
Criteria IA to IIID as in Table I. N = negative result; NDx = nondiagnostic result; P = positive result.

**TABLE III Patients With 0-, 1-, or 2-Vessel CAD**

| | I: Clinical | | | | II: Exercise Electrocardiography | | | | III: Exercise/Delayed Rest Thallium-201 Imaging | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | A | B | C | D | A | B | C | D | A | B | C | D |
| 18 | P | N | ... | N | P | P | N | N | P | N | N | ... |
| 19 | N | P | P | N | P | P | N | P | P | P | P | P |
| 20 | N | N | N | N | P | P | N | P | P | N | N | ... |
| 21 | N | P | ... | N | N | ... | N | N | N | N | ... | N |
| 22 | N | P | ... | N | P | P | N | N | N | N | ... | N |
| 23 | N | N | N | N | P | P | N | P | N | N | N | ... |
| 24 | N | N | N | N | P | P | N | P | N | N | N | ... |
| 25 | P | P | P | N | P | P | N | N | N | N | ... | N |
| 26 | N | P | ... | N | N | ... | N | N | P | N | ... | N |
| 27 | N | P | ... | N | N | ... | N | N | N | N | ... | N |
| 28 | N | N | N | N | N | N | N | N | P | N | ... | ... |
| 29 | P | P | ... | N | P | P | N | N | N | N | ... | N |
| 30 | N | N | ... | N | N | N | N | N | N | N | N | ... |
| 31 | N | P | ... | N | N | ... | N | N | N | N | N | N |
| 32 | N | N | N | N | P | P | N | P | N | N | N | ... |
| 33 | N | P | ... | N | N | ... | N | N | P | N | ... | N |
| 34 | P | P | P | N | P | P | N | P | P | N | ... | N |
| 35 | P | P | ... | N | P | P | P | P | P | N | ... | N |
| 36 | N | N | N | N | N | N | N | N | N | N | N | ... |
| 37 | N | P | P | N | N | ... | N | N | N | N | ... | N |
| 38 | P | N | N | N | P | P | N | N | N | N | N | ... |
| 39 | N | N | N | N | N | N | N | N | N | N | N | ... |
| 40 | N | N | N | N | N | N | N | N | N | N | N | ... |
| P | 6 | 12 | 4 | 0 | 12 | 12 | 1 | 7 | 8 | 1 | 1 | 1 |
| N | 17 | 11 | 9 | 23 | 11 | 5 | 22 | 16 | 15 | 22 | 11 | 11 |
| NDx | ... | ... | ... | ... | ... | 6 | ... | ... | ... | ... | 11 | 11 |

Abbreviations as in Table II.

($p > 0.577$) as shown in Table IV for criterion IA. Again, the p value seems most useful to identify criteria which fail the minimal expectation for any diagnostic test, that is, to distinguish 2 groups of patients with versus patients without high-risk disease. In contrast, criterion IB discriminated patients with high-risk disease ($p < 0.017$) by their failure to achieve 85% of age-predicted maximal heart rate. This heart rate criterion was sensitive (88%) (Fig. 3) but lacked specificity (48%), because of peak heart rates <85% of predicted values during propranolol therapy in several patients with less extensive disease (Tables II, III, and V). The heart rate criterion could not distinguish high-risk CAD in the 20 patients receiving propranolol (dose range 30 to 160 mg/day), but discriminated successfully between high-risk and less extensive disease in patients not re-

**TABLE IV Ranking Criteria Which Fail to Discriminate Anatomically High-Risk CAD After MI**

| | Criterion | Sensitivity | Specificity | p |
|---|---|---|---|---|
| ID | BP decrease | 18 ± 9 | 100 ± 5 | <0.069 |
| IIA | S-T (+) (All patients) | 71 ± 11 | 48 ± 10 | <0.199 |
| IIB | S-T (+) (Dx only) | 90 ± 9 | 29 ± 11 | <0.251 |
| IIIA | Tl-201 (+) Ex > Rest* | 47 ± 12 | 65 ± 10 | <0.323 |
| IID | S-T (+) outside MI | 35 ± 12 | 70 ± 12 | <0.504 |
| IA | Chest pain | 24 ± 10 | 74 ± 9 | <0.577 |

* Thallium-201 image positive with exercise defect worse than delayed rest defect.

Ranking is in ascending order of the p value for Fisher's exact test. Criteria with p >0.05 for the difference between groups failed the minimal requirement for any diagnostic test, that is, to distinguish 2 groups with versus without high-risk disease. BP = blood pressure; Dx = diagnosis; Ex = exercise.

**TABLE V Effects of Propranolol Therapy on the Prediction of Anatomically High-Risk Disease After MI by the Criteria Which Used Peak Heart Rate Achieved During the Exercise Test**

| | Low-Risk CAD | High-Risk CAD |
|---|---|---|
| Patients Not Taking Propranolol | | |
| >85% APMHR | 9 | 0 |
| <85% APMHR | 4 | 7 |
| | p = 0.004 | |
| Patients Receiving Propranolol, 40 to 160 mg/day | | |
| >85% APMHR | 2 | 2 |
| <85% APMHR | 8 | 8 |
| | p = 0.709 (not significant) | |

APMHR = age-predicted maximal heart rate.

ceiving propranolol (p <0.00052) (Table V). In 20 patients not taking propranolol, no patients with high-risk CAD achieved 85% of the predicted heart rate (criterion IC). The group with left main or 3-vessel disease achieved the same percentage of age-predicted maximal heart rate whether they were (73.3 ± 11.5%) or were not (72.0 ± 16.0%) receiving propranolol. On the other hand, in the group with 0-, 1-, or 2-vessel disease, the patients taking propranolol had a lower heart rate (69.4 ± 17.4%) than those not receiving the drug (86.2 ± 7.6%; p <0.05). During exercise testing, arterial blood pressure decreased in 3 patients with 3-vessel disease (1 also had left main disease). Criterion ID did not significantly discriminate the anatomically high-risk group by the Fisher's exact test (p = 0.069) because of its low sensitivity. The modified z statistic yielded p = 0.024, but this test fails to account for small numbers.[45]

**Exercise electrocardiographic data (criterion IIA to IID):** The S-T segment response of the electrocardiogram to exercise was positive in 12 of 17 patients with high-risk CAD, but also in 12 of 23 patients with less extensive disease. Thus, criterion IIA, which is widely used, could not distinguish the high-risk subgroup (p = 0.199). The 2 patients with positive S-T responses who were receiving digitalis were considered positive for high-risk CAD by criteria IIA, IIC, and IID. Criterion IIB classified as nondiagnostic the patients with these electrocardiographic readings and the patients with negative S-T responses but peak heart rate <85% of the predicted maximum. Despite dropping these 13 patients with nondiagnostic S-T responses, criterion IIB could not discriminate high-risk CAD (p = 0.251), primarily because of the low specificity of the S-T response (Table IV).

The electrocardiogram was positive and the heart rate was <70% of predicted in 6 of 17 high-risk patients (1 of whom had left main disease) and in only 1 of 23 patients with less extensive disease. Criterion IIC discriminated high-risk disease (p = 0.016) because of its high specificity. Criterion IID, which indicated the high-risk subgroup when S-T responses were positive in leads not involved by the MI, was positive in 6 of 17 patients with high-risk CAD (2 of 3 with left main disease), but also in 7 of 23 patients with less extensive disease, so that this criterion also failed to discriminate high-risk from less extensive CAD (p = 0.504) (Tables II and III).

**Thallium-201 myocardial imaging data (criteria IIIA to IIID):** Thallium imaging revealed defects during exercise, delayed resting imaging, or both, in 38 of 40 patients, and showed an increase in the apparent dimensions of the left ventricular cavity on the exercise image relative to the rest image in 1 of the 2 patients with no perfusion deficits visible on thallium imaging.

Figure 2 illustrates the criteria for reading the thallium images to identify left main or 3-vessel disease. Criterion IIIA was considered positive for high-risk CAD when a defect present on exercise disappeared or improved dramatically on the delayed rest image. Defects disappeared on delayed rest images in 16 patients, only half of whom had high risk CAD. Thus, this criterion alone could not discriminate 3-vessel or left main disease from less severe disease (p = 0.323) (Tables II and III).

In contrast, criterion IIIB required thallium imaging to be positive in the vascular distribution of a coronary artery which was not involved by the previous MI, defined by Q waves on the electrocardiogram, as shown in Figure 2. Criterion IIIB discriminated most successfully the patients with high-risk CAD (p = 0.00052), with 65 ± 12% sensitivity and 96 ± 4% specificity (Fig. 3).

Criterion IIIC used the same thallium reading but classified separately 16 patients as nondiagnostic because they had negative results on thallium imaging by this regional criterion; however, they had inadequate stress, that is, peak heart rate <85% of predicted. Criterion IIIC discriminated successfully between high-risk and less extensive CAD (p = 0.000054, Fig. 3). Sensitivity (92 ± 8%) and specificity (92 ± 8%) were excellent by criterion IIIC.

Criterion IIID applied the same thallium reading of defects outside the vascular distribution of the infarct to the 27 patients who failed to achieve 85% of maximal predicted heart rate. Sensitivity was 67 ± 12% and specificity was 92 ± 8% to allow discrimination of patients with left main or 3-vessel disease (p = 0.0029).

**Combined criteria:** It was possible to combine criteria to improve sensitivity and specificity. For example, we considered a test result positive for anatomically

high-risk CAD if any 1 of the following criteria was positive: IC, heart rate <85% of that predicted in a patient not taking propranolol; ID, a blood pressure decrease during exercise; or IIIB, thallium-201 imaging positive outside the vascular distribution of the myocardial infarction. This combined criterion test was 82 ± 8% sensitive and 83 ± 8% specific to discriminate left main or 3-vessel disease ($p = 0.000055$). The predictive value was 78 ± 10% and the predictive error was 14 ± 7%. This retrospectively defined combined criterion is not shown in Figure 3.

The sensitivity of thallium imaging for defects outside the infarct to identify high-risk CAD (criterion IIIB) was higher in patients with previous inferior wall infarction (100 ± 9%) than in patients with previous anterior wall infarction (45 ± 15%, $p = 0.037$, Table VI).

**Influence of left ventricular dysfunction on noninvasive test results:** Because of the possible influence of irreversible myocardial damage itself on the results of exercise test criteria, we correlated global left ventricular ejection fraction with the results of exercise test criteria to predict high-risk CAD. First, we used analysis of variance to determine that this group of patients after MI showed no relation between ejection fraction and the extent of CAD, confirming the previous reports from this laboratory.[40] Next, we found that 5 of the criteria showed no association between the ejection fraction and the noninvasive test results, using a 2 by 5 contingency table and chi-square test. We also found that the ejection fraction at rest did not correlate with the percentage of age-predicted maximal heart rate achieved during exercise testing: ($r = -0.11$, $p > 0.4$), using analysis of variance to compare the slope of the linear regression equation to zero.[45] Thus, using resting left ventricular ejection fraction as an index of the degree of irreversible damage resulting from the MI, we were not able to demonstrate any influence of the extent of myocardial dysfunction on either the extent of CAD or the noninvasive criteria to discriminate extensive CAD.

**TABLE VI Differential Detection of High-Risk CAD After Inferior Versus Anterior Wall MI**

| Patients With Anatomically High-Risk Disease | | |
|---|---|---|
| | Sensitivity | |
| Criterion | Inferior MI (n = 6) | Anterior MI (n = 11) |
| IA. Chest pain on treadmill | 17 ± 15% | 27 ± 13% |
| IB. Heart rate <85% of predicted | 100 ± 9% | 82 ± 12% |
| IIA. S-T positive (all patients) | 50 ± 20% | 82 ± 12% |
| IID. S-T positive outside infarct | 17 ± 15% | 45 ± 15% |
| IIIB. Thallium-201 positive outside infarct | 100 ± 9%* | 45 ± 15%* |
| **Patients Without High-Risk Disease** | | |
| | Specificity | |
| Criterion | Inferior MI | Anterior MI |
| IA. Chest pain on treadmill | 71 ± 17% | 79 ± 12% |
| IB. Heart rate <85% of predicted | 43 ± 19% | 50 ± 13% |
| IIA. S-T positive (all patients) | 29 ± 17% | 57 ± 13% |
| IID. S-T positive outside infarct | 57 ± 19% | 71 ± 12% |
| IIIB. Thallium-201 positive outside infarct | 86 ± 13% | 100 ± 6% |

* $p = 0.037$, comparing anterior versus inferior infarcts by Fisher's exact test. Other differences were not significant.

## Discussion

Management of patients after a first MI could be improved by a noninvasive prediction of which patients have a poor prognosis and, therefore, might be most likely to benefit from aggressive therapy.[1–3] It would be most desirable to identify patients at high risk specifically, because of extensive CAD which is potentially reversible by surgery[31,32,49–51] rather than those patients at high risk due to irreversible left ventricular damage.[5,6,52] We set out to identify patients with left main or 3-vessel disease by exercise test criteria because recent evidence suggests that coronary bypass surgery may improve prognosis in such patients.[1,2,31,32,49–51]

**Thallium imaging criteria:** The best criterion to distinguish high-risk CAD in this study was to detect thallium image defects outside the coronary vascular distribution of the MI (criterion IIIB). This finding is consistent with reports that exercise thallium imaging can identify jeopardized myocardium after MI[53] and can assess perfusion of specific coronary vascular distributions.[29,30,41,42] One preliminary report indicates that thallium imaging is not useful to detect multivessel disease after MI,[54] although another indicates that thallium imaging is moderately useful.[55] In the present study the sensitivity of thallium imaging in detecting high-risk CAD was greater after inferior wall infarction than after anterior wall infarction. This differential sensitivity of thallium imaging to detect ischemia of the anterior wall after inferior infarction is consistent with the finding in other patients from this laboratory that thallium imaging detects ischemia in the distribution of a stenotic left anterior descending coronary artery with greater sensitivity than in the distribution of a stenotic circumflex or right coronary artery; thallium imaging, however, detects infarcts (in contrast to ischemia) with equal sensitivity in the distribution of any 1 of the 3 vessels.[56] Thus, thallium detects infarcts with equal sensitivity regardless of location, but identifies transient hypoperfusion of noninfarcted myocardium supplied by a stenotic left anterior descending with greater sensitivity than other stenosed coronary arteries.

It should be noted that the only false-positive finding on thallium imaging in the present study occurred in the only patient who had an inferior wall infarct and 2-vessel disease involving the proximal left anterior descending artery. Such patients may be at higher risk than patients with other 2-vessel disease.[49] The greater sensitivity of thallium imaging to detect anterior wall ischemia after inferior wall infarction suggests that thallium imaging may detect this group reliably (Table VI). The sensitivity to thallium imaging to detect every diseased vessel in these patients was 48% (Tables II and III), lower than the 66% sensitivity reported by Massie et al[30] ($p < 0.02$). Massie et al required that a vessel be stenosed by 70% to be considered diseased, whereas we

required only 50% narrowing of luminal diameter in 2 views. Nine of our patients had 50 to 69% stenosis, and findings on thallium imaging were positive in the distribution of only 2 of these 9 vessels. Also, 66% of their patients achieved ≥85% of their predicted heart rate, while only 28% of our patients achieved this heart rate during exercise. Differences in criteria for coronary stenosis and peak heart rate achieved during exercise could explain the differences in the sensitivity of thallium imaging for identifying each abnormal vessel in this study and the study by Massie et al.[30]

Also, the overall sensitivity of thallium imaging to detect high-risk CAD by identifying defects outside the infarct was improved marginally from 65 ± 13 to 92 ± 8% ($p = 0.108$) by classifying separately 16 patients who had negative thallium imaging outside the infarct region but who had inadequate exercise stress, that is, who failed to achieve 85% of their predicted heart rate (Tables II and III).

Classifying these 16 test results as nondiagnostic increased sensitivity marginally with no decrease in specificity (96 ± 4 to 92 ± 8%), and represents the usual practice in calculating sensitivity and specificity for exercise electrocardiography.[15,17] It should be emphasized that sensitivity of our criteria to detect high-risk CAD was not the same as the sensitivity to detect any perfusion defect. Thus, findings on thallium imaging were abnormal in 38 of 40 patients, including the defects representing the MI. Thallium defects during exercise, which disappeared on the delayed rest image, did not distinguish high-risk CAD ($p = 0.323$) consistent with reports by others.[54] This criterion may have identified exercise-induced ischemia within the same coronary vascular distribution as the MI, since most of these patients had a history typical of angina pectoris. It has been found in dogs after infarction that the increase in blood flow during stress to noninfarcted tissue in the subepicardium which overlies the infarct is less than the flow increase to normal subepicardium; this could explain ischemia after MI even in single-vessel disease.[57]

**Exercise electrocardiographic criteria:** These data indicate that if the S-T segment response to exercise is positive at <70% predicted heart rate, there is a high probability (86 ± 13%) of left main or 3-vessel disease in this population where there was a 43% prevalence of high-risk CAD. This criterion IIC was specific (96 ± 4%) but not sensitive (33 ± 8%) for high-risk CAD (Fig. 3).

These data are consistent with the suggestion that a positive S-T segment response to a low cardiac work load indicates severe, extensive CAD.[19] All other S-T segment criteria failed to discriminate high-risk disease, as shown in Table IV. Even the diagnostic quality exercise electrocardiographic tests (criterion IIB) were not able to discriminate high-risk CAD because of low specificity (48 ± 10%), which may be related to the reported electrophysiologic effects of the old MI on the S-T segment response.[20,21] Others have also noted that the leads in which the S-T segment is positive during exercise do not correlate closely with the vascular distributions of stenotic coronary arteries.[58]

Weiner et al[15] reported a good predictive value (79%) of positive exercise electrocardiographic results for multivessel disease after infarction, where the population had a 59% prevalence, and patients with nondiagnostic test results were excluded (as in our criterion IIB). The predictive value of diagnostic exercise electrocardiography for multivessel disease was also 79% in our patients, not different from the results of Weiner et al. Another study by Chaitman et al[17] reported that the S-T response had a sensitivity of 76% and specificity of 61% to identify 3-vessel disease after a single inferior wall infarct. Chaitman et al excluded 39% of their patients for nondiagnostic tests, using the same guidelines as our criterion IIB. Our data support the conclusion of Chaitman et al[17] that exercise electrocardiography added little to the clinical history of chest pain to identify 2- or 3-vessel disease after infarction. Several reports indicate that exercise electrocardiography early after MI predicts short-term prognosis.[12–14] Many of the patients in these studies[12–14] achieved relatively low heart rates, so that these data may compare with our criterion IIC, positive S-T results at <70% of predicted heart rate.

The short-term mortality rate after MI, however, is probably related more closely to infarct size and the extent of left ventricular dysfunction than to the extent of CAD.[4,6] Coronary bypass surgery exerts little beneficial effect on resting left ventricular function[59] and appears most helpful in the presence of extensive CAD and normal left ventricular function.[31,50] Thus, it must be emphasized that studies which link S-T response early after infarction to the short-term prognosis[12–14] have not been shown to identify patients whose poor prognosis can be improved by therapy. The data in the present study suggest that exercise electrocardiography after infarction might actually be more useful if performed to a low work load, because a positive S-T result at a low work load (<70% age-predicted maximal heart rate) has a somewhat higher predictive value for 3-vessel or left main disease (86 ± 13%) than does a positive S-T at any heart rate (50 ± 15%).

**Clinical criteria during exercise testing:** The clinical criterion IB of failure to achieve 85% of predicted heart rate was useful in discriminating high-risk CAD ($p = 0.017$, Fig. 3). It was sensitive (88 ± 7%) but had limited specificity (48 ± 10%) in the entire group of patients because 20 to 40 patients were taking propranolol at the time of the test. In patients receiving propranolol, the heart rate criterion could not discriminate high-risk CAD (Table V) because beta blockade decreased the chronotropic response to exercise. In contrast, in 20 patients not receiving propranolol, failure to achieve 85% of predicted heart rate (criterion IC) was 100 ± 8% sensitive and 69 ± 13% specific in discriminating high-risk CAD ($p = 0.00052$). These data indicated that an exercise treadmill test limited by development of symptoms, hypotension, or 2 mm S-T depression can provide very useful data about the extent of CAD 3 to 24 months after MI, especially if the patient is not taking propranolol. This finding extends reports by others that chronotropic incompetence during exercise testing is a useful indicator of CAD.[60,61]

Blood pressure decreased during exercise in only 3 patients, but all 3 had 3-vessel disease, and 1 had additional left main disease (Tables III and IV). Thus, criterion ID failed to significantly discriminate the high-risk group ($p = 0.069$). These findings support the predictive value of exercise-induced hypotension as an indicator of severe, extensive CAD[62,63]; however, an increase in blood pressure during exercise, per se, has no value in ruling out severe CAD because of the low sensitivity of criterion ID (Table IV).

Chest pain during the exercise treadmill test was of no value in discriminating left main and 3-vessel disease from less extensive CAD ($p = 0.577$). As indicated earlier, ischemia could occur in the subepicardium that survives within the vascular distribution of the predominantly subendocardial infarction.[58] Consistent with this, 4 of 13 patients with single-vessel disease had chest pain during exercise and even more had a clinical history typical of angina. These data indicate that angina pectoris could occur after infarction in single-vessel disease as well in 3-vessel disease; further, no patient with left main disease had chest pain during the exercise test. Thus, neither chest pain during an exercise test nor a history typical of angina pectoris provides a reliable indicator of anatomically high-risk CAD. This finding in a population of 40 patients referred for cardiac catheterization for medical indications may not be true in all patients. Indeed, the presence of angina pectoris was a major factor leading physicians to refer most of these patients. Further, exertional angina may be an indication for coronary angiography and surgery for the purpose of relieving symptoms.

**Clinical implications: indications for coronary angiography:** The results of this study suggest guidelines for deciding whether or not to refer a patient for coronary angiography after a first MI. An important objective in the management of such patients is to identify those whose prognosis may be limited by potential ischemia of noninfarcted myocardium.[1,2] Coronary angiography seems indicated because of the high probability of left main trunk or 3-vessel disease in any patient who has 1 or more of the following findings: (1) a defect on thallium imaging outside the coronary vascular distribution of the MI, (2) a decrease in blood pressure during exercise testing, (3) a positive S-T segment response at <70% of predicted heart rate, or (4) failure to achieve 85% of predicted heart rate in patients not taking propranolol and in the absence of limiting noncardiac disease.

In contrast, if the physician managing a patient after MI is considering coronary angiography primarily to rule out left main or 3-vessel disease, then these tests may help him decide that there is such a low probability of high-risk CAD that angiography can be avoided in some patients. If a patient has all of the following findings: (1) negative thallium imaging results in vascular distributions outside the MI, (2) an increase in blood pressure during exercise, and (3) a peak heart rate >85% of the age-predicted maximum, then the chance of left main or 3-vessel disease should be very low (predictive error 14 ± 7% in our study population with a 43% prevalence of anatomically high-risk disease). In a patient without disabling symptoms, the indications for coronary angiography would be weak if the above normal findings were present.

The present study of primarily symptomatic patients, with a 43% prevalence of high-risk CAD shows a good predictive value for several of these criteria to detect high-risk CAD. Population prevalence influences predictive value and predictive error of a test.[43,44] The true prevalence of left main or 3-vessel disease after a first infarct is not certain, but the ranges of prevalence of multivessel disease, 3-vessel disease, or left main disease in the present study are similar to those in other studies.[7,8,10,11,15–17,31,32,39,40,49,51,53–55] It is likely that the prevalence of high-risk CAD in populations of patients who are selected by having a first infarct varies much less than does the prevalence of any CAD in different populations. Figure 4 indicates the effect of variation in the prevalence of high-risk CAD in a population on the predictions by defects on thallium imaging outside the infarct or by exercise electrocardiography. Considering the numbers of patients involved, these graphs serve to illustrate important clinical trends, but they cannot predict the exact probability of high-risk CAD in a particular patient. Thus, differences in prevalence of high-risk CAD within the range discussed would have only small effects on predictive value and predictive error of these tests. Even if asymptomatic patients have a lower prevalence, for example, 10 to 20%, a negative test would further reduce the likelihood of high-risk CAD. Conversely, positive findings on thallium imaging outside the infarct would indicate a 56 to 72% probability of high-risk CAD in the same patient population. Thus, these tests can probably help clinical management of patients who are completely asymptomatic after their first infarct.

The results of these exercise test criteria did not correlate with the resting left ventricular ejection fraction, suggesting that these exercise results were not determined by the extent of irreversible left ventricular damage 3 to 24 months after MI. This finding is important because it offers the first support for the premise that these criteria may predict the potentially reversible component of a poor prognosis after an infarct, and, thus, be quite useful when screening patients after a first MI to determine who might benefit from surgery. Noninvasive exercise tests with thallium imaging offer a more cost-effective way to identify patients who are at high risk due to extensive CAD after a first MI than would widespread use of coronary angiography in every patient. Furthermore, the present study indicates that exercise thallium imaging is more accurate than exercise electrocardiography to identify 3-vessel and left main coronary disease. These differences should be noted in considering recent reports of exercise electrocardiography after infarction.[64–67]

Patients in the present study had exercise tests 3 to 24 months after their first myocardial infarction (most between 3 and 6 months). Had we studied all patients 2 to 4 weeks after infarction, the results might have differed, particularly for the clinical observations (criteria IA to ID). The S-T response to exercise might have changed over time, 2 weeks to 2 years after infarction,

but it seems less likely that the results of thallium imaging of defects outside the infarct would change. More relevant to our study, it seems less likely that there would be major changes in noninvasive test results after a person had fully recovered from infarction for 3 months. Thus, the results of the present study are most applicable to patients who have fully recovered from a first infarct for 3 to 24 months.

Most deaths occur within the first 6 months after infarction,[1,4] and several studies have performed exercise tests 2 to 4 weeks after infarction in an attempt to identify these patients.[13,14,53,64–67] A major limitation of these studies is that most of the early deaths are related to electrical and mechanical complications of large infarcts, and it is not clear that medical or surgical therapy will alter the natural history for these patients. For this reason we were more interested in identifying patients who had extensive CAD jeopardizing noninfarcted myocardium since medical and surgical therapy should be more effective in this group.

**Cost-effectiveness of exercise testing after MI (Table VII):** It is extremely difficult to measure cost-effectiveness of medical diagnostic tests,[25,68] but the cost of exercise tests with electrocardiography and thallium imaging require justification. Estimation of effectiveness or quality of care is most difficult, but we made 3 assumptions for our population. First, we assumed that good quality of care would require identification of the maximal number of patients with left main or 3-vessel disease while performing the minimal number of cardiac catheterizations. The potential for poor quality of care due to suboptimal management of high-risk CAD seems more serious than does the small risk and inconvenience of extra cardiac catheterizations. Some patients would require angiography for other reasons such as intractable anginal symptoms. Calculating costs is also difficult, but we made several assumptions about our population and the relative costs of the tests, as shown in Table VII. A different diagnostic approach is shown in each panel, A to E. Panel A assumes that every patient needs every test after MI; this is the most expensive approach, as expected. Panel B assumes that every patient after infarction needs angiography, and noninvasive tests should be avoided as unreliable and costly. Widespread application of this approach would greatly increase the number of coronary angiograms. The approach does save 15% relative to approach A, but this saving may be misleading because of the need for angiography in every patient after MI. Panel C assumes that patients with typical angina after an infarct should all have angiography without noninvasive tests, and patients without angina should have exercise electrocardiography and be referred to catheterization if the S-T segment response is positive. This approach would fail to identify 1 of 17 patients with high-risk CAD,[2] but saves 23% relative to approach A.

Panel D assumes that all patients should have exercise electrocardiography, and those with a positive S-T response should have angiography. The 44% financial saving in this approach is offset by missing 5 of 17 (29%) patients with high-risk CAD because of the low sensitivity of the S-T response.

**TABLE VII Estimated Cost-Effectiveness of Screening Patients for Left Main or 3-Vessel CAD After MI by Exercise Tests With Electrocardiography (Ex-ECG) and Thallium-201 (Tl-201) Imaging and Coronary Angiography**

| | Cost × N (Pts) | = Total | Pts With Left Main/3-Vessel Disease Missed |
|---|---|---|---|
| **A. All Tests in Every Patient** | | | |
| ECG & Tl-201 | $450 × 40 | = $ 18,000 | |
| Angiography | $3,000 × 40 | = $120,000 | |
| | | = $138,000 | None missed |
| **B. Angiography in All Patients, No Exercise Tests** | | | |
| ECG & Tl-201 | $0 | = $0 | |
| Angiography | $3,000 × 40 | = $120,000 | |
| | | = $120,000 | None missed |
| **C. Exercise ECG (but no Tl-201) in Patients Without Typical Angina, Angiography if Patient Has Typical Angina or Positive Exercise ECG Results** | | | |
| ExECG | $150 × 10 | = $ 1,500 | |
| Angiography | $3,000 × 35 | = $105,000 | |
| | | = $106,500 | Misses 1 of 17 pts |
| **D. Exercise ECG in all Patients, Angiography if Positive ECG Results** | | | |
| ExECG | $150 × 40 | = $ 6,000 | |
| Angiography | $3,000 × 24 | = $72,000 | |
| | | = $78,000 | Misses 5 of 17 pts |
| **E. Exercise Tl-201 in all Patients; Angiography if Tl-201 is Positive Outside the Infarct Region, or if Blood Pressure Decreases During Exercise, or if a Patient Without Propranolol Fails to Achieve 85% of Predicted Heart Rate** | | | |
| Tl-201 | $300 × 40 | = $12,000 | |
| Angiography | $3,000 × 20 | = $60,000 | |
| | | = $72,000 | Misses 1 of 17 pts |

Cost = number (N) of patients tested × test fee. Fee = $150 for electrocardiography (ECG) and $300 for thallium-201. Pts = patients.

Panel E uses the approach suggested by our data: all patients should have exercise testing with thallium imaging and clinical observation. Electrocardiography would be used only to monitor for arrhythmias. Patients are referred for angiography if they have thallium defects outside the vascular distribution of the infarct, or if they have a decrease in blood pressure during exercise, or if patients not taking propranolol fail to achieve 85% of their age-predicted maximal heart rate during exercise. The small extra cost of thallium imaging is offset by the increased accuracy of the test when patients with negative thallium imaging at adequate heart rates are not referred for angiography. The financial saving is 48% relative to approach A, 40% relative to approach B (angiography in all patients after MI), 32% relative to approach C, and 8% relative to approach D. While only 1 of 17 patients with anatomically high-risk disease is missed by approach E, 5 of 17 high-risk patients were missed by approach D.

Again, these estimates of cost-effectiveness are not definitive; however, they illustrate the high cost of ex-

cessive tests, the potential decline in quality of care if an unreliable test such as the exercise electrocardiogram is relied upon too heavily, and an apparent justification of exercise testing with thallium imaging as a cost-effective approach to screening patients for high-risk CAD after MI. The population of the present study represented patients selected by their physicians for cardiac catheterization because of a probability of high-risk disease. If the general population of patients has a lower prevalence of high-risk CAD, then Figure 4 would predict a higher percentage of patients with negative findings on thallium imaging. This trend would reduce further the cost of approach E relative to performing angiography in all patients after MI.

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## References

1. **Hurst JW, Logue RB, Walter PF.** The clinical recognition and medical management of coronary atherosclerotic heart disease. In: Hurst JW, Logue RB, Schlant RC, Wenger NK, eds. The Heart, Arteries and Veins. 4th ed. New York: McGraw-Hill, 1978:1156–1290.
2. **Gorlin R.** Coronary artery disease. In: Smith LH Jr, ed. Major Problems in Internal Medicine. Vol. 2. Philadelphia: WB Saunders, 1976:173–194.
3. **Braunwald E.** Treatment of the patient after myocardial infarction: the last decade and the next. N Engl J Med 1980;302:290–293.
4. **Davis HT, DeCamilla J, Bayer LW, Moss AJ.** Survivorship patterns in the post-hospital phase of myocardial infarction. Circulation 1979;60:1252–1258.
5. **Braunwald E, Maroko PR.** Reduction of infarction size—an idea whose time (for testing) has come. Circulation 1974;50:206–209.
6. **Sobel BE, Bresnahan SF, Shell WE, Yoder RD.** Estimation of infarct size in man and its relation to prognosis. Circulation 1971;46:640–650.
7. **Proudfit WL, Bruschke AVG, Sones FM.** Natural history of obstructive coronary artery disease: ten-year study of 601 non-surgical cases. Prog Cardiovasc Dis 1978;21:53–63.
8. **Reeves TJ, Oberman A, Jones WB, Sheffield T.** Natural history of angina pectoris. Am J Cardiol 1974;33:4213–4430.
9. **Norris RM, Caughey DE, Mercer CJ, Scott PJ.** Prognosis after myocardial infarction: six year follow-up. Br Heart J 1974;36:786–787.
10. **Harris PJ, Harrell FE Jr, Lee KL, Behar VS, Rosati RA.** Survival in medically treated coronary artery disease. Circulation 1979;60:1259–1269.
11. **Miller RR, DeMaria AN, Vismara LA, Saiel AF, Maxwell KS, Amsterdam EA, Mason DT.** Chronic stable inferior myocardial infarction: unsuspected harbinger of high-risk proximal left coronary artery obstruction amenable to surgical revascularization. Am J Cardiol 1977;39:954–960.
12. **Kavanagh T, Shephard RJ, Chisholm AW, Qureshi S, Kennedy J.** Prognostic indexes for patients with ischemic heart disease enrolled in an exercise-centered rehabilitation program. Am J Cardiol 1979;44:1225–1234.
13. **Sami M, Kraemer H, DeBusk RF.** The prognostic significance of serial exercise testing after myocardial infarction. Circulation 1979;60:1238–1246.
14. **Theroux P, Waters DD, Halphen C, Debaisieux JC, Mizgala HR.** Prognostic value of exercise testing soon after myocardial infarction. N Engl J Med 1979;301:341–345.
15. **Weiner DA, McCabe C, Klein MD, Ryan TJ.** ST segment change post-infarction: predictive value for multivessel coronary disease and left ventricular aneurysm. Circulation 1978;58:887–891.
16. **Castellanet MJ, Greenberg PS, Ellestad MH.** Comparison of ST segment changes on exercise testing with angiographic findings in patients with prior myocardial infarction. Am J Cardiol 1978;42:29–35.
17. **Chaitman BR, Waters DD, Corbara F, Bourassa MG.** Prediction of multivessel disease after inferior myocardial infarctions. Circulation 1978;57:1085–1090.
18. **Morris SN, McHenry RL.** Role of exercise stress testing in healthy subjects and patients with coronary heart disease. Controversies in cardiology—I. Am J Cardiol 1978;42:659–666.
19. **Cohn K, Kamm B, Fetein N, Brand R, Goldschlager N.** Use of treadmill score to quantify response and predict extent of coronary disease. Circulation 1979;59:286–296.
20. **Kasser IS, Bruce RA.** Comparative effects of aging and coronary heart disease on submaximal and maximal exercise. Circulation 1969;39:759–774.
21. **Cohn PF, Vokonas PS, Herman MV, Gorlin R.** Post exercise EKG in patients with abnormal resting EKG. Circulation 1971;43:648–654.
22. **Pichard AD.** Coronary arteriography—for everyone? Am J Cardiol 1976;38:533–535.
23. **Phibbs B.** Sounding board: the abuse of coronary arteriography. N Engl J Med 1979;301:1394–1396.
24. **Bristow JD, Burchell HB, Campbell RW, Ebert PA, Hall RJ, Leonard JJ, Reeves TJ.** Report of the ad hoc committee on indications for coronary arteriography. Circulation 1977;55:969A–974A.
25. **Enthoven AC.** Shattuck lecture: cutting cost without cutting the quality of care. N Engl J Med 1978;298:1229–1238.
26. **Ritchie J, Trobaugh G, Hamilton G, Gould KL, Narahara K, Murray J, Williams D.** Myocardial imaging with thallium 201 at rest and during exercise: Comparison with coronary arteriography and resting and stress electrocardiography. Circulation 1977;56:66–71.
27. **Zaret BL.** Myocardial imaging with radioactive potassium and its analogs. Prog Cardiovasc Dis 1977;20:81–94.
28. **Pitt B, Strauss HW.** Clinical applications of myocardial imaging with thallium-201. In: Willerson JT, ed. Nuclear Cardiology. (Brest AN, ed. Cardiovascular Clinics 10: Series 2). Philadelphia: FA Davis, 1979:125–137.
29. **Dash H, Massie BM, Botvinick EH, Brundage BH.** The non-invasive indentification of left main and three-vessel coronary artery disease by myocardial stress perfusion scintigraphy and treadmill exercise electrocardiography. Circulation 1979;60:276–284.
30. **Massie BM, Botvinick EH, Brundage BH.** Correlation of thallium-201 scintigrams with coronary anatomy: factors affecting region by region sensitivity. Am J Cardiol 1979;44:616–622.
31. **Takaro T, Hultgren HN, Lipton MJ, Detre KM.** The VA cooperative randomized study of surgery for coronary occlusive disease. II. Subgroup with significant left main lesions. Circulation 1976;54:Suppl III:III-107–III-117.
32. **Read RC, Murphy ML, Hultgren HN, Takaro T.** Survival of men treated for chronic stable angina pectoris: a cooperative randomized study. J Thorac Cardiovasc Surg 1978;75:1–9.
33. **Sones FM, Shirey EK.** Cine coronary arteriography. Mod Concepts Cardiovasc Dis 1972;31:735–739.
34. **Judkins MD.** Selective coronary arteriography. Radiology 1967;89:815–823.
35. **Patterson RE, Horowitz SF, Eng C, Rudin A, Meller J, Halgash DA, Pichard AD, Goldsmith SJ, Herman MV, Gorlin R.** Can exercise electrocardiography and thallium-201 myocardial imaging exclude the diagnosis of coronary artery disease? Bayesian analysis of the clinical limits of exclusions and indications for coronary angiography. Am J Cardiol 1982;49:1127–1135.
36. **Pichard AD, Martinez E, Weiner I, Martinez E, Horowitz SF, Patterson RE, Meller J, Goldsmith SJ, Gorlin R, Herman MV.** Regional myocardial perfusion imaging with thallium 201 in the diagnosis of left anterior descending coronary artery disease. Am Heart J 1981;102:30–36.
37. **Bruce RA, Irving JB.** Exercise electrocardiography. In Ref 1:336–348.
38. **Pohost GM, Zir LM, Moore RH, McKusick KA, Guiney TE, Beller GA.** Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. Circulation 1977;55:294–302.
39. **Williams RA, Cohn PF, Vokonas PS, Young E, Herman MV, Gorlin R.** Electrocardiographic, arteriographic and ventriculographic correlations in transmural myocardial infarction. Am J Cardiol 1973;31:595–596.
40. **Miller RR, Amsterdam EA, Gogren HG, Massumi RA, Zelis R, Mason DT.** Electrocardiographic and cineangiographic correlations in assessment of the location, nature and extent of abnormal left ventricular segmental contraction in coronary artery disease. Circulation 1974;49:447–454.
41. **Rigo P, Bailey IK, Griffith LSC, Pitt B, Burow RD, Wagner HN Jr, Becker LC.** Value and limitations of segmental analysis of stress thallium myocardial imaging for localization of coronary artery disease. Circulation 1980;61:973–981.
42. **Lenaers A, Block P, van Thiel E, Lebedelle M, Becquevort P, Erbsmann F, Ermans AM.** Segmental analysis of Tl-201 stress myocardial scintigraphy. J Nucl Med 1977;18:509–516.
43. **Lusted LB.** Introduction to Medical Decision Making. Springfield, IL: Charles C Thomas, 1968:1–46.
44. **Feinstein AR.** On the sensitivity, specificity and discrimination of diagnostic tests. In: Clinical Biostatistics. St. Louis: CV Mosby, 1977:214–228.
45. **Dixon WJ, Massey FJ Jr.** Introduction to Statistical Analysis. 3rd ed. New York: McGraw Hill, 1969:150–215,237–255.
46. **Rifkin RD, Hood WB Jr.** Bayesian analysis of electrocardiographic exercise stress testing. N Engl J Med 1977;297:681–686.
47. **Hamilton GW, Trobaugh GB, Ritchie JL, Gould KL, DeRouen TA, Williams DL.** Myocardial imaging with $^{201}$Thallium: an analysis of clinical usefulness based on Bayes' theorem. Semin Nucl Med 1978;7:358–364.
48. **Diamond GA, Forrester JS.** Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979;300:1350–1358.
49. **Sheldon WC, Rincon G, Pichard AD, Razavi M, Cheavechai C, Loop FD.** Surgical treatment of coronary artery disease: pure graft operations, with a study of 741 patients followed 3–7 years. Prog Cardiovasc Dis 1975;18:237–251.
50. **Cohn MV, Gorlin R.** Main left coronary artery disease: clinical experience from 1964 to 1973. Circulation 1975;52:275–278.
51. European Coronary Study Group. Coronary bypass surgery in stable angina pectoris: survival at two years. Lancet 1979;1:889–893.
52. **Cohn PF, Gorlin R, Collins JJ, Cohn L.** The left ventricular ejection fraction as a guide in the surgical treatment of coronary and valvular heart disease. Am J Cardiol 1974;34:136–143.
53. **Turner JD, Schwartz KM, Logic JR, Sheffield LT, Kansal S, Roitman DI, Mantle JA, Russell RD Jr, Rackley CE, Rogers WJ.** Detection of residual jeopardized myocardium 3 weeks after myocardial infarction by exercise testing with thallium$^{201}$ myocardial scintigraphy. Circulation 1980;61:729–737.
54. **Bamrah VS, Keelan MH, Soin JS, Siegel RD, Llaurado JP, Tresch DD, Tristani FE, Brooks HL.** Thallium$^{201}$ exercise scintigraphy for detection of multivessel disease in patients with prior inferior myocardial infarction (abstr). Am J Cardiol 1980;45:398.
55. **Gibson RS, Taylor GJ, Steffins PB, Watson DD, Beller GA.** Comparison of thallium$^{201}$ scintigraphy with coronary arteriography for assessment of extent of coronary artery disease two weeks post-myocardial infarction

(abstr). Clin Res 1980;28:173A.
56. **Eng C, Patterson RE, Horowitz SF, Halgash D, Gorlin R, Herman MV.** The significance of differential regional responses to exercise in coronary artery disease (abstr). Circulation 1979;60:Suppl II:II-266.
57. **Patterson RE, Jones-Collins BA, Aamodt R.** Impaired collateral blood flow reserve early after nontransmural myocardial infarction in conscious dogs. Am J Cardiol 1982;50:1133–1140.
58. **Kaplan MA, Harris CN, Aronow WS, Parker DP, Ellestad HM.** Inability of the submaximal treadmill stress test to predict the location of coronary disease. Circulation 1973;47:250–256.
59. **Kent KM, Borer JS, Green MV, Bacharach SL, McIntosh CL, Conkle DM, Epstein SE.** Effects of coronary artery bypass on global and regional left ventricular function during exercise. N Engl J Med 1978;298:1434–1439.
60. **Bruce RA, Fisher LD, Cooper MN, Gey GO.** Separation of effects of cardiovascular disease and age on ventricular function with maximal exercise. Am J Cardiol 1974;34:757–763.
61. **Chin CF, Messenger JC, Greenberg PS, Ellestad MH.** Chronotropic incompetence in exercise testing. Clin Cardiol 1979;2:12–18.
62. **Irving JB, Bruce RA, DeRouen TA.** Variations in and significance of systolic pressure during maximal exercise (treadmill) testing. Relation to severity of coronary artery disease and cardiac mortality. Am J Cardiol 1977;39:841–850.
63. **Morris SN, Phillips JF, Jordan JW, McHenry PL.** Incidence and significance of decreases in systolic blood pressure during graded treadmill exercise testing. Am J Cardiol 1978;41:221–228.
64. **Starling MR, Crawford MH, Kennedy GT, O'Rourke RA.** Treadmill exercise tests predischarge and six weeks post-myocardial infarction to detect abnormalities of known prognostic value. Ann Intern Med 1981;94:721–727.
65. **Schwartz KM, Turner JD, Sheffield LT, Roitman DI, Kansal S, Papapietro SE, Mantle JA, Rackley CE, Russell RO, Rogers WJ.** Limited exercise testing soon after myocardial infarction: correlation with early coronary and left ventricular angiography. Ann Intern Med 1981;94:727–734.
66. **Fuller CM, Raizner AE, Verani MS, Nahormek PA, Chahine RA, McEntee CW, Miller RR.** An accurate predictor of multivessel coronary disease and subsequent cardiac events. Ann Intern Med 1981;94:734–739.
67. **Stang JM, Lewis RP.** Early exercise tests after myocardial infarction. Ann Intern Med 1981;94:814–815.
68. **Grines PF, Mayewski RJ, Mushlin AI, Greenland P.** Selection and interpretation of diagnostic tests and procedures: principles and applications. Ann Intern Med 1981;94:553–600.

When you can measure what you are speaking about and express it in numbers, you know something about it; when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind.

Lord Kelvin, 1824–1907

# Papillary Muscle Rupture Complicating Acute Myocardial Infarction: Analysis of 17 Patients

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**The records of 17 patients (10 men and 7 women) with the diagnosis of acute papillary muscle rupture secondary to acute myocardial infarction (AMI) were reviewed to determine the clinical course and pathologic features of this entity. Eight patients underwent operation after papillary muscle rupture had been diagnosed, and 9 had the diagnosis confirmed at autopsy without a prior surgical procedure. The ages were 44 to 80 years (mean 64). The site of AMI was inferolateral in 15 and anterior in 2. The recorded onset of mitral regurgitation ranged from <24 hours to 28 days after AMI (mean 6 days). Of the 11 patients presenting with pulmonary congestion alone, 6 remained stable and had subsequent mitral valve replacement and coronary artery bypass graft operation; however, 5 patients' condition initially stabilized with medical therapy and then suddenly deteriorated after a variable period (1 to 60 days), followed by death. Of the 6 patients who presented with systemic hypotension and pulmonary congestion, 4 were treated medically and died; 1 of the 2 who had surgical treatment survived. The extent of the AMI at autopsy was small and was limited to the subendocardium in half of the patients. Significant coronary artery disease was limited to a single vessel in 7 of 14 patients. The unpredictable and rapid clinical deterioration and the limited extent of coronary atherosclerotic disease and infarct size suggest that early surgical repair should be undertaken in patients with papillary muscle rupture after AMI.**

Papillary muscle rupture, a rare but well-documented complication of AMI, usually occurs 2 to 7 days after AMI and leads to acute mitral regurgitation (MR), pulmonary edema, cardiogenic shock, or some combination of these findings.[1] If this rupture is untreated, the prognosis is poor; an 80% mortality rate in the first week has been reported.[2] Wei et al[1] estimated that 0.4 to 5.0% of all deaths after AMI are associated with papillary muscle rupture. Prompt diagnosis, hemodynamic stabilization (with intraaortic balloon support, if necessary), and mitral valve replacement combined with coronary artery bypass operation may improve the poor natural history. We reviewed the records of patients diagnosed as having papillary muscle rupture at the Mayo Clinic from 1939 to 1981, with particular attention to the clinical course and pathologic features.

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## Clinical Profile

Excluded from the analysis were patients with chordal rupture, papillary muscle dysfunction, and papillary muscle rupture unassociated with coronary heart disease. Seventeen patients (10 men and 7 women) had papillary muscle rupture secondary to AMI. Of these patients, 8 had undergone operation for papillary muscle rupture (Group 1), and 9 had the diagnosis confirmed at autopsy (Group 2) and had not undergone operation. The ages of the overall group ranged from 44 to 80 years (mean 64); the mean age was 58 years in Group 1 and 69 years in Group 2. Only 1 patient had a history of documented prior AMI that healed. Four patients had had stable exertional angina before the AMI, and 12 patients had no history of angina or AMI. Three patients had a history of systemic hypertension.

All patients had a recent AMI substantiated by electrocardiographic changes, postmortem examination, or both. Electrocardiograms were available in 14 patients; the site of AMI was inferior in 10, anterior in 1, and of undetermined location in 3. The AMI was subendocardial in 8 patients and transmural in 6 patients. The recorded onset of MR ranged from <24 hours to 28 days after clinical AMI (mean interval 6 days), occurring earlier than 24 hours in 3 patients and later

**TABLE I Clinical Features and Hemodynamic Data for Group 1**

| Case | Age (yr) & Sex | Location of AMI | Type of AMI | Interval (days), AMI to Rupture | Type of Rupture | Interval (days), Rupture to Operation | Percent Narrowing of Coronary Arteries* | | | | CI (liters/ min/m²) | EF (%) | LVEDP or PAW (mm Hg) | V Wave (mm Hg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | LAD | R | LC | LOM | | | | |
| 1 | 56M | Inferior | Transmural | 9 | Partial | 120 | ... | ... | ... | ... | 2.6 | ... | 17 | 65 |
| 2 | 72F | Inferior | Subendocardial | 4 | Partial | 100 | ... | ... | ... | ... | 2.8 | ... | 28 | 50 |
| 3 | 54F | Anterior | Subendocardial | 28 | Partial | 81 | 60 | 100 | † | † | ... | ... | 10 | ... |
| 4 | 53M | Inferior | Transmural | 4 | Partial | 72 | † | 100 | † | † | 2.3 | 60 | 25 | 58 |
| 5 | 54M | Inferior | Subendocardial | ? | Partial | 120 | 60 | 100 | 100 | † | 2.3 | 32 | 23 | ... |
| 6 | 59M | Inferior | Subendocardial | ? | Partial | 80 | 75 | 100 | † | † | ... | 57 | 31 | ... |
| 7‡ | 67M | Inferior | Transmural | 1 | Entire | 17 | ... | ... | ... | ... | 1.9§ | ... | 22 | 66 |
| 8‡ | 47F | Inferior | Transmural | 5 | Partial | 150 | † | 100 | † | † | 2.5 | 54 | 24 | 38 |

* Diameter reduction by angiogram. † ≤50% diameter reduction. ‡ Died postoperatively. § Measured by bedside hemodynamic monitoring.
AMI = acute myocardial infarction; CI = cardiac index; EF = ejection fraction; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; LOM = left obtuse marginal coronary artery; LVEDP = left ventricular end-diastolic pressure; PAW = pulmonary artery wedge pressure; R = right coronary artery.

**TABLE II Clinical and Pathologic Features of Patients in Group 2**

| Case | Age (yr) & Sex | Interval (days), AMI to Rupture | Interval (days), Rupture to Death | Ruptured Papillary Muscle | Extent of Rupture | Previous AMI | Type of AMI | Location of AMI | Size of AMI (cm) | Percent Narrowing of Coronary Arteries* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | LAD | R | LC |
| 9 | 57M | 1 | 1 | Posteromedial | Entire | None | Transmural | Inferior | 9 × 5 | ... | ... | T |
| 10 | 80F | 5 | 1 | Posteromedial | 1 of 2 heads | None | Subendocardial | Inferior | 4 × 3 | ... | T | ... |
| 11 | 77F | 4 | 3 | Posteromedial | 2 of 5 heads | None | Transmural | Inferior | 3 × 1 | 90 | 100 | 95 |
| 12 | 77M | 10 | 2 | Posteromedial | 1 of 2 heads | Inferior | Subendocardial | Inferior | 1 × 1.5 | 95 | 100 | ... |
| 13 | 77M | 5 | <1 | Anterolateral | ½ entire head | None | Subendocardial | Lateral | 3 × 2 | ... | ... | ... |
| 14 | 44M | 1 | 60 | Posteromedial | 1 of 2 heads | None | Transmural | Inferior | 6 × 3 | ... | 95 | 95 |
| 15 | 68F | 6 | <1 | Posteromedial | 2 of 5 heads | None | Subendocardial | Inferior | 1 × 3 | 90 | ... | 90 |
| 16 | 73F | 5 | 30 | Posteromedial | 1 of 2 heads | Inferior | Subendocardial | Inferior | 2 × 3 | ... | 95 | ... |
| 17† | 66M | 5 | <1 | Posteromedial | Entire | None | Transmural | Inferior | 5 × 4 | ... | ... | 95 |

* Percent obstruction of cross-sectional area. † Three-cm tear halfway through the inferior wall.
T = thrombus; other abbreviations as in Table I.

than 5 days in 4 patients (Tables I and II). A loud precordial holosystolic murmur was heard in all but 2 patients; these 2 patients had severe pulmonary edema with shock and died within 24 hours after the onset of papillary muscle rupture. One of these 2 patients had total rupture of the papillary muscle. Auscultatory evidence of pulmonary congestion was present in all patients. Eleven patients presented with pulmonary congestion alone, and 6 patients had pulmonary congestion in association with systemic hypotension (systolic blood pressure <90 mm Hg).

## Methods

**Noninvasive:** Of the 6 patients in Group 1 in whom papillary muscle rupture was diagnosed after 1972, 4 underwent M-mode echocardiography. Three studies demonstrated the typical flail mitral leaflet with systolic posterior motion, in combination with shaggy echoes and diastolic flutter; the remaining study demonstrated a hyperdynamic septum with increased D-E excursion of the mitral valve. The posterior left ventricular wall was hypokinetic in 2 studies, and normal wall motion was seen in the other 2 studies. Three patients underwent 2-dimensional echocardiography. Two patients had localized hypokinesia of the inferobasal wall, and the third patient had a large inferior akinetic area extending from the apex to the base. Partial rupture of the head of the posteromedial papillary muscle could be seen in 2 of the 3 patients; the muscle was attached to the chordae and "swinging" into the left atrium.

**Invasive:** Cardiac catheterization was performed in 6 patients, and bedside hemodynamic monitoring (Swan-Ganz catheterization) was done in 1 additional patient (Table I). The mean pulmonary arterial wedge pressure in these patients was 21 mm Hg (range 17 to 31), with a peak V wave mean of 55 mm Hg (range 38 to 66). The mean cardiac index was 2.4 liters/min/$m^2$ (range 1.9 to 2.8). In all 6 patients who underwent left ventricular cineangiography, dense opacification of the left atrium confirmed the presence of severe MR. Coronary cineangiography was performed in 5 patients; 2 had severe (>75% stenosis) 3-vessel disease, 1 had 2-vessel disease, and 2 had single-vessel right coronary artery disease (Fig. 1). Left ventriculography revealed ventricular dilatation and regional wall abnormalities in all 5 patients. One patient had global reduction in left ventricular function; the remaining 4 patients had normal ventricular function. The mean left ventricular ejection fraction was 51% (range 32 to 60%). In 1 patient, a radiolucent mass—thought to be the head of the ruptured papillary muscle—was noted to prolapse into the left atrium during systole.

**Course and management:** Operation was performed in 8 of 17 patients from 1968 to 1981. Seven had elective mitral valve replacement performed 76 to 155 days after AMI. All patients in whom elective operation was performed had satisfactory left ventricular function and a cardiac index ≥2.3 liters/min/$m^2$. One Ionescu-Shiley, 1 Smeloff-Cutter, and 6 Starr-Edwards prostheses were used. Concomitant coronary bypass grafting was performed in 3 patients; 1 had 3 grafts (right coronary, obtuse marginal, and left anterior descending arteries), 1 had 2 grafts (right coronary and left anterior descending arteries), and the third had a single graft (right coronary artery). All 7 patients survived the operative procedure. One patient died in the postoperative period from a pulmonary artery rupture from an occluding Swan-Ganz catheter balloon.

One patient underwent an emergency operation 18 days after a large transmural inferior AMI. This patient underwent operation because of sudden cardiogenic shock; because of hemodynamic deterioration, he could not be weaned from cardiopulmonary bypass. Preoperative 2-dimensional echocardiography had demonstrated a large akinetic inferior wall extending from the base to the apex of the left ventricle and rupture of the posteromedial papillary muscle. The cardiac index was 1.9 liters/min/$m^2$.

Of 11 patients who presented with congestive heart failure unaccompanied by hypotension, 6 remained stable preoperatively; however, 5 patients had sudden deterioration and death occurring at 1, 3, 6, 30, and 60 days, respectively, after the onset of mitral regurgitation (Fig. 2). Of 6 patients who presented with pulmonary edema and hypotension, 4 died within the first 24 to 48 hours. One patient's condition stabilized with use of vasodilators and an intraaortic balloon pump and a successful operation was performed 72 days later. In another patient, treatment with vasodilators resulted in a stabilized condition; 2-dimensional echocardiography disclosed a partial rupture of the papillary muscle. Seven days later, abrupt deterioration necessitated surgical intervention. At operation, complete rupture of the papillary muscle was found. The patient died.

**Pathologic material (Table II):** From 1939 to 1972, 9 patients who did not undergo an operation died after the onset of MR and had postmortem examinations. Five deaths occurred <48 hours after the onset of congestive heart failure.

The posteromedial mitral papillary muscle was involved in 8 patients; 1 patient had rupture of the anterolateral mitral papillary muscle. Among all specimens, 2 had complete dehiscence of the papillary muscle. The other 7 hearts demonstrated either partial rupture of the posteromedial papillary muscle (rupture of 1 of 2 or 2 of 5 heads) or incomplete rupture of a single trunk.

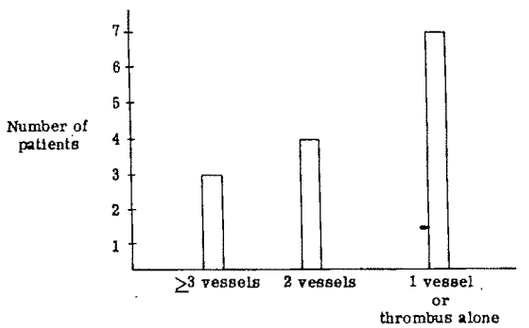



**FIGURE 1.** Extent of coronary artery disease in patients (from Groups 1 and 2) with papillary muscle rupture. Significant disease was defined as >75% stenosis of the cross-sectional diameter.

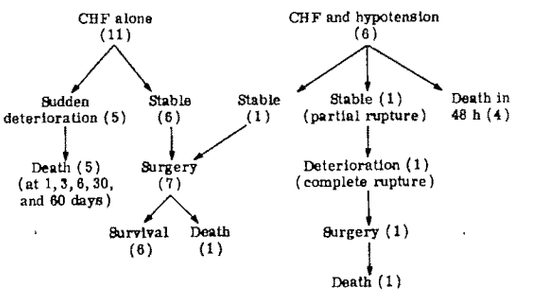



**FIGURE 2.** Clinical course of patients with rupture of papillary muscle. CHF = congestive heart failure.

Inferoposterior AMI was transmural in 4 patients and was limited to the subendocardium in 5 patients; 2 of the subendocardial infarctions were clinically suspected to have been transmural because of the presence of Q waves in the electrocardiogram. Five infarcts involved a relatively small area of the myocardium (<6 $cm^2$). Both total papillary muscle ruptures were associated with extensive transmural infarcts. Three patients had had previous AMI that healed.

The extent of coronary arterial disease was determined by examination of serial cross sections of the coronary arteries at 3-mm intervals. Obstruction of ≥75% of the cross-sectional area was considered significant (Fig. 1). Four patients had significant obstruction in 2 or 3 coronary arteries. Two patients had single-vessel disease. In the remaining 3 patients, a thrombus with no apparent underlying atherosclerotic lesion was present at the site of occlusion.

## Discussion

Cardiogenic shock after AMI can be caused by many factors but usually is the consequence of extensive myocardial damage; the prognosis for affected patients is dismal despite new therapeutic options.[3] Thus, the incentive to identify a potentially reversible cause of cardiogenic shock is great. Approximately 15% of all patients with fatal AMI have complications attributable to some degree of myocardial rupture and may be potentially salvageable.[1,4] In 1 reported series,[5] 85% of patients with myocardial rupture had rupture of the free wall of the left ventricle, 10% had a ventricular septal defect, and 5% had an acute papillary muscle rupture. The first antemortem diagnosis of a ruptured papillary muscle was reported in 1948[6]; since then, several series of papillary muscle rupture—totaling more than 160 patients—have been reported.[2,5,7–11]

The arterial supply to the papillary muscles consists of small coronary vessels derived from the large epicardial arteries, which in turn traverse the entire thickness of the left ventricular wall and the papillary muscles themselves. The excessive length of the arteries and their subendocardial location may account for the susceptibility to ischemia.[2,12] Because of a single blood supply from the posterior descending artery to the posteromedial papillary muscle, the latter is involved with ruptures 6 to 12 times more frequently than the anterolateral muscle, which has a dual blood supply from the left anterior descending and left circumflex coronary arteries.[1,2,5,12]

The clinical course is characterized by the onset of pulmonary edema or hypotension (or both), usually 2 to 7 days after an AMI.[1] A systolic murmur is usually heard but may seem inconsequential because of the dynamics of acute MR and resultant pressure equalization between the left atrium and the left ventricle.[13] In the setting of an AMI, ventricular septal defect[14–16] and papillary muscle dysfunction[17] must be considered when a new systolic murmur appears in association with clinical deterioration.

The 2-dimensional echocardiogram has been shown to be useful in this differential diagnosis. Direct visualization of a ventricular septal defect has been demonstrated by 2-dimensional echocardiography.[15,16] The echocardiogram may also be useful in distinguishing papillary muscle dysfunction from rupture.[9] Papillary muscle dysfunction is usually found in conjunction with large transmural AMI and major wall motion abnormalities. The papillary muscle itself may appear echodense and notably hypokinetic; these factors result in improper coaptation of the mitral leaflets.[18] Alternatively, papillary muscle rupture may result in a flail mitral leaflet and extension of a portion of the flail leaflet into the left atrium during systole. Coarse diastolic or systolic fluttering of the flail leaflet may be seen.[19,20] In 2 previous reports,[9,21] the belly of the papillary muscle itself had ruptured and could be directly visualized as a mass attached to the chordae, as was seen in 2 of the 3 patients described in our study.

Treatment of papillary muscle rupture has consisted of medical and surgical management. Medical treatment alone has been unsuccessful in most of these patients. Studies in the presurgical era showed a poor prognosis: 33% of the patients died immediately, 50% died within the first 24 hours, and only 6% survived longer than 2 months.[2] Vasodilator therapy, intraaortic balloon pumping, and surgical procedures with improved myocardial protection have increased the number of survivors with this previously fatal complication.[7,8,11,22,23] Replacement of the mitral valve in a patient with papillary muscle rupture was first performed successfully by Austen et al[10] in 1965. With a satisfactorily functioning left ventricle, patients have survived rupture of the entire trunk of the papillary muscle with surgical intervention.[22] Recently, mitral valve repair has been successful in this situation.[24]

The optimal timing of surgical intervention remains unclarified. Patients with acute MR after AMI have a reported 35 to 50% mortality when an operation is performed within 30 days after the acute event.[4,8] If operation is delayed for more than 3 months after AMI, operative mortality is reported to be lowered to 15 to 25%.[4,8] This delay in surgical intervention results in a selection process whereby patients with relatively good ventricular function and less severe MR eventually become candidates for valve replacement or repair. This strategy may result in excellent surgical survival; however, overall salvage of patients with acute MR due to papillary muscle rupture might be improved by proceeding with valve replacement (and coronary artery bypass grafting, if necessary) early after the diagnosis is made, even in patients whose symptoms are controlled. With the use of diuretic drugs and the newer afterload reduction agents, stabilization for 1 to 3 months may be possible; nonetheless, the labile course with rapid clinical deterioration and death seen even after stabilization in our series shows that this delay is not without risk.

The pathologic features of coronary artery disease associated with the papillary muscle rupture in this study are of important clinical relevance. Half of the postmortem examinations showed small areas of myocardial infarction limited to the subendocardium, surrounding the papillary muscle. This relatively small area of infarction associated with papillary muscle rupture has been reported by others.[1] Conceivably, patients with smaller infarctions may be more prone to ruptures, as their relatively good ventricular function may result in a greater "shearing" force at the site of potential ruptures. The extent of coronary artery disease seen in

patients undergoing angiography or at autopsy was also, in most cases, not extensive. Seven of 14 had either single-vessel disease or the absence of significant coronary artery disease (Fig. 1). Both the relatively minimal involvement of the myocardium and the moderate extent of coronary artery disease portend a good prognosis if the hemodynamic abnormality itself can be corrected.

Mortality in the postoperative period is primarily due to inadequate myocardial function and recurrent myocardial infarction.[7] Concomitant coronary artery bypass grafting should be considered. Because 2-dimensional echocardiography provides regional and global assessment of left ventricular function, it may eliminate the need for left ventricular angiography, especially in those patients who remain hemodynamically unstable. We do, however, recommend early coronary cineangiography to delineate the coronary anatomy before valve replacement or repair.

Although papillary muscle rupture is an uncommon complication of AMI, it is life-threatening and may be potentially curable. When a new systolic murmur develops in the setting of an AMI, the pathogenesis may be elucidated by 2-dimensional echocardiography. An early surgical approach seems reasonable in patients with acute papillary muscle rupture; this will probably result in an increase in surgical mortality but may improve overall patient salvage. In stable patients, deterioration may be sudden and unpredictable, and thus delay in the timing of operation is risky. In patients with hypotension, mortality with medical therapy is high; no patient in our study survived on medical therapy alone. This prompts us to consider early surgical intervention in all patients with papillary muscle rupture, irrespective of their clinical presentation.

## References


1. **Wei JY, Hutchins GM, Bulkley BH.** Papillary muscle rupture in fatal acute myocardial infarction: a potentially treatable form of cardiogenic shock. Ann Intern Med 1979;90:149–152.
2. **Sanders RJ, Neubuerger KT, Ravin A.** Rupture of papillary muscles: occurrence of rupture of the posterior muscle in posterior myocardial infarction. Dis Chest 1957;31:316–323.
3. **McEnany MT, Kay HR, Buckley MJ, Daggett WM, Erdmann AJ, Mundth ED, Rao RS, de Toeuf J, Austen WG.** Clinical experience with intraaortic balloon pump support in 728 patients. Circulation 1978;58:Suppl I:I-124–I-132.
4. **Kouchoukos NT.** Surgical treatment of acute complications of myocardial infarction. Cardiovasc Clin 1981;11(3):141–149.
5. **Vlodaver Z, Edwards JE.** Rupture of ventricular septum or papillary muscle complicating myocardial infarction. Circulation 1977;55:815–822.
6. **Cederqvist L, Söderström J.** Papillary muscle rupture in myocardial infarction: a study based upon an autopsy material. Acta Med Scand 1964; 176:287–292.
7. **Merin G, Giuliani ER, Pluth JR, Wallace RB, Danielson GK.** Surgery for mitral valve incompetence after myocardial infarction. Am J Cardiol 1973;32:322–324.
8. **Buckley MJ, Mundth ED, Daggett WM, Gold HK, Leinbach RC, Austen WG.** Surgical management of ventricular septal defects and mitral regurgitation complicating acute myocardial infarction. Ann Thorac Surg 1973;16: 598–607.
9. **Mintz GS, Victor MF, Kotler MN, Parry WR, Segal BL.** Two-dimensional echocardiographic identification of surgically correctable complications of acute myocardial infarction. Circulation 1981;64:91–96.
10. **Austen WG, Sanders CA, Averill JH, Friedlich AL.** Ruptured papillary muscle: report of a case with successful mitral valve replacement. Circulation 1965;32:597–601.
11. **Morrow AG, Cohen LS, Roberts WC, Braunwald NS, Braunwald E.** Severe mitral regurgitation following acute myocardial infarction and ruptured papillary muscle: hemodynamic findings and results of operative treatment in four patients. Circulation 1968;37:Suppl II:II-124–II-132.
12. **Fox AC, Glassman E, Isom OW.** Surgically remediable complications of myocardial infarction. Prog Cardiovasc Dis 1979;21:461–484.
13. **Roberts WC, Perloff JK.** Mitral valvular disease: a clinicopathologic survey of the conditions causing the mitral valve to function abnormally. Ann Intern Med 1972;77:939–975.
14. **Bishop HL, Gibson RS, Stamm RB, Beller GA, Martin RP.** Role of two-dimensional echocardiography in the evaluation of patients with ventricular septal rupture postmyocardial infarction. Am Heart J 1981;102:965–971.
15. **Scanlan JG, Seward JB, Tajik AJ.** Visualization of ventricular septal rupture utilizing wide-angle two-dimensional echocardiography. Mayo Clin Proc 1979;54:381–384.
16. **Farcot JC, Boisante L, Rigaud M, Bardet J, Bourdarias JP.** Two-dimensional echocardiographic visualization of ventricular septal rupture after acute anterior myocardial infarction. Am J Cardiol 1980;45:370–377.
17. **Heikkilä J.** Mitral incompetence as a complication of acute myocardial infarction. Acta Med Scand [Suppl] 1967;475:1–139.
18. **Godley RW, Weyman AE, Feigenbaum H, Rogers EW, Green D.** Patterns of mitral leaflet motion in patients with probable papillary muscle dysfunction (abstr). Am J Cardiol 1979;43:411.
19. **Ahmad S, Kleiger RE, Connors J, Krone R.** The echocardiographic diagnosis of rupture of a papillary muscle. Chest 1978;73:232–234.
20. **Mary DA, Pakrashi BC, Ionescu MI.** Papillary muscle rupture following myocardial infarction: successful treatment by resection of akinetic left ventricular area, mitral valve replacement, and aorta to coronary artery bypass graft. Thorax 1973;28:390–393.
21. **Erbel R, Schweizer P, Bardos P, Meyer J.** Two-dimensional echocardiographic diagnosis of papillary muscle rupture. Chest 1981;79:595–598.
22. **DeBusk RF, Kleiger RE, Ebnother CL, Daily PO, Harrison DC.** Successful early operation for papillary muscle rupture. Chest 1970;58:175–178.
23. **Glancy DL, Stinson EB, Shepherd RL, Itscoitz SB, Roberts WC, Epstein SE, Morrow AG.** Results of valve replacement for severe mitral regurgitation due to papillary muscle rupture or fibrosis. Am J Cardiol 1973;32:313–321.
24. **Gula G, Yacoub MH.** Surgical correction of complete rupture of the anterior papillary muscle. Ann Thorac Surg 1981;32:88–91.

# Comparative Rates of Resolution of QRS Changes After Operative and Nonoperative Acute Myocardial Infarcts

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**An independently developed and previously validated QRS scoring system for estimating myocardial infarct size has been used to compare the development and regression of changes associated with myocardial infarcts occurring in 2 different clinical settings. It is known that QRS changes suggesting myocardial infarction occur after coronary artery bypass grafting. This study compares the magnitudes and time courses of these QRS changes in 40 patients with the QRS changes observed in a control group of 46 patients with nonoperative acute myocardial infarcts. Only patients in both groups who had a baseline electrocardiogram (ECG) with no evidence of previous myocardial infarcts, ventricular hypertrophy, or bundle branch block were included. Both groups attained similar peak QRS scores during the acute phase but different rates of resolution of scores were observed. During the subsequent 2 months, regression of QRS changes occurred more rapidly in the perioperative group than in the control group (43 versus 19%). Rates of regression were similar in both groups during the remainder of the follow-up period, attaining total decreases of 62% in the operative group and 37% in the nonoperative group by 18 months. These results could mean either that factors other than acute infarction are responsible for the perioperative QRS changes or that the infarct healing process in the 2 clinical settings are quite different.**

Many studies have used the ECG to estimate the incidence of perioperative myocardial infarction. This has been complicated by observations that in some patients there is rapid resolution of QRS changes[1] or that new Q waves are due to the "unmasking" of old infarcts.[2] These observations have led to questions regarding the comparability of perioperative with nonoperative myocardial infarcts as diagnosed by the ECG.

Changes in the QRS complex of the standard 12-lead ECG have been shown to correlate with both the size of infarcts as determined at postmortem examination[3–5] and the extent of damage as determined by radionuclide ventriculography[6] during the first year after acute infarction. This study examines the hypothesis that QRS changes suggestive of perioperative myocardial infarction that persist until hospital discharge will undergo a subsequent rate of resolution which exceeds that of nonoperative infarcts. Infarct size calculated from the QRS score may appear similar to that in the nonoperative infarcts initially, but subsequent variations in resolution of the QRS changes would indicate that ultimately the perioperative infarcts involved less myocardium.

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**TABLE I QRS Scoring System***

| Lead | Duration (ms) | Amplitude Ratios | Maximum Points |
|---|---|---|---|
| I | Q ≥30 (1) | R/Q ≤1 (1) | 2 |
| II | Q ≥40 (2) | | |
| | Q ≥30 (1) | | 2 |
| aVL | Q ≥30 (1) | R/Q ≤1 (1) | 2 |
| aVF | Q ≥50 (3) | R/Q ≤1 (2) | |
| | Q ≥40 (2) | | |
| | Q ≥30 (1) | R/Q ≤2 (1) | 5 |
| $V_1$ | Any Q (1) | | |
| | R ≥50 (2) | | |
| | R ≥40 (1) | R/S ≥1 (1) | 4 |
| $V_2$ | Any Q or R ≤20 (1) | | |
| | R ≥60 (2) | | |
| | R ≥50 (1) | R/S ≥1.5 (1) | 4 |
| $V_3$ | Any Q or R ≤30 (1) | | 1 |
| $V_4$ | Q ≥20 (1) | R/Q or R/S ≤0.5 (2) | |
| | | R/Q or R/S ≤1 (1) | 3 |
| $V_5$ | Q ≥30 (1) | R/Q or R/S ≤1 (2) | |
| | | R/Q or R/S ≤2 (1) | 3 |
| $V_6$ | Q ≥30 (1) | R/Q or R/S ≤1 (2) | |
| | | R/Q or R/S ≤3 (1) | 3 |

* The number of points awarded for meeting each criterion is in parentheses.

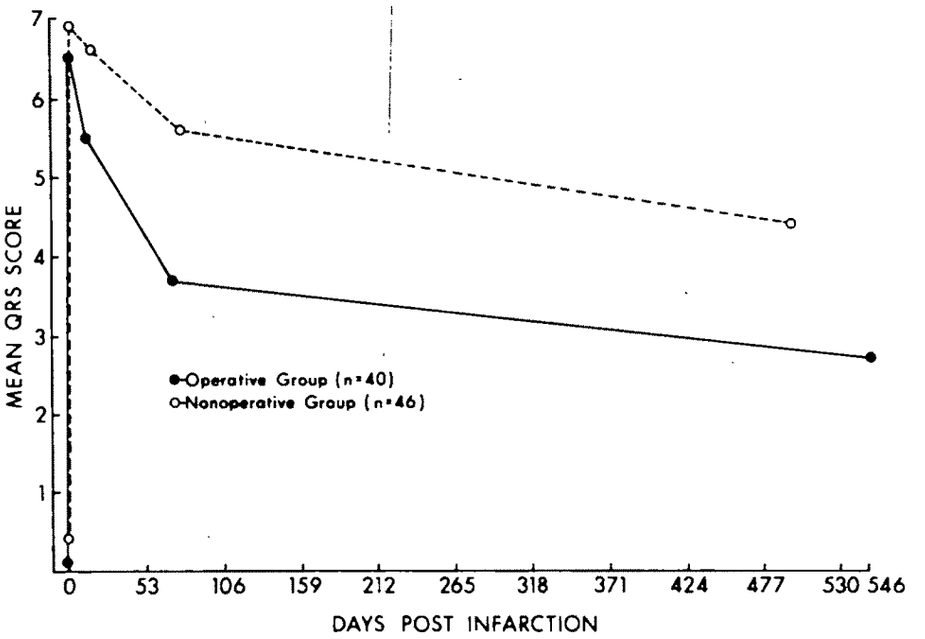



**FIGURE 1.** These curves illustrate the resolution of mean QRS scores in the operative and nonoperative groups. The points indicated on both curves represent the scores obtained on the 12-lead ECG from baseline (preoperative or admission), day 1 to 5 (maximum score), day 14, day 60, and 18 months.

## Methods

**QRS scoring method:** Points were assigned on the basis of absolute duration of Q and R waves and amplitude ratios of the QRS components in 10 leads of the standard 12-lead ECG (Table I). This system consists of a total of 29 points and a score of >2 has a 98% specificity for identification of a myocardial infarct in the absence of confounding cardiac problems.[3]

**Patient population:** Twelve-lead ECGs were reviewed from all patients who underwent coronary artery bypass grafting at Duke University Medical Center or who were admitted to the Duke University Medical Center coronary care unit between 1972 and 1978. Patients with a previous myocardial infarct, a persistent intraventricular conduction abnormality (left anterior or posterior fascicular block, left or right bundle branch block), or ventricular hypertrophy by the Estes (left ventricular hypertrophy)[7] or Sokolow (right ventricular hypertrophy)[8] criteria were eliminated from the study. The effect of these conditions on the QRS complex could limit its ability to indicate myocardial infarct size. Patients were included in the study only if they had a baseline ECG with <3 points and a subsequent ECG that gained at least 2 additional points. In the nonoperative group, the baseline ECG usually was obtained in the emergency room and in the operative group it was acquired during the 24 hours before surgery. A patient from the operative group was included in the study only if QRS changes indicative of an acute infarct appeared within 24 hours after the surgical procedure. Also, only patients with a QRS score which remained greater than that of the baseline ECG for at least 14 days were included.

ECGs from the following intervals were analyzed: baseline; daily through day 5; and closest to day 14, to day 60, and to 18 months after the acute infarct. ECGs were obtained successfully in 100% of the baseline, day 0 to 5, and day 14 intervals. Follow-up ECGs were obtained at 60 days in 95% of the operative group and 96% of the nonoperative group. At 18 months, ECGs were obtained in 75% of the operative group and 86% of the nonoperative group.

Total resolution of the QRS score was defined as a return of the QRS score to the baseline level. Near-total resolution was defined as return of the QRS score to within 1 point of baseline.

**Statistical methods:** A linear regression line was fitted for the natural log of the scores of each patient against the square root of time. The 2 groups were compared using the individual slopes (rate of change) and intercepts of the regression lines with the Wilcoxon ranked sums test. Thus, the initial value and the rate of resolution of the QRS changes were compared rather than the static scores around each particular time interval.

The percentage of patients with complete resolution of the QRS score was compared using Fisher's exact test.

**TABLE II Anatomic Distribution of Acute Myocardial Infarcts**

| Infarct Location | Operative Group (n = 40) | Nonoperative Group (n = 46) |
|---|---|---|
| Anterior | 19 | 15 |
| Inferior | 14 | 25 |
| Posterolateral | 2 | 3 |
| Multiple | 5 | 3 |

## Results

There were 40 patients in the operative group and 46 patients in the nonoperative group. The anatomic distribution of their infarcts by ECG is shown in Table II. According to the ECG, all patients in the operative group had infarcts in the distribution of a grafted coronary artery.

The development and regression of mean QRS scores in both groups are illustrated in Figure 1. The mean baseline level of QRS scores was similar in the groups (0.2 points in the operative group and 0.4 points in the nonoperative group). During the first 5 days after the

acute event, the scores increased to similar mean peaks of 6.5 in the operative group and 6.9 in the nonoperative group ($p = 0.85$). The distribution of peak QRS scores within the 2 groups was also similar. Between days 5 and 60, the slope of the curve relating QRS score to time was steeper in the operative group than in the nonoperative group ($p = 0.03$). While QRS scores continued to decrease between day 60 and 18 months in both groups, the slopes of the curves were similar. In the operative group, the mean QRS score at 18 months was closer to the baseline score than to the peak score, having decreased by 62%. The mean decrease in QRS score by 18 months in the nonoperative group was 37%.

Table III depicts the number of patients in each group who had total or near-total resolution of their QRS changes during follow-up. At 60 days, 11% of the operative group had total resolution compared with none of the nonoperative group ($p = 0.05$). At 18 months, no significant difference in total resolution could be found between the 2 groups. At both time periods, however, more operative patients had near-total resolution than nonoperative patients ($p = 0.02$ at 60 days; $p = 0.03$ at 18 months).

## Discussion

The QRS scoring system developed by Selvester et al[9] and simplified and modified by Wagner et al[3] is based on the computer simulation of the human myocardial activation sequence documented by Durrer et al.[10] It achieves high specificity in normal controls[3] and correlates with the anatomic extent of single infarcts in the anterior[4] and inferior[5] aspects of the left ventricle. In the present study, the peak QRS score of the group with operative infarcts was similar to that of the nonoperative group, suggesting either that similar extents of infarction developed in both groups or that the initial extent of infarction was not as large as indicated by the QRS score in the operative group.

QRS changes tend to resolve gradually after acute infarcts.[11–13] In the studies that compared the QRS score with the anatomic infarct size,[4,5] the correlation between the size estimated from the final ECG before death and the observed size was similar when the necrosis was acute and when there was a fibrotic scar. This observation suggests that the reason for QRS resolution is the "resolution" of the infarct itself. The "healing" process results in the resolution of edema and cellular infiltration of the inflammatory response and retraction of the scar tissue. This is accompanied by hypertrophy of adjacent myocardium. Thus, the percentage of left ventricle that contains nonviable tissue may be greater during the necrotic stage than in the fibrotic stage of myocardial infarction.

**TABLE III Resolution of QRS Changes in Patient Groups**

| | 60 Days | | 18 Months | |
|---|---|---|---|---|
| | Total* | Near-Total† | Total* | Near-Total† |
| Operative group | 4/38 (11%) | 13/38 (34%) | 7/30 (23%) | 16/30 (53%) |
| Nonoperative group | 0/44 (0%) | 4/44 (9%) | 5/39 (13%) | 7/39 (18%) |
| | $p = 0.05$ | $p = 0.02$ | $p = 0.26$ | $p = 0.03$ |

* Return to baseline QRS score; † return to within 1 point of baseline QRS score.

Perioperative infarcts are marked by contraction-band necrosis, indicating that a period of occlusion has been followed by reperfusion.[14] Intraoperative studies indicate that these infarcts frequently begin early during the operative procedure.[15–18] The infarcts are located in areas supplied by patent grafts in 80% of instances.[19–22] These infarcts are frequently not followed by significant wall motion abnormality[23,24] and, as documented in the present study, are accompanied by a more rapid and complete resolution of QRS score than are nonoperative infarcts. These studies suggest that the myocardial infarcts occurring during coronary artery bypass grafting may serve as an experimental model by which reperfusion of a developing area of necrosis could be evaluated.

Blood flow is essential[25] for wound healing. Thus, reperfusion after the onset of an acute myocardial infarct might facilitate the healing process and result in a decreased ratio of infarcted to noninfarcted myocardium. Shaw et al[26] have demonstrated that the wound produced by a left ventricular venting during coronary bypass surgery results in akinesis or dyskinesis when the blood supply to the area is impaired, but causes no detectable wall motion abnormality when flow is unimpaired. Therefore, it is possible that the operative and nonoperative groups had infarcts which were initially of similar size, but the resolution or healing of the operative infarcts was augmented by prompt reperfusion. This would result in a subsequent decrease in the ratio of infarcted to normal myocardium.

It is important to consider possible alternate explanations for the differences observed in QRS resolution between the operative and nonoperative groups. The rapid decrease in QRS score in the operative group during the first 2 months (Fig. 1) might be caused by an initial overestimation of infarct size with subsequent disappearance of the confounding factor. Bresnahan et al[27] found that reperfusion vastly increases the fluid in infarct tissue. Ganz et al[28] observed prompt increase in Q-wave size immediately after intracoronary streptokinase infusion in patients with acute infarcts. A study by Bassan et al[2] demonstrated the reappearance of Q waves indicative of remote preoperative infarcts immediately after aortocoronary bypass surgery. Since all of the QRS changes in the operative group indicated infarction in the distribution of a grafted vessel, the increase in fluid caused by operative infarct reperfusion may have exaggerated the peak QRS scores. The subsequent reabsorption of the fluid could explain the accelerated rate of QRS resolution in the operative group.

It is possible that the QRS changes in the operative group were produced or augmented by operative events other than myocardial infarction. Salem et al[1] have observed new Q waves appearing transiently after cardiac surgery in patients with large posterior pericardial

effusions. However, inclusion in the present study required persistence of the new operative QRS changes until hospital discharge. Therefore it is unlikely that such transient events could have been responsible for the QRS changes observed.

The QRS changes which appear after aortocoronary bypass surgery resolve during the subsequent 2 months at a significantly more rapid rate than do similar appearing changes in nonoperative patients. This suggests that use of the ECG for evaluation of either the presence or the extent of perioperative myocardial infarcts would be better performed at this later time. It has been demonstrated[29] that postoperative creatine kinase isoenzyme measurements overestimate the amount of myocardial damage. It is also possible that immediate postoperative QRS changes may overestimate either the initial extent of the operative infarct or the final extent which will be present when the healing process has been completed.

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## References

1. **Salem BI, Schnee M, Leatherman LL, de Castro CM, Benrey J.** Electrocardiographic pseudo-infarction pattern: appearance with a large posterior pericardial effusion after cardiac surgery. Am J Cardiol 1978;42:681–689.
2. **Bassan MM, Oatfield R, Hoffman I, Matloff J, Swan HJC.** New Q waves after aortocoronary bypass surgery. Unmasking of an old infarction. N Engl J Med 1974;290:349–353.
3. **Wagner GS, Freye CJ, Palmeri ST, Roark SF, Stack NC, Ideker RE, Harrell FE, Selvester RH.** Evaluation of a QRS scoring system for estimating myocardial infarct size. I. Specificity and observer agreement. Circulation 1982;65:342–347.
4. **Ideker RE, Wagner GS, Ruth WK, Alonso DR, Bishop SP, Bloor CM, Fallon JT, Gottlieb GJ, Hackel DB, Phillips HR, Reimer KA, Roark SF, Rogers WJ, Savage RM, White RD, Selvester RH.** Evaluation of a QRS scoring system for estimating myocardial infarct size. II. Correlation with quantitative anatomic findings for anterior infarcts. Am J Cardiol 1982;49:1604–1614.
5. **Ruth WK, Ideker RE, Wagner GS, Alonso DR, Bishop SP, Bloor CM, Fallon JT, Gottlieb GT, Hackel DB, Phillips HR, Reimer KA, Roark SF, Rogers WJ, Savage RM, Selvester RH, Ward RM.** Estimation of myocardial infarct size using a QRS scoring system (abstr). Circulation 1979;60:Suppl II:II-189.
6. **Palmeri ST, Harrison DG, Cobb F, Morris KG, Harrell FE, Ideker RE, Selvester RH, Wagner GS.** A QRS scoring system for assessing left ventricular function after myocardial infarction. N Engl J Med 1982;306:4–9.
7. **Romhilt DW, Greenfield JC Jr, Estes DH Jr.** Vectorcardiographic diagnosis of left ventricular hypertrophy. Circulation 1968;37:15–19.
8. **Sokolow M, Lyon TP.** The ventricular complex in right ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J 1949;38:273–294.
9. **Selvester RH, Solomon J, Sapoznikov D.** Computer simulation of the electrocardiogram. In: Cady LD Jr, ed. Computer Techniques in Cardiology. New York: Marcel Dekker, 1979:417.
10. **Durrer D, van Dam RTh, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC.** Total excitation of the isolated human heart. Circulation 1970;41:899–912.
11. **Kalbfleisch JM, Shadaksharapp KS, Conrad LL, Sarkar NK.** Disappearance of the Q-deflection following myocardial infarction. Am Heart J 1968;76:193–198.
12. **Helfant RH.** Q wave in coronary heart disease: newer understanding of their clinical implications. Am J Cardiol 1976;38:662–664.
13. **Halat R, Worthington FX, Castellanos A, Lemberg L.** Unusual normalization of the electrocardiogram on the 6th day of myocardial infarction. J Electrocardiol 1971;4:363–368.
14. **Bulkley BH, Hutchins GM.** Myocardial consequences of coronary artery bypass graft surgery. The paradox of necrosis in areas of revascularization. Circulation 1977;56:906–913.
15. **Senyk J, Malm A, Bornmyr S.** Intraoperative cardiothermography. A new method for detecting ischemic areas in the heart muscle and for investigating the results of revascularization procedures in coronary surgery. Eur Surg Res 1971;3:1–12.
16. **Gray RJ, Shell WE, Conklin C, Ganz W, Shah PK, Miyamoto AT, Matloff JM, Swan HJC.** Quantification of myocardial injury during coronary artery bypass graft. Circulation 1978;58:Suppl I:I-38–I-42.
17. **Gray RJ, Harris WS, Shah PK, Miyamoto ATM, Matloff JM, Swan HJC.** Coronary sinus blood flow and sampling for detection of unrecognized myocardial ischemia and injury. Circulation 1977;56:Suppl II:II-58–II-61.
18. **Roe CR, Wagner GS, Curtis SE, Cobb FR, Irvin RG.** Relation of creatine kinase isoenzyme MB to postoperative electrocardiographic diagnosis in patients undergoing coronary-artery bypass surgery. Clin Chem 1979;25:93–98.
19. **Campeau L, Corchet D, Lespérance J, Bourassa MG, Grondin CM.** Postoperative changes in aortocoronary saphenous vein grafts revisited: angiographic studies at two weeks and at one year in two series of consecutive patients. Circulation 1975;52:369–377.
20. **Lawrie GJ, Lie JT, Morris GC Jr, Beazley HL.** Vein graft patency and intimal proliferation after aortocoronary bypass: early and long-term angiopathologic correlations. Am J Cardiol 1976;38:856–862.
21. **Wetheimer M, Liddle HV.** Results of direct coronary artery graft reconstruction: a five year clinical and arteriographic appraisal. Ann Thorac Surg 1975;20:538–549.
22. **Selden SF, Borer JS, Kent KM, Rosing DR, McIntosh CL, Epstein SE.** Long-term anatomic fate of coronary-artery bypass grafts and functional status of patients five years after operation. N Engl J Med 1978;298:1213–1217.
23. **Assad-Morell JL, Frye RL, Connolly DC, Gau GT, Pluth JR, Barnhorst DA, Wallace RB, Davis GD, Elveback LR, Danielson GK.** Relation of intraoperative or early postoperative transmural myocardial infarction to patency of aortocoronary bypass grafts and to diseased ungrafted coronary arteries. Am J Cardiol 1975;35:767–773.
24. **Almabilan A, Hamby RI, Hoffman I, Hartstein ML, Wisoff BG.** New Q waves after bypass grafting: correlations between graft patency, ventriculogram and surgical venting technique. J Electrocardiol 1976;9:321–327.
25. **Madden JW.** Wound healing: biologic and clinical features. In: Sabiston DC Jr, ed. Textbook of Surgery. The Biological Basis of Modern Surgical Practice. Vol. 1. 11th ed. Philadelphia: WB Saunders, 1977:288–292.
26. **Shaw RA, Kong Y, Pritchett ELC, Warren SG, Oldham N, Wagner GS.** Ventricular apical vents and postoperative focal contraction abnormalities in patients undergoing coronary artery bypass surgery. Circulation 1977;55:434–438.
27. **Bresnahan GF, Roberts R, Shell WE, Ross J Jr, Sobel BE.** Deleterious effects due to hemorrhage after myocardial reperfusion. Am J Cardiol 1974;33:82–86.
28. **Ganz W, Buchbinder N, Marcus H, Mondkar A, Maddahi T, Charuzi Y, O'Connor L, Shell W, Fishbein MC, Kass R, Miyamoto A, Swan HJC.** Intracoronary thrombolysis in evolving myocardial infarction. Am Heart J 1981;101:4–13.
29. **Ström S, Bendz R, Olin C.** Myocardial injury and CK-MB release during aortic valve surgery with selective coronary perfusion. Clin Cardiol 1981;4:155–161.

# Evaluation of a QRS Scoring System for Estimating Myocardial Infarct Size

## III. Correlation With Quantitative Anatomic Findings for Inferior Infarcts

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**This study evaluated by quantitative autopsy correlation a previously developed scoring system for estimating the size of myocardial infarcts based on the QRS complex of the electrocardiogram. This system was tested using electrocardiograms from patients with infarcts shown by autopsy to predominate in the inferior third of the left ventricle. The study was limited to patients whose electrocardiogram did not indicate left or right ventricular hypertrophy, left or right bundle branch block, or left anterior or posterior fascicular block. Thirty-one patients from 6 medical centers met these criteria.**

**In the electrocardiogram of 28 of the 31 patients (90%), lead aVF exhibited a Q wave of at least 30 ms. The correlation coefficient between the total QRS score and the percent infarction of the left ventricle was 0.74. In patients without confounding factors in the electrocardiogram and with single infarcts, the electrocardiogram provides a marker for infarcts in the inferior third of the left ventricle and a quantitative QRS scoring system provides an estimate of infarct size.**

While several new, sophisticated methods are potentially capable of determining the size of myocardial infarcts, it is still important to evaluate the standard 12-lead electrocardiogram because it is readily available, inexpensive, and noninvasive. Although changes in the QRS complex are recognized for their ability to document the presence of various locations of myocardial infarcts, relatively little has been determined about their ability to indicate infarct size. Recent studies from a multicenter collaboration have demonstrated that a simplified version of a previously developed scoring system based on quantitative aspects of the QRS complex attains a correlation of 0.80 with the size of anatomically documented anterior infarcts.[1,2] Previous studies have suggested that the electrocardiogram might be less capable of defining infarcts in the other principal locations in which they occur, that is, inferior and posterolateral aspects of the left ventricle.[3] It is important that the capability of any method for indication of infarct size be evaluated for all infarct locations. Accordingly, this study was performed to determine the correlation between the simplified version of the QRS scoring system and anatomically documented inferior myocardial infarcts.

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### Methods

**Criteria for inclusion:** Deceased patients from the Massachusetts General Hospital, Cornell University Medical College, the University of Alabama at Birmingham, the University of California at San Diego, United Hospitals of St. Paul, and Duke University Medical Center were included in the study if they met the following criteria: (1) quantitative postmortem examination revealed a myocardial infarct primarily in the inferior third of the left ventricle (Fig. 1). It was required that this infarct either be the only infarct present or

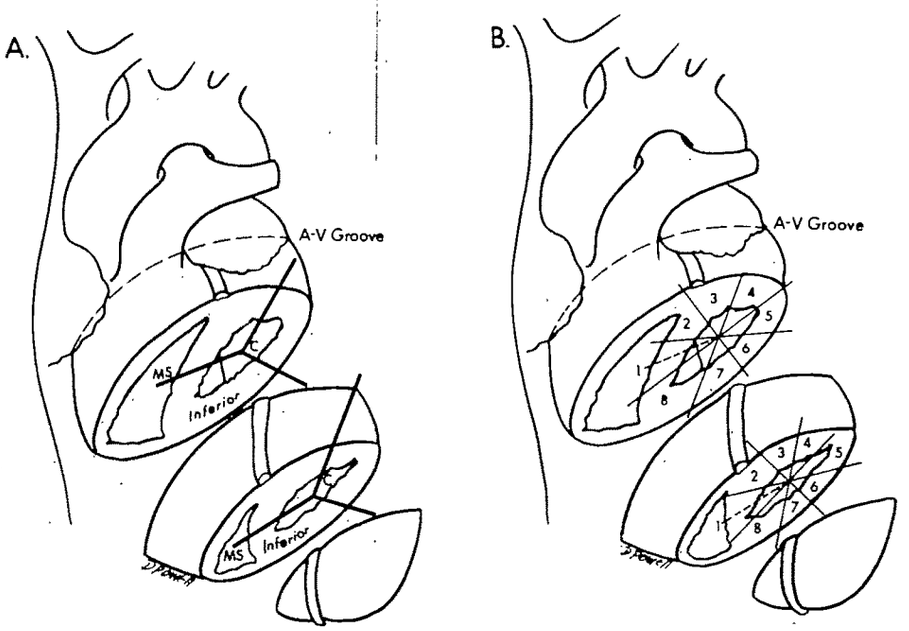



**FIGURE 1.** Division of the left ventricle into thirds (**A**) and octants (**B**). This study includes all cases in which the inferior third of the left ventricle had the largest percent infarction. C = centroid of the outline of the left ventricular epicardium and right septal border; MS = point in the mid-septum halfway between the anterior and posterior endocardial insertions of the right ventricle into the septum. **B**, the **dashed line** MS to C bisects octant 1.

that it be fibrotic and clearly distinguished from a second and fatal acute infarct. In this latter instance only the fibrotic infarct was considered for this study. (2) An electrocardiogram was available that was taken when only the infarct considered in the study was present. This electrocardiogram could not exhibit left or right ventricular hypertrophy, left or right bundle branch block, or left anterior or posterior fascicular block as defined by the IBM program for electrocardiographic analysis.[4] The electrocardiogram must have been taken within 1 year of the paient's death. The final available electrocardiogram was used for the study.

**Quantitative anatomic evaluation:** The hearts, all obtained between 1969 and 1979, were initially dissected by similar protocols at the 6 institutions. The ventricles were cut transverse to the long axis into 5 to 7 slices of approximately equal thickness. Coronary dominance, amount of atherosclerotic coronary arterial disease, and transmural extent of infarction were determined as previously described.[2] To be considered transmural, an infarct had to extend from the endocardium to involve at least 1 cm of the epicardial surface.[2]

The size of the infarct was quantified by computer-assisted planimetry as described previously.[5] Infarct size excludes viable muscle within the infarcted region. For infarcts at least 1 week old at the time of the patient's death, the method includes a correction for estimated wall thinning caused by the infarct. No correction was made for wall thinning in infarcts <1 week old because such thinning was assumed to be caused by expansion and stretching of the infarcted tissue[6] rather than by phagocytosis and scar contraction.

The dominant location of the infarct was determined by comparing the percent infarction of the anterior, posterolateral, and inferior thirds of the left ventricle (Fig. 1A). This study includes all hearts in which the greatest percent infarction was in the inferior third. The percent infarction for each of 24 sectors of the left ventricle was also calculated. The sectors divide the heart into octants in the transverse plane (Fig. 1B) for basal, middle, and apical thirds of the left ventricle as described in the second study in this series.[2]

**Electrocardiographic evaluation:** The point score to estimate infarct size developed by Selvester et al[7-9] and simplified and modified by Wagner et al[1] (Table I) was determined for each electrocardiogram. Points are awarded for duration of Q or R waves and for R to Q and R to S ratios from 10 of the 12 standard leads. R to Q ratio points may only be awarded if Q-wave duration criteria have been satisfied for that lead. However, R to S ratio points may be awarded without consideration of any other criteria for that lead. If there are multiple criteria of a single type (such as Q-wave duration) for a lead, the points achieved by the maximal satisfied criterion are awarded.

## Results

Thirty-one patients met the criteria for inclusion in the study. Twenty-seven were men (mean age 56) and 4 were women (mean age 65). Eighteen of the infarcts were >30 days old when the patient died, 6 between 7 and 30 days old, and 7 were <7 days old. Of the 18 patients with infarcts >30 days old, 10 had a second, fatal infarct.

**TABLE I Simplified QRS Scoring System**

| Lead | Duration (ms) | | Amplitude Ratios | | Maximal Points |
|---|---|---|---|---|---|
| I | Q ≥30 | (1) | R/Q ≤1 | (1) | 2 |
| II | Q ≥40 | (2) | | | |
| | Q ≥30 | (1) | | | 2 |
| aVL | Q ≥30 | (1) | R/Q ≤1 | (1) | 2 |
| aVF | Q ≥50 | (3) | R/Q ≤1 | (2) | |
| | Q ≥40 | (2) | | | |
| | Q ≥30 | (1) | R/Q ≤2 | (1) | 5 |
| $V_1$ | Any Q | (1) | | | |
| | R ≥50 | (2) | | | |
| | R ≥40 | (1) | R/S ≥1 | (1) | 4 |
| $V_2$ | Any Q or R ≤10 | (1) | | | |
| | R ≥60 | (2) | | | |
| | R ≥50 | (1) | R/S ≥1.5 | (1) | 4 |
| $V_3$ | Any Q or R ≤20 | (1) | | | 1 |
| $V_4$ | Q ≥20 | (1) | R/Q or R/S ≤0.5 | (2) | |
| | | | R/Q or R/S ≤1 | (1) | 3 |
| $V_5$ | Q ≥30 | (1) | R/Q or R/S ≤1 | (2) | |
| | | | R/Q or R/S ≤2 | (1) | 3 |
| $V_6$ | Q ≥30 | (1) | R/Q or R/S ≤1 | (2) | |
| | | | R/Q or R/S ≤3 | (1) | 3 |

**TABLE II Transmural Extent of Infarcts**

| | Number of Hearts | | | | |
|---|---|---|---|---|---|
| Level of LV | TM | SEn | SEp | IM | Zero |
| Base | 12 | 19 | 0 | 0 | 0 |
| Middle | 17 | 12 | 1 | 1 | 0 |
| Apex | 4 | 12 | 5 | 6 | 4 |

IM = intramural; LV = left ventricle; SEn = subendocardial; SEp = subepicardial; TM = transmural; zero = no infarct in that level.

**Anatomic evaluation:** The mean total heart weight was 462 g. The right coronary artery was dominant in 29 hearts. Maximal narrowing in the dominant coronary artery was 90 to 100% in all cases. The percentage of the left ventricle that was infarcted ranged from 4 to 41% (mean 15).

Eighteen hearts had transmural involvement in at least 1 level of the left ventricle. Sixteen of 18 infarcts involving >10% of the left ventricle had transmural involvement in at least 1 level. Eleven of 13 infarcts involving ≤10% of the left ventricle had no levels with transmural involvement. Infarcts were more often transmural in the basal and middle thirds than in the apical third (Table II). Eleven of the 13 (85%) nontransmural infarcts in the basal and middle thirds were subendocardial. In the apical third, however, 11 of the 23 (48%) nontransmural infarcts were intramural or subepicardial. Four hearts had no apical involvement.

The inferior free wall (octant 7) was the most commonly involved area with the basal and middle levels containing infarct in 100 and 97% of the hearts, respectively (Table III). The infarcts involved the inferior aspect of the septum and immediately adjacent free wall (octant 8) in 94% of the hearts. Involvement of the midseptum (octant 1) was uncommon, with only 2 infarcts reaching all 3 levels. Many infarcts extended laterally into octant 6 but fewer infarcts extended more laterally into the middle of the "free wall" (octant 5) (Table III). In contrast to anterior infarcts,[2] no infarct predominating in the inferior third had circumferential apical involvement.

**Electrocardiographic evaluation:** Q waves in leads II, III, and aVF are commonly considered indicative of inferior infarcts. Table IV indicates the Q wave durations observed in these 3 leads in the study patients. Q waves of ≥30 ms were present in leads II, aVF, and III in 20, 28, and 22 electrocardiograms, respectively. Forty ms or greater Q waves were present in leads II, aVF, and III in 3, 19, and 14 electrocardiograms, respectively. Thus, 28 of the 31 patients (90%) had a 30 ms Q wave in at least 1 inferiorly oriented electrocardiogram lead, while only 19(61%) had a 40 ms Q wave in at least 1 of these leads.

The mean QRS score for the 31 patients was 5 points, with a range of 0 to 11 (Fig. 2). All but 1 of the patients received points and 26 patients (84%) received >2 points. Of the total of 150 points received by all 31 patients, 119 points (80%) were gained from leads aVF and II. Three patients had no QRS points from either leads aVF or II. One of these patients had no points and 2 had only 1 point, contributed by a Q wave in lead $V_1$. The anatomic size of these infarcts varied from 4 to 10% of the left ventricle and the 2 with a Q wave in $V_1$ did not have more anteroseptally located infarcts.

Five of the 31 patients (16%) received points for increased duration or amplitude of the R wave in leads $V_1$ or $V_2$ (Fig. 2) which has been reported to indicate "true posterior" infarction.[10–12] Ten other patients (32%) received points for a Q wave in lead $V_1$ or a diminished R wave in leads $V_2$ or $V_3$, which have been reported to indicate "anteroseptal" infarction.[13] Eleven of the 31 patients (35%) met criteria for points in leads $V_4$, $V_5$, or $V_6$ which have been reported to indicate apical infarction.[1,14,15] None of the patients met criteria for points from leads I or aVL, which have been reported to indicate "high lateral" infarction.[14,15]

**Comparison of antomic and electrocardiographic estimated infarct size:** A diagram of the location of the infarct and the electrocardiogram is shown for 1 representative patient in Figure 3. The percent infarction of the left ventricle versus the total point score is plotted for all patients in Figure 4. For the 26 patients in whom the electrocardiograms scored >2 points, the mean infarct occupied 17% of the left ventricle (range 4 to 41%). For the 5 patients with electrocardiogram scores of ≤2 points, the mean infarct occupied 7% of the left ventricle (range 4 to 10%).

The correlation coefficient between the number of points and infarct size was 0.74. The slope of the regression line was 2.5, indicating that each QRS point represents infarction of 2.5% of the left ventricle. The standard error of the estimate was 6.6%.

Twenty-seven of the 31 hearts contained infarcts in the apical third of the left ventricle, although only 11 electrocardiograms received points for leads $V_4$ to $V_6$ (Fig. 2). In many patients, however, the amount of apical infarction was small. In the 11 patients receiving points in leads $V_4$ to $V_6$, the mean infarct extent in the apical third of the left ventricle was 12%, significantly greater

**TABLE III Number and Percentage of Hearts With Infarction of Each Octant**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Base | 9 (29%) | 0 (0%) | 0 (0%) | 3 (10%) | 15 (48%) | 26 (84%) | 31 (100%) | 29 (94%) |
| Middle | 5 (16%) | 0 (0%) | 0 (0%) | 1 (3%) | 10 (32%) | 24 (77%) | 30 (97%) | 29 (94%) |
| Apex | 3 (10%) | 0 (0%) | 0 (0%) | 0 (0%) | 6 (19%) | 15 (48%) | 24 (77%) | 19 (61%) |

($p = 0.04$) than the mean infarct extent of 6% in the 20 patients without QRS points in leads $V_4$ to $V_6$.

Eighteen of the 31 hearts contained infarcts which extended laterally (octant 5). Only 5 electrocardiograms received points for increased R-wave duration in lead $V_1$ or $V_2$. The mean percent infarction of octant 5 in these hearts was 32%, significantly greater ($p = 0.005$)

**TABLE IV Incidence of Q Waves in Inferior Leads**

| Q-Wave Duration | Lead II | Lead aVF | Lead III |
|---|---|---|---|
| No Q | 4 | 2 | 1 |
| >0 but <30 ms | 7 | 1 | 8 |
| ≥30 but <40 ms | 17 | 9 | 8 |
| ≥40 ms | 3 | 19 | 14 |

| PATIENT | I Q ≥ 30 msec R/Q ≤ 1 | II Q ≥ 40 msec Q ≥ 30 msec | aVL Q ≥ 30 msec R/Q ≤ 1 | aVF Q ≥ 50 msec Q ≥ 40 msec Q ≥ 30 msec R/Q ≤ 1 R/Q ≤ 2 | $V_1$ Q R ≥ 50 msec R ≥ 40 msec R/S ≥ 1 | $V_2$ Q R ≤ 20 msec R ≥ 60 msec R ≥ 50 msec R/S ≥ 1.5 | $V_3$ Q R ≤ 30 msec | $V_4$ Q ≥ 20 msec R/Q ≤ 0.5 R/S ≤ 0.5 R/Q ≤ 1 R/S ≤ 1 | $V_5$ Q ≥ 30 msec R/Q ≤ 1 R/S ≤ 1 R/Q ≤ 2 R/S ≤ 2 | $V_6$ Q ≥ 30 msec R/Q ≤ 1 R/S ≤ 1 R/Q ≤ 3 R/S ≤ 3 | TOTAL POINTS | ACUTE MI | ANATOMIC SIZE OF MI AS % LV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I 1 | | ● | | ● ● | | | | | | | 5 | ● | 22 |
| I 2 | | ● | | ● ● | | | | ● | ● | ● | 8 | ● | 41 |
| I 3 | | ● | | ● ● | | | | | | | 4 | | 11 |
| I 4 | | | | ● | | | ● | | | | 3 | | 7 |
| I 5 | | ● | | ● ● | ● | ● ● | | | | ● ● | 11 | | 38 |
| I 6 | | | | ● | | | | ● | ● | | 3 | | 14 |
| I 7 | | ● | | ● | | ● | | | | | 4 | | 18 |
| I 8 | | ● | | ● | | ● | | ● | | | 5 | | 10 |
| I 9 | | ● | | ● ● | ● | | | ● | | | 8 | | 16 |
| I 10 | | ● | | ● ● | | | ● | ● | | ● | 10 | | 26 |
| I 11 | | ● | | ● | | ● | ● ● | ● | | ● | 6 | | 10 |
| I 12 | | | | ● | | ● | ● | | | | 3 | | 9 |
| I 13 | | ● | | ● ● | ● | ● | | | | | 8 | | 21 |
| I 14 | | ● | | ● ● | | | | | | | 4 | | 16 |
| I 15 | | ● | | ● ● | | | | | ● | ● | 7 | | 11 |
| I 16 | | ● | | ● | | | | ● | | | 3 | | 17 |
| I 17 | | ● | | ● ● | | | | | | | 5 | | 4 |
| I 18 | | ● | | ● ● | | | | | | | 5 | | 13 |
| I 19 | | ● | | ● ● | | | | | | | 4 | ● | 9 |
| I 20 | | ● | | ● ● | ● | ● ● | | | | | 10 | ● | 37 |
| I 21 | | | | ● | ● | | | | | | 3 | | 10 |
| I 22 | | ● | | ● ● | | | | | | | 6 | ● | 13 |
| I 23 | | | | ● | | | | | | | 1 | | 5 |
| I 24 | | ● | | ● ● | | | | | | ● | 8 | ● | 22 |
| I 25 | | ● | | ● | | ● ● | | | | ● | 5 | ● | 9 |
| I 26 | | | | ● | ● | ● | | | | | 4 | | 12 |
| I 27 | | | | | ● | | | | | | 1 | | 4 |
| I 28 | | | | ● ● | | | | | | | 4 | | 23 |
| I 29 | | | | | | | | | | | 0 | | 10 |
| I 30 | | | | | ● | | | | | | 1 | | 10 |
| I 31 | | | | ● | | | | | | | 1 | | 4 |
| PATIENT TOTAL | 0 0 | 3 17 | 0 0 | 6 13 9 14 2 | 5 1 1 1 | 0 4 0 5 3 | 1 4 | 4 0 0 0 3 | 1 0 0 0 2 | 5 0 0 1 3 | | | |

**FIGURE 2.** QRS point scores for each patient. Anatomically estimated infarct size is at the right of the figure. MI = myocardial infarct; LV = left ventricle.

than the mean infarct size of 5% in the 26 patients not receiving such points.

Eleven of the 31 hearts contained infarct in ≥1 level of octant 1 within the mid-septum, although only 8 electrocardiograms received points for Q waves or diminished R waves in leads $V_1$ to $V_3$. The amount of the middle third of octant 1 infarcted in the 8 patients receiving points for Q waves or diminished R waves in leads $V_1$ to $V_3$ (mean infarction of 0%) was not significantly greater than the mean amount infarcted for the 23 patients not receiving these points (mean infarction of 4%).

## Discussion

**Terminology of infarct location:** The inferior aspect of the left ventricle is the site of approximately 40% of all myocardial infarcts. This incidence is similar to that for anterior infarcts, but both the anatomic location and electrocardiographic changes for inferior infarcts are less well understood than for anterior infarcts. The term *inferior* or *diaphragmatic* is applied when the frontal plane leads II, III, and aVF are involved, and the term *true posterior* is applied when the right precordial leads are involved. However, it has not been clear pre-

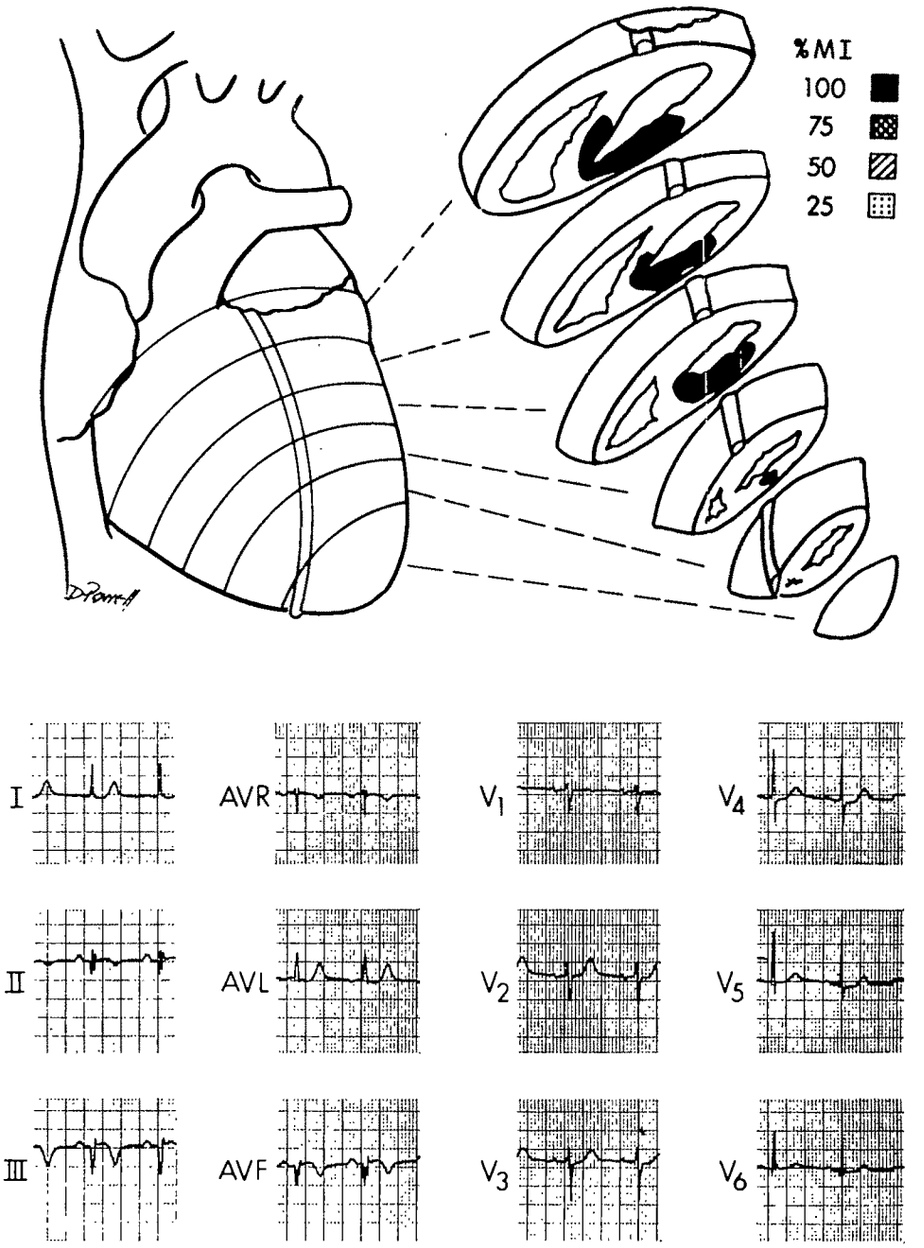



**FIGURE 3.** Myocardial infarct (MI) location and electrocardiogram for Patient 22. The infarct was acute, solid, and occupied 13% of the left ventricle. Six QRS points were awarded; Q ≥50 ms and R/Q ≥1 in lead aVF, and a Q ≥30 ms in lead II.

cisely which areas of the myocardium lie in the inferior versus the true posterior locations.

Originally, infarcts now called inferior were called posterior and those now called true posterior were called lateral. Barnes and Ball,[16] in a series of 1,000 consecutive necropsies, delineated 3 primary locations of infarcts: (1) infarcts in the anterior septum, adjacent free wall, and apex, ascribed to disease of the left anterior descending coronary artery, (2) infarcts in the posterior septum and adjacent free wall, usually due to right coronary artery disease, and (3) infarcts in the free wall opposite the septum resulting from disease in the circumflex coronary artery. A series of studies during the late 1940s by Myers[13,14,17-21] presented electrocardiographic criteria for the localization of myocardial infarcts based on pathological correlation. More recent studies have extended these qualitative observations by quantifying the pathologic and electrocardiographic aspects of myocardial infarcts.[22-26]

Sayen[27] showed that optimal evaluation of the relation between the electrocardiogram and anatomic extent of myocardial infarcts requires division of the left ventricle circumferentially into thirds that correspond roughly to the vascular beds of the 3 major coronary arteries. These locations are termed *anterior*, *inferior*, and *posterolateral*, respectively, in this report. In a previous study from Duke, only anterior and posterior locations were considered and, because of the small number of patients, no attempt was made to distinguish inferior from posterolateral.[3] Acquisition of additional patients from other medical centers permitted separation of the general group with posterior infarcts into those with primarily inferior location included in this study and primarily posterolateral location included in a subsequent study. The pathologists working with the Myocardial Infarction Research Units and the Specialized Centers of Research in Ischemic Heart Disease adopted a common protocol for evaluation of the hearts of patients with coronary disease.[28] The hearts had been carefully evaluated and preserved and were thus available for inclusion in this collaborative project.

A QRS scoring system has been proposed by Selvester et al[7-9] from computer simulation of human heart activation. This has been described extensively elsewhere. A previous study documented both the specificity of the QRS scoring system in normal control subjects and the intra- and interobserver variability of performing the scoring on a standard 12-lead electrocardiogram.[1]

Through collaboration, the anatomical extent of a large number of single infarcts in the distributions of each of the major coronary arteries was correlated with the changes in the QRS complex which had been proposed for infarct sizing by Selvester et al. Patients with infarcts primarily in the anterior third of the left ventricle have been the subject of a previous study.[2] This study considers those 31 patients with infarction primarily involving the inferior third of the left ventricle as indicated in Figure 1.

**Quantitative anatomy of inferior infarcts:** This study confirms quantitatively the location of these infarcts previously reported by Barnes[16,29,30] and by Sayen et al.[27] All of the infarcts involve the basal third of octant 7 in the inferior free wall, and all but 1 include the middle third of this octant (Table III). These are the 2 regions least commonly involved by infarcts predominating in the anterior third of the left ventricle.[2]

The transmural extent of inferior infarcts varies. Large infarcts tend to be transmural while small infarcts tend to involve primarily the subendocardial region. As noted previously,[3] some infarcts that are only subendocardial at the base become transmural in the middle third and intramural or subepicardial near the apex. They become intramural or subepicardial because the distal portion of the anterior descending branch of the left coronary artery supplies the more endocardial aspects of the inferior apex. The posterior descending artery supplies the more superficial aspects.[31] Though it is often assumed clinically that inferior or diaphragmatic infarcts are primarily apical, the opposite is true. Inferior infarcts involve more of the base and middle of the left ventricle than of the apex (Fig. 3). Large infarcts form a wedge pointing toward the apex, with their widest portion at the base of the left ventricle (Table III). Inferior infarcts do not involve the apex circumferentially as do anterior infarcts.[2] Many of the infarcts extend more into the lateral wall than into the septum at the base. They rarely involve more than the posterior one-third of the interventricular septum because of the much longer septal perforating vessels from the anterior descending branch of the left coronary artery.[31]

**QRS identification of inferior infarcts:** Askenazi et al[32] and Starr et al[33] determined that Q waves in lead aVF alone were as sensitive as Q waves in leads II, III, and aVF together. The present study further determines that a 30 ms Q wave rather than a 40 ms Q wave in lead aVF is a sensitive indicator of infarction in the inferior third of the left ventricle. A 30 ms Q wave is present in aVF in 90% of the patients, including all of those with transmural infarcts and 9 of the 12 with nontransmural involvement. Only 19 of the 31 patients (65%) had at least a 40 ms Q wave in lead aVF. The specificity of a 30 ms Q wave in lead aVF has been de-

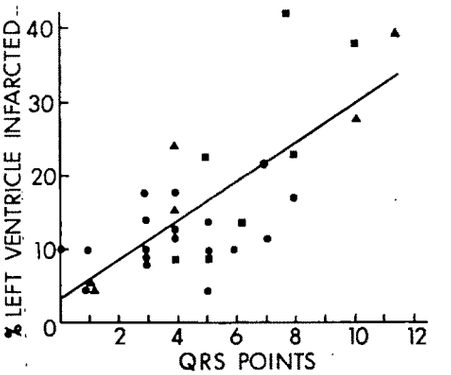



**FIGURE 4.** Comparison of the point score for electrocardiogram sizing of infarcts predominating in the inferior third of the left ventricle with the percent infarction of the left ventricle. Those infarcts <7 days old at the time of the patient's death are shown by **squares**, those 7 to 30 days old by **triangles**, and those >30 days old by **circles**. The regression line is shown (% infarct − 2.5 × points + 2.9; r = 0.74; standard error of the estimate = 6.6).

termined for normal individuals and for patients with anterior infarcts.[1,2,34] A study from this series found only a 2.6% prevalence of a 30 ms Q wave in aVF in 349 normal subjects.[1] None of the 21 patients with single infarcts located predominantly in the anterior third of the left ventricle had a 30 ms Q wave in lead aVF.[2] Therefore, a 30 ms Q wave in lead aVF provides a better criterion for identification of inferior myocardial infarcts since it achieves a sensitivity in this study of 90% and has a previously proven specificity of 97%.

The 90% sensitivity of a 30 ms Q wave in lead aVF can be reconciled with other reports that many infarcts are not associated with Q waves[35,36] by considering the design of the present study. Patients were excluded if >1 infarct was present at autopsy or if criteria for left or right ventricular hypertrophy, left or right bundle branch block, or left anterior or posterior fascicular block were present on the electrocardiogram. The electrocardiogram may be less sensitive and specific if these confounding factors are present.

**Correlation of QRS points and infarct location:** The computer simulation developed by Selvester et al[9] indicated the following. An increase in R-wave size in the right precordial leads should indicate involvement extending more laterally into the posterior free wall of the left ventricle. QRS changes in the left precordial leads should indicate involvement of the posterior and lateral aspects of the apex. Loss of R waves or the development of Q waves in the right precordial leads should indicate involvement in the middle aspect of the interventricular septum.

More than half of the patients in this study had infarcts which extended posterolaterally into ≥1 level of octant 5 (Table III). This involvement was somewhat underestimated by the point score as only 5 of the patients received points for increased R waves in the right precordial leads. However, the mean amount of infarct in octant 5 in these 5 patients (32%) was significantly greater than the mean amount infarcted in the remaining 26 patients (5%).

The posterolateral aspect of the left ventricle lies between the insertions of the anterior and posterior fascicles of the left bundle and therefore would be activated later than other aspects of the left ventricle.[37] Though R- and S-wave dimensions are not usually considered for diagnosis of myocardial infarcts, additional scoring criteria based upon them may be important for determining infarct size in this area of the left ventricle.

The average amount of apical involvement in patients with QRS points from the left precordial leads was greater than for patients without such QRS changes. However, the electrocardiograms of some patients with substantial apical involvement did not receive points from leads $V_4$ to $V_6$. Thus, the relation between the amount of apical involvement and the QRS score from leads $V_4$ to $V_6$ is not as close for inferior infarcts as for anterior infarcts.[2] The anterior infarcts usually have much greater involvement of even the inferior aspect of the apex and these anterior infarcts tend to involve the subendocardium which activates earlier than the subepicardium.[37] Therefore, that part of the apex supplied by the posterior descending coronary artery might, if infarcted, cause changes later in the QRS complex. As with posterior free wall involvement, extension into the inferior apex might be better described by criteria considering those later aspects of the QRS complex which are not evaluated in this study.

The QRS scoring system did not correlate well with more anterior involvement of the interventricular septum. The 2 patients with the largest amount of septal involvement did not have Q waves in lead $V_1$ or $V_2$. However, both infarcts also involved the posterior free wall opposite the septum (octant 5). As suggested by Myers et al,[18] the loss of electrical activity in the septum might be cancelled by loss of electrical activity in the opposite wall.

The 8 patients who received points for Q waves or diminished R waves in the right precordial leads did not have involvement of the septum which extended more anteriorly than was typical for patients with inferior infarcts. One possible explanation for loss of R waves in the right precordial leads is right ventricular involvement. The right ventricles had previously been removed from some of the hearts in this study. A second series of hearts is now being acquired with right ventricles still attached to permit evaluation of the correlation between the loss of R waves in the right precordial leads and the extent of both anterior septal and right ventricular infarction.

**Conclusions:** The simplified version of the QRS point score developed by Selvester et al[7–9] correlates significantly (r = 0.74) with the size of infarcts predominating in the inferior one-third of the left ventricle. Each point represents infarction of 2.5% of the left ventricle. Correlation between the electrocardiogram and the anatomic size is similar, regardless of the age of the infarct, that is, fibrotic, organizing, and acute. Most (90%) of these infarcts can be identified by ≥30 ms Q wave in lead aVF. The relatively large standard error of the estimate should be considered when the point score is used for an individual patient; the 95% confidence limits are ±13% of the left ventricle. While the QRS score has been shown to correlate (r = 0.80) with left ventricular ejection fraction in 12 patients with combined anterior and inferior infarcts,[38] further anatomic studies are needed to determine the limitations of the scoring system when applied to patients with >1 infarct or with a complex electrocardiogram exhibiting ventricular hypertrophy or intraventricular conduction delay.

## References

1. **Wagner GS, Freye CJ, Palmeri S, Roark SF, Stark N, Ideker RE, Harrell FE, Selvester RH.** Evaluation of a QRS scoring system for estimating myocardial infarct size. I. Specificity and observer agreement. Circulation 1982;65:342–347.
2. **Ideker RE, Wagner GS, Ruth WK, Alonso DR, Bishop SP, Bloor CM, Fallon JT, Gottlieb GJ, Hackel DB, Phillips HR, Reimer KA, Roark SF, Rogers WJ, Savage RM, White RD, Selvester RH.** Evaluation of a QRS scoring system for estimating myocardial infarct size. II. Correlation with quantitative anatomic findings for anterior infarts. Am J Cardiol 1982;49:1604–1614.
3. **Savage RM, Wagner GS, Ideker RE, Podolsky SA, Hackel DB.** Correlation of postmortem findings with electrocardiographic changes in patients with myocardial infarction. Circulation 1977;55:279–285.
4. **IBM Health Care Support.** Electrocardiogram (ECG) Analysis Program, Version 2. Physician's Guide GH20-1935-0. White Plains, NY: IBM, 1976.

5. **Ideker RE, Behar VS, Wagner GS, Starr JW, Starmer CF, Lee KL, Hackel DB.** Evaluation of asynergy as an indicator of myocardial fibrosis. Circulation 1978;57:715–725.
6. **Hutchins GM, Bulkley BH.** Infarct expansion versus extension: two different complications of acute myocardial infarction. Am J Cardiol 1978;41: 1127–1132.
7. **Selvester RH, Wagner JO, Rubin HB.** Quantitation of myocardial infarct size and location by electrocardiogram and vectorcardiogram. In: Snellin HA, ed. Boerhave Course in Quantitation in Cardiology. The Netherlands: Leyden University Press, 1972:31–44.
8. **Selvester RH.** Criteria for atrial enlargement and infarct size (applicable to computer diagnostic programs). In: Hooper J, ed. Conference Proceedings Computerized Interpretation of the Electrocardiogram. Hyattsville, MD: US Department of Health, Education, and Welfare, 1975:81–100.
9. **Selvester RH, Solomon J, Sapoznikow D.** Computer simulation of the electrocardiogram In: Cady D, ed. Computer Techniques in Cardiology. New York: Marcel Dekker, 1979:417–453.
10. **Levy L II, Jacobs HJ, Chastant HP, Strauss HB.** Prominent R wave and shallow S wave in lead $V_1$ as a result of lateral myocardial infarction. Am Heart J 1950;40:447–452.
11. **Perloff JK.** The recognition of strictly posterior myocardial infarction by conventional scalar electrocardiography. Circulation 1964;30:706–718.
12. **Tullock JA.** The electrocardiographic features of high posterolateral myocardial infarction. Br Heart J 1952;14:379–386.
13. **Myers GB, Klein HA, Stofer BE.** I. Correlation of electrocardiographic and pathologic findings in anteroseptal infarction. Am Heart J 1948;36:535–575.
14. **Myers GB, Klein HA, Stofer BE.** VII. Correlation of electrocardiographic and pathologic findings in lateral infarction. Am Heart J 1949;37:374–417.
15. **Dunn WJ, Edwards JE, Pruitt RD.** The electrocardiogram in infarction of the lateral wall of the left ventricle: a clinicopathologic study. Circulation 1956;14:540–555.
16. **Barnes AR, Ball RG.** The incidence and situation of myocardial infarction in one thousand consecutive post mortem examinations. Am J Med Sci 1932;183:215–225.
17. **Myers GB, Klein HA, Hiratzka T.** II. Correlation of electrocardiographic and pathologic findings in large anterolateral infarcts. Am Heart J 1948;36: 838–881.
18. **Myers GB, Klein HA, Hiratzka T.** III. Correlation of electrocardiographic and pathologic findings in anteroposterior infarction. Am Heart J 1949; 37:205–236.
19. **Myers GB, Klein HA, Hiratzka T.** IV. Correlation of electrocardiographic and pathologic findings in infarction of the interventricular septum and right ventricle. Am Heart J 1949;37:720–770.
20. **Myers GB, Klein HA, Hiratzka T.** V. Correlation of electrocardiographic and pathologic findings in posterior infarction. Am Heart J 1949;38:547–592.
21. **Myers GB, Klein HA, Hiratzka T.** VI. Correlation of electrocardiographic and pathologic findings in posterolateral infarction. Am Heart J 1949;38: 837–862.
22. **Haveida CJ, Sohi GS, Flowers NC, Horan LG.** The pathologic correlates of the electrocardiogram: complete left bundle branch block. Circulation 1982;65:445–451.
23. **Rautaharju PM, Warren JW, Jain V, Wolf HK, Nielsen CL.** Cardiac infarction injury score: an electrocardiographic coding scheme for ischemic heart disease. Circulation 1981;64:249–256.
24. **Pipberger HV, McCaughan D, Littmann D, Pipberger HA, Cornfield J, Dunn RA, Batchlor CD, Berson AS.** Clinical application of a second generation electrocardiographic computer program. Am J Cardiol 1975;35:597–608.
25. **Cabin HS, Roberts WC.** Comparison of amount and extent of coronary narrowing by atherosclerotic plaque and of myocardial scarring at necropsy in anterior and posterior healed transmural myocardial infarction. Circulation 1982;66:93–99.
26. **Cowan MJ, Reichenbach DD, Bruce RA, Fisher L.** Estimation of myocardial infarct size by digital computer analysis of the VCG. J Electrocardiol 1982;15:307–316.
27. **Sayen JJ, Sheldon WF, Wolferth CC.** The heart muscle and the electrocardiogram in coronary disease. III. A new classification of ventricular myocardial damage derived from the clinicopathologic findings in 100 patients. Circulation 1955;12:321–337, 530–542.
28. **Walston A, Hackel DB, Estes EH.** Acute coronary occlusion and the "power failure" syndrome. Am Heart J 1970;79:613–619.
29. **Barnes AR.** Correlation of initial deflections of ventricular complex with situation of acute myocardial infarction. Am Heart J 1934;9:728–741.
30. **Barnes AR.** Electrocardiogram in myocardial infarction. Review of one hundred and seven clinical cases and one hundred and eight cases proved at necropsy. Arch Intern Med 1935;55:457–483.
31. **James TN.** Anatomy of the Coronary Arteries. Hagerstown, MD: Harper & Row, 1961:68–69.
32. **Askenazi J, Meroko PR, Lesch M, Braunwald E.** Usefulness of ST segment elevations as predictors of electrocardiographic signs of necrosis in patients with acute myocardial infarction. Br Heart J 1977;39:764–770.
33. **Starr JW, Wagner GS, Behar VS, Walston A III, Greenfield JC Jr.** Vectorcardiographic criteria for the diagnosis of inferior myocardial infarction. Circulation 1974;49:829–836.
34. **Hiss RG, Lamb LE, Allen MF.** Electrocardiographic findings in 67,375 asymptomatic subjects. X. Normal values. Am J Cardiol 1960;6:200–231.
35. **Woods JD, Laurie W, Smith WG.** The reliability of the electrocardiogram in myocardial infarction. Lancet 1963;2:265–269.
36. **Shettigar UR, Hultgren HN, Pfeifer JF, Lipton MJ.** Diagnostic value of Q-waves in inferior myocardial infarction. Am Heart J 1974;88:170–175.
37. **Durrer D, van Dam RTh, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC.** Total excitation of the isolated human heart. Circulation 1970;41:899–912.
38. **Palmeri ST, Harrison DG, Cobb FR, Morris KG, Harrell FE, Ideker RE, Selvester RH, Wagner GS.** A QRS scoring system for assessing left ventricular function after myocardial infarction. N Engl J Med 1982;306:4–9.

# Segmental Right Ventricular Function After Acute Myocardial Infarction: Two-Dimensional Echocardiographic Study in 63 Patients

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**Right ventricular (RV) segmental contraction was studied in 63 patients with acute myocardial infarction (MI), using 2-dimensional (2-D) echocardiography. Group A included 32 patients with ischemic RV dysfunction: 19 had a disproportionate increase in right atrial pressure at the time of the examination (Group AI) and in 13 patients, right atrial pressure was normal when the echocardiogram was obtained (Group AII). Group B included 31 patients without ischemic RV dysfunction. Akinesia or dyskinesia of the RV wall was found in 30 patients: 19 from Group AI, 8 from Group AII, and 3 from Group B. Asynergy could be identified in all segments of the RV wall including the outflow tract, RV apex, and anterior wall, but was more frequently found in the posterior wall (29 patients), best seen in the transversal subcostal short-axis view. A significant difference was found either in the frequency of wall motion abnormalities or in the number of segments with asynergy among the 3 groups ($p < 0.001$). However, asynergy of the RV wall may be present in some patients with normal right heart hemodynamic function, suggesting that asynergy may be more sensitive than hemodynamic function in the diagnosis of acute RV infarction. Paradoxical septal motion was found in 8 patients, all in Group AI, and all had a right atrial pressure equal to or greater than pulmonary capillary pressure.**

A strong correlation between segmental left ventricular contraction abnormalities and myocardial ischemia or infarction has been demonstrated by several techniques including cineangiography,[1] radioisotopic ventriculography,[2] and 2-D echocardiography.[3,4] For this reason, regional abnormalities of left ventricular wall motion have become a hallmark of both acute and chronic coronary artery disease. Although ischemic RV involvement and primary RV dysfunction are common findings in patients with acute MI, little attention has been paid to the study of regional RV contraction. Asynergy of the RV free wall has been demonstrated in patients with acute MI using radionuclide[2,5–7] or angiographic techniques,[7] but very few studies with 2-D echocardiography have been reported.[8,9] However, the identification of such abnormalities may constitute an important clue in the diagnosis of RV MI.

This report describes a prospective study of regional RV performance in acute transmural MI using 2-D echocardiography. The goals of the study were (1) to identify the abnormalities in segmental RV function after acute MI, and (2) to compare both hemodynamic and 2-D echocardiographic criteria of ischemic RV involvement.

## Methods

**Patients:** We studied 70 patients admitted to the coronary care unit with the diagnosis of acute transmural MI according to recognized clinical, electrocardiographic, and laboratory data. Location of the MI was defined as "posterior" by the presence of abnormal Q waves (>0.04 second) in leads $D_2$, $D_3$,

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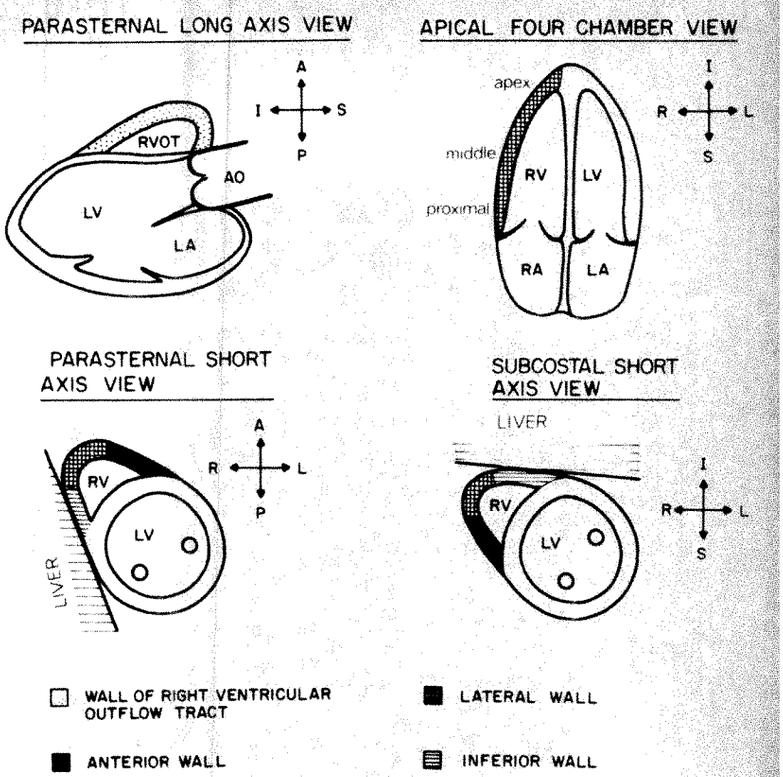



**FIGURE 1.** Schematic representation of the different echocardiographic views studied. A = anterior; AO = aorta; I = inferior; L = left; LA = left atrium; LV = left ventricle; P = posterior; R = right; RA = right atrium; RV = right ventricle; RVOT = right ventricular outflow tract; S = superior.

and aVF. "Anterior" MI was defined by the presence of abnormal Q waves in 2 or more adjacent precordial leads ($V_1$-$V_6$).

The study was initially begun including only those patients with acute posterior MI in whom hemodynamic monitoring had been performed. However, because 2 patients with acute anterior MI were found to have hemodynamic criteria of ischemic RV dysfunction, a group of 5 additional unselected patients with acute anterior MI were included.

Patients with acute MI without hemodynamic monitoring were not included. Patients with previously known MI, chronic congestive failure, pericardial disease, valvular heart disease, or chronic obstructive lung disease were not included. Of the initial 70 patients, 7 were excluded because of failure to obtain satisfactory 2-D echocardiograms of the right ventricle in at least 1 transversal plane (parasternal or subcostal short-axis views). Thus, a total of 63 patients (52 men, and 11 women, aged 36 to 78 years) were included.

**Hemodynamic monitoring:** Hemodynamic monitoring was performed in all patients. Right atrial, pulmonary artery, and pulmonary capillary wedge pressures were recorded in millimeters of mercury with a Hewlett-Packard 1280 transducer on a Siemens Elema Mingograph 34 through a Swan-Ganz thermodilution catheter.

Hemodynamic determinations were made at least every 8 hours. Monitoring was begun at admission and maintained for 3 to 5 days, being discontinued when the condition of the patient was considered as stable (subset I or II according to Forrester[10]) and had no hemodynamic variations for at least 24 hours.

**Criteria of RV dysfunction:** The diagnosis of ischemic RV dysfunction was made when the relation between right atrial and pulmonary capillary pressure was indicative of primary RV dysfunction, according to the results of a previous study.[11] Although this relation varies according to the level of pulmonary capillary pressure, for practical purposes right atrial mean pressure must be >10 mm Hg and either greater than, equal to, or not more than 5 mm Hg less than pulmonary capillary pressure. This criterion was found sensitive (73%) and very specific (100%) for the diagnosis of acute RV MI.[11] In patients with a right atrial pressure <10 mm Hg in the absence of pulmonary congestion, a volume loading test with dextran 40 was performed to identify ischemic RV dysfunction not present in basal conditions.[11,12]

**Echocardiographic examination:** Real-time 2-D echocardiographic examination was performed with the patient in the supine position or 30° to 60° left lateral decubitus using a wide angle (90°) mechanical sector scanner (Mark III, Advanced Technology Laboratory) and a 3 MHz transducer. Echocardiograms were obtained 3 to 12 hours after the last hemodynamic determination. In this period of time, the clinical condition of the patients included in the study was considered stable, without episodes of pain, dyspnea, arrhythmias, or variations in blood pressure.

Visualization of the ventricles and the ventricular septum in the long-axis, 4-chamber, and short-axis planes was obtained from parasternal, apical, and subcostal positions. Transverse planes were obtained from both parasternal and subcostal positions. All echocardiographic recordings were obtained in normal (90°) and amplified (45°) dimensions, and stored on a Sanyo VJC 7100 tape recording system. Individual frames selected for the figures were photographed using a Polaroid® film from the videotape. There was significant degradation of the stop frame image because only 1 of the 2 fields could be visualized.

A simultaneous electrocardiogram was recorded. The initiation of the QRS complex was used as an end-diastolic marker, and the end of systole was assumed to correspond to the end of the T wave. Imaging of the endocardial outline was obtained by playing through preceding and succeeding beats, using both real-time and slow motion playback.

Only RV free wall and ventricular septal motion were considered. The RV wall was divided into several segments (Fig. 1), and each was analyzed for wall motion abnormalities. Wall motion was qualitatively classified as *normal* (inward motion of the endocardium during systole) (Fig. 2), *akinetic* (absence of motion) (Fig. 3), or *dyskinetic* (outward motion of the endocardium during systole) (Fig. 4 and 5). Ventricular septal motion was considered as normal when the septum was displaced toward the left ventricular cavity in systole, akinetic when no septal movement could be appreciated, and dyskinetic or paradoxical when both sides of the septum were displaced toward the RV cavity during systole (Fig. 4 and 5).

All echocardiograms were interpreted independently by 2 observers, without previous knowledge of the hemodynamic data of each patient. In case of discrepancy, the studies were reviewed and an agreement was reached.

**Groups:** The patients were classified into 2 groups: *Group A* included 32 patients with definite ischemic RV dysfunction in at least 1 hemodynamic determination during the monitoring period. Nineteen of the 32 patients had a relation between right atrial and pulmonary capillary pressures indicative of ischemic RV dysfunction at the time of the echocardiographic examination (Group AI); The 13 remaining patients had transient ischemic RV dysfunction with a normal pressure relation at the time of the echocardiographic study (Group AII). Twenty-two patients had electrocardiographic evidence of posterior MI, 2 of anterior MI, and 8 of posterior plus anterior MI. *Group B* included 31 patients without hemodynamic criteria of ischemic RV dysfunction during the entire period of hemodynamic monitoring. Acute MI was posterior in 20 patients, anterior in 5, and posterior plus anterior in 6.

**Statistical analysis:** All statistical analyses were performed using nonparametric tests: chi-square test and Fisher's exact test. Significant values were considered those corresponding to $p < 0.05$. Only hemodynamic data corresponding to the last hemodynamic determination before the echocardiographic examination were considered for statistical analysis.

## Results

**Hemodynamic findings:** By definition, only Group A patients had a right atrial-pulmonary capillary pressure relation indicative of ischemic RV dysfunction. In all patients from Group AI, ischemic RV dysfunction was spontaneous, whereas in 5 patients from Group B it was observed only after volume loading.

**Two-D echocardiographic findings: Right ventricular segmental wall motion:** The number of patients with asynergy and the number of segments with abnormal wall motion found in each group in the different echocardiographic views are shown in Table I.

*Transverse plane:* Regional abnormalities in segmental wall motion were observed in 29 patients: 19 in Group AI, 7 in Group AII, and 3 in Group B. (Fig. 3 and 4).

When subcostal and parasternal views were compared, no difference was found in either the number of patients with wall motion abnormalities, the number of segments with asynergy, or the type of asynergy, between both short-axis views obtained. However, 2 patients had akinesia of the inferior RV wall in the subcostal short-axis view although the movement of these segments was considered normal in the parasternal short-axis view. Good quality images of the subcostal transversal plane were obtained in 62 patients; adequate imaging of the parasternal transversal plane could only be obtained in 42 patients.

In the longitudinal parasternal view, dyskinesia of the RV outflow tract was observed in 1 patient (Group AI). In the remaining 50 patients in whom good quality echocardiographic images were obtained, contraction of the RV outflow tract was normal.

In the *apical 4-chamber view*, asynergy of the lateral RV wall occurred in 9 patients (Fig. 5), 8 of whom were in Group AI. In the other patient, included in Group AII, akinesia of the RV apex was the only abnormality.

**Ventricular septal motion:** In Group A, septal motion was normal in 18 patients (56%), akinetic in 5 (16%), and dyskinetic in 9 (28%). Paradoxical motion of the ventricular septum was always accompanied by some alteration in the movement of the RV posterior wall ($p < 0.001$) (Fig. 4). In group B, septal motion was normal in 24 patients (77%), and akinetic in the remaining 7 (23%).

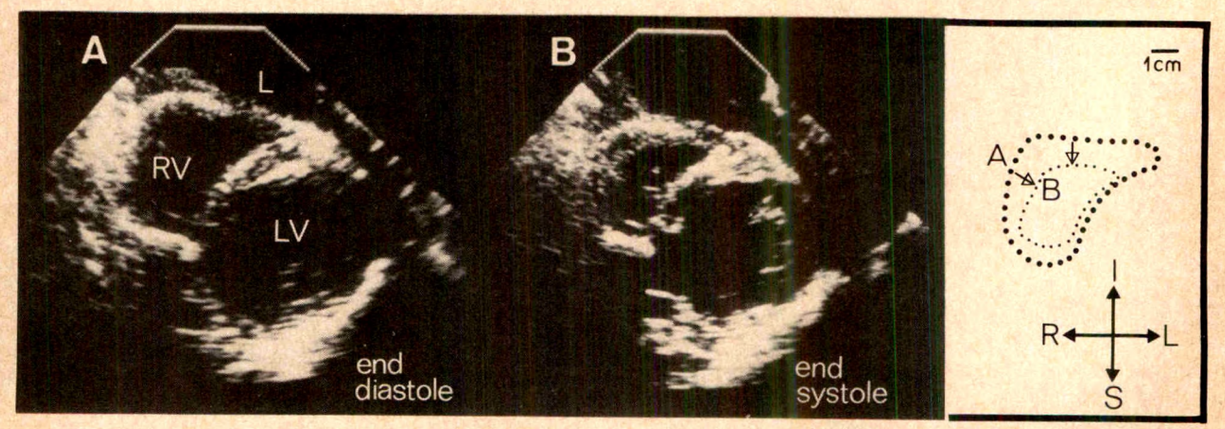



**FIGURE 2.** Subcostal short-axis view of both ventricles. Normal motion of the RV wall and interventricular septum. L = liver or lateral; other abbreviations as in Figure 1.

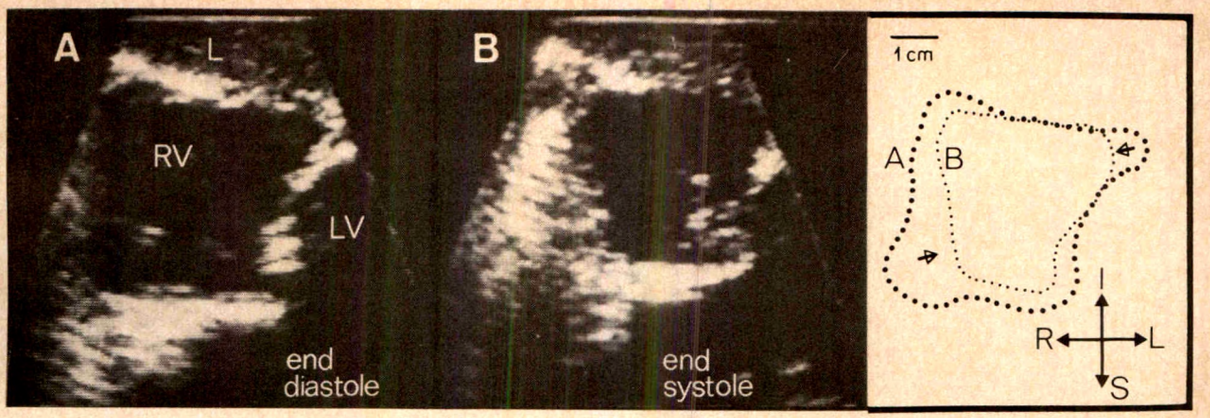



**FIGURE 3.** Subcostal short-axis view: akinesia of the inferior RV wall. Abbreviations as before.

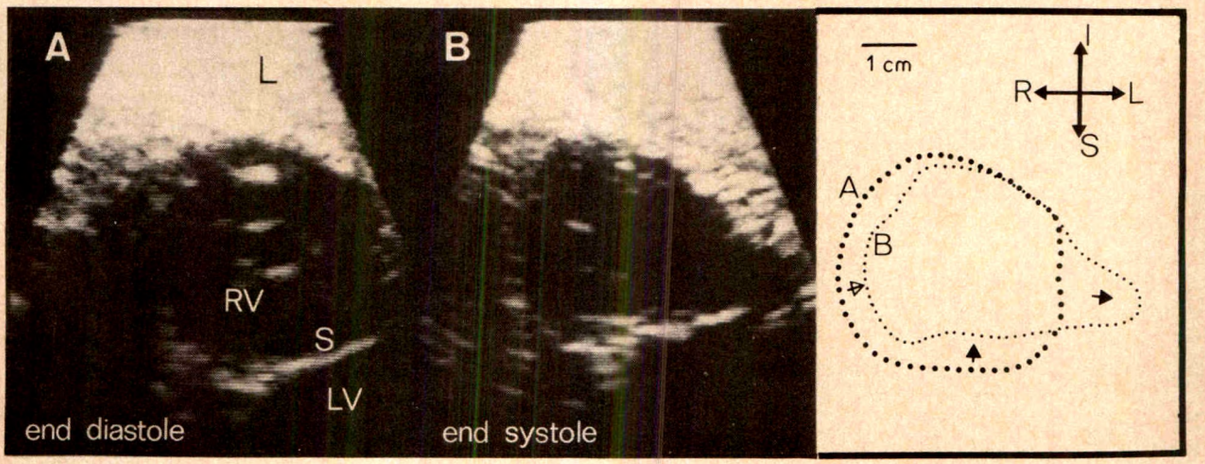



**FIGURE 4.** Subcostal short-axis view: dyskinesia of the inferior RV wall adjacent to the interventricular septum. Paradoxical septal motion. **Open arrows,** normal contraction. **Solid arrows,** dyskinesia. S = interventricular septum or superior; other abbreviations as before.

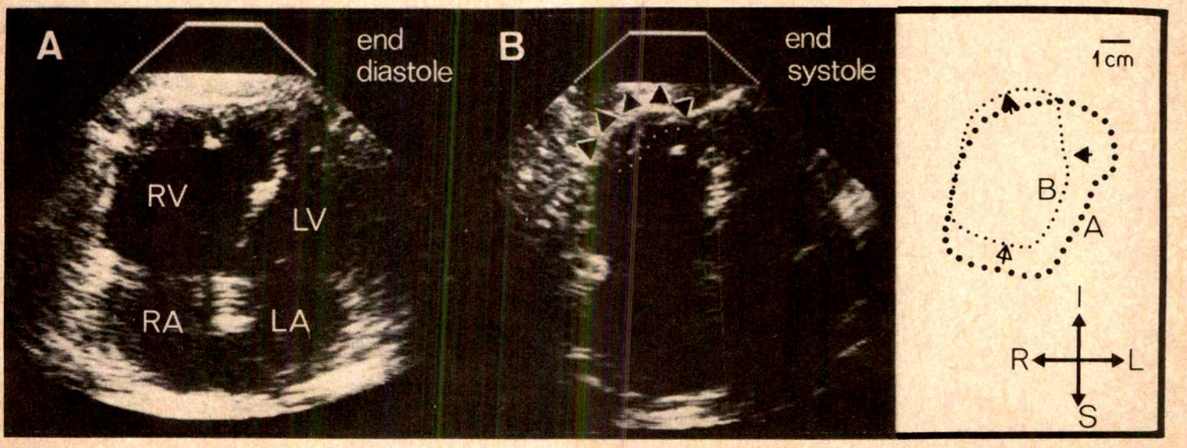



**FIGURE 5.** Apical 4-chamber view: dyskinesia of the RV apex. Paradoxical septal motion. A thrombus can be identified in the RV apex. Abbreviations as before.

**TABLE I Frequency of Asynergy in the Different Groups: RV Wall Motion**

| | All 2-D Echocardiographic Views | | Number of Segments With Asynergy | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Transverse View | | | | Four-Chamber View | | | | Long-Axis View | |
| Patients | Normal | Asynergy | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 | 0 | 1 |
| | | | | | | Group AI | | | | | | |
| N | 0 | 19 | 0 | 7 | 8 | 4 | 7 | 5 | 3 | 0 | 15 | 1 |
| % | ... | 100 | ... | 37 | 42 | 21 | 47 | 33 | 20 | ... | 94 | 6 |
| | | | | | | Group AII | | | | | | |
| N | 5 | 8 | 6 | 7 | 0 | 0 | 11 | 1 | 0 | 0 | 13 | 0 |
| % | 38.5 | 61.5 | 46 | 54 | ... | ... | 91.7 | 8.3 | ... | ... | 100 | ... |
| | | | | | | Group B | | | | | | |
| N | 28 | 3 | 28 | 2 | 1 | 0 | 28 | 0 | 0 | 0 | 22 | 0 |
| % | 90 | 10 | 90 | 6 | 3 | ... | 100 | ... | ... | ... | 100 | ... |
| | $p < 0.001$ | | | $p < 0.001$ | | | | $p < 0.001$ | | | | |

**Correlation between hemodynamics and 2-D echocardiographic findings:** *Right ventricular wall:* A significant relation was found between hemodynamic data of ischemic RV dysfunction and alterations in segmental RV wall motion. A highly significant difference was found either in the frequency of wall motion abnormalities or the number of segments with asynergy among the 3 groups of patients ($p < 0.001$) (Table I). Furthermore, a highly significant difference was also found between the incidence and number of segments with abnormal wall motion and the presence of a right atrial pressure equal to or greater than the pulmonary capillary pressure ($p < 0.001$) (Table II), indicating that the severity of asynergy is related to the severity of ischemic RV dysfunction.

*Ventricular septum:* A significant relation was found between the presence of dyskinetic or paradoxical septal motion and the hemodynamic data indicative of ischemic RV dysfunction ($p < 0.001$). All 9 patients with paradoxical septal motion were included in Group AI and all had a right atrial pressure equal to or higher than pulmonary capillary pressure. However, 2 patients without paradoxical septal motion also had a right atrial pressure equal to or greater than pulmonary capillary pressure when the echocardiographic examination was performed.

**TABLE II Frequency of Asynergy in Relation to Hemodynamic Data**

| | Number of Segments With Asynergy | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| RAP <PCP | | | |
| Number of patients | 0 | 2 | 9 |
| Percent | ... | 3 | 14 |
| RAP ≥PCP | | | |
| Number of patients | 33 | 14 | 5 |
| Percent | 52 | 22 | 8 |
| | | $p < 0.001$ | |

PCP = pulmonary capillary pressure; RAP = right atrial pressure.

## Discussion

**Segmental RV contraction in acute MI:** Asynergy of the RV wall has been reported in patients with RV MI.[2,5–9] Our results demonstrate that abnormalities in segmental RV wall motion are common in patients with acute MI and can easily be appreciated by 2-D echocardiography. The actual frequency of such abnormalities cannot be accurately defined from this study because not all patients with acute MI admitted to the coronary care unit were included.

Although acute RV infarction is generally associated with posterior left ventricular infarction,[11,13] a small number of patients with anterior MI also had RV asynergy, correlating well with hemodynamic alterations consistent with ischemic RV dysfunction.

Asynergy may be identified in all segments of the RV wall, including the outflow tract, ventricular apex, and the anterior wall, but is, in general, specifically located in the posterior RV wall. Asynergy of other regions without posterior wall involvement is rare, and in this study was found in only 1 patient. Moreover, anatomicopathologic studies indicate that in most cases, RV infarctions are confined to the posterior RV wall[11,13] which can be identified only in the transversal plane. The transversal plane is the most useful echocardiographic view for the identification of such abnormalities.

The greater frequency of wall motion abnormalities in the long-axis and 4-chamber planes reported in previous studies[8,9] can be attributed to a more rigid criteria of patient selection, inclusion being restricted to patients with strong clinical evidence of RV infarction.

**Segmental RV contraction and RV infarction:** Recent echocardiographic and anatomic studies[3,4] demonstrated that necrotic segments of the left ventricle almost always present motion abnormalities, but the latter far less frequently imply MI, and a number of nonnecrotic myocardial segments show segmental wall motion abnormalities. In the absence of transmural

MI, asynergy has been attributed to local ischemia,[3,4] small inlands of infarcted tissue,[4] and myocardial dysfunction due to mechanical tethering in zones adjacent to the MI.[14]

These findings indicate that wall motion abnormalities found in 2-D echocardiography are very sensitive but not very specific for MI. On the basis of these previous studies performed on the left ventricle, one can hypothesize that regional abnormalities of RV contraction may be sensitive for the detection of RV infarction, but may be present in patients with right RV ischemia without MI.

**Correlation between hemodynamics and wall motion abnormalities:** We found a strong relation between the hemodynamic alterations indicative of ischemic RV dysfunction and the presence and extent of abnormalities in regional wall motion demonstrated by 2-D echocardiography. All Group AI patients had some contraction abnormalities; those patients with the most severe ischemic RV dysfunction (right atrial pressure equal to or higher than pulmonary capillary pressure) presented a higher number of RV wall segments with abnormal motion (Table II). The same results have been found in 2 previous studies. Yung-Dae et al[8] presented 13 patients with severe RV dysfunction and wall motion abnormalities; 10 patients reported by D'Arcy et al[9] with clinical or anatomic evidence of RV infarction had RV asynergy.

Nevertheless, the hemodynamic criteria of right ventricular dysfunction followed in this study were less rigid, and considering the aforementioned hemodynamic changes as sensitive and specific for right ventricular infarction, there are certain discrepancies between hemodynamic and wall motion abnormalities that deserve further comment.

*Abnormal wall motion and transient ischemic RV dysfunction:* In an important number of patients (8 of the 13 from Group AII), abnormalities in RV wall motion were still present after normalization of the hemodynamic variables of ischemic RV dysfunction. The same results were found by Yung-Dae et al[8] in 5 patients with clinical data of RV infarction. This finding may be of interest when considering ischemic right ventricular involvement in subacute or chronic heart disease.[15] However, further studies are needed to evaluate the long-term evolution of RV wall dynamics after acute myocardial infarction.

*Normal wall motion and transient ischemic RV dysfunction:* From another point of view, some patients with transient RV dysfunction (5 of 13 patients from Group AII) had normal RV wall motion. When one considers that the hemodynamic alterations, even if transient, are highly specific of RV infarction,[11] this finding may be explained by several mechanisms: (1) Although asynergy usually persists for several days or weeks after acute MI,[2,16] some wall motion abnormalities can be transient, even in the presence of transmural MI,[2] if some islands of normal tissue are preserved, and may be manifested only under stress conditions such as exercise.[15] (2) Hypokinesia has not been evaluated in this study, and although it is less specific for MI than akinesia or dyskinesia,[3] it cannot be completely forgotten. Also, small abnormalities in ventricular motion can only be identified studying the complete cardiac cycle.[17] Further methodologic refinement and the application of computer-aided techniques would allow a more precise evaluation and quantification of regional wall motion and endocardial thickening, the latter being a sensitive and specific variable of ventricular function in acute MI.[4] (3) Small defects can be occult to the echocardiographic examination if several transverse planes are not obtained.[3] (4) There is always the possibility that the transient and borderline hemodynamic changes in ischemic RV dysfunction may be due to ischemia rather than necrosis. This hypothesis is supported by the fact that 3 of 5 patients from Group AII with normal regional wall motion showed hemodynamic alterations of ischemic RV dysfunction only after dextran administration, and asynergy may not be found when the hemodynamic condition of the patient improves.

*Abnormal wall motion and normal hemodynamic function:* Three patients had abnormal RV motion without primary RV dysfunction during the hemodynamic monitoring. Abnormal wall motion can be the result of transient ischemia rather than infarction.[3,4] Two patients from Group B with RV asynergy presented a QS pattern and S-T segment elevation in leads $V_{3R}$ and $V_{4R}$ in the absence of anterior necrosis, a finding highly indicative of acute RV infarction.[18] This finding strongly suggests that wall motion abnormalities can be more sensitive than hemodynamics in detecting acute RV necrosis. This may be especially true when left ventricular function is impaired, preventing a close relation between right atrial and pulmonary capillary pressures suggestive of RV involvement.[11] This may have occurred in 2 of the 3 patients in this study, who had severe pulmonary congestion and a normal right atrial/pulmonary capillary pressure relation.

**Ventricular septal motion:** Paradoxical motion of the ventricular septum is a common finding in patients with acute RV infarction[7-9,19-21] and may be attributed to RV volume overload, tricuspid regurgitation, or alterations in RV compliance. In these circumstances, RV diastolic pressure equals or exceeds simultaneous left ventricular pressure, producing an inversion of the ventricular septum toward the left ventricle during diastole (Fig. 5), whereas during systole the septum moves toward the right ventricle because of the higher left ventricular systolic pressure. This behavior of the septal motion may distort the left ventricular geometry, impairing left ventricular function.[19]

## References


1. **Hutchins GM, Bulkley BH, Ridolfi RL, Griffith LSC, Lohr FT, Piasio M.** Correlation of coronary arteriograms and left ventriculograms with pos mortem studies. Circulation 1977;56:32–37.
2. **Reduto LA, Berger HJ, Cohen LS, Gottschalk A, Zaret BL.** Sequential dionuclide assessment of left and right ventricular performance after ac transmural myocardial infarction. Ann Intern Med 1978;89:441–447.
3. **Weiss JL, Bulkley BH, Hutchins GM, Mason SJ.** Two-dimensional ec cardiographic recognition of myocardial injury in man: comparison postmortem studies. Circulation 1981;63:401–408.
4. **Lieberman AN, Weiss JL, Jugdutt BI, Becker LC, Bulkley BH, Garr JG, Hutchins GM, Kallman CA, Weisfeldt ML.** Two-dimensional echo diography and infarct size: relationship of regional wall motion and thicke to the extent of myocardial infarction in the dog. Circulation 198 739–746.
5. **Pitt B, Strauss HW.** Myocardial perfusion imaging and gated cardiac t

pool scanning. Clinical application. Am J Cardiol 1976;38:739–746.
6. **Marmor A, Geltman EM, Biello DR, Sobel BE, Siegel BA, Roberts R.** Functional response of the right ventricle to myocardial infarction: dependence on the site of left ventricular infarction. Circulation 1981;64: 1005–1011.
7. **Lorell B, Leinbach RC, Pohost GM, Gold HK, Dinsmore RE, Hutter AM Jr, Pastore JO, DeSanctis RW.** Right ventricular infarction. Clinical diagnosis and differentiation from pericardial tamponade and pericardial constriction. Am J Cardiol 1979;43:465–471.
8. **Yung-Dae P, Shintaro B, Seiki N, Hiroshi S, Yasuharu N, Kazuo H, Tsunehiko N, Katsuhiko H.** Assessment of asynergy in right ventricular infarction with real time two-dimensional echocardiography (abstr). Circulation 1980;62:Suppl III:III-329.
9. **D'Arcy B, Nanda NC.** Two-dimensional echocardiographic features of right ventricular infarction. Circulation 1982;65:167–173.
10. **Forrester JS, Diamond GA, Swan HJC.** Correlative classification of clinical and hemodynamic function after acute myocardial infarction. Am J Cardiol 1977;39:137–145.
11. **Lopez-Sendon J, Coma-Canella I, Gamallo C.** Sensitivity and specificity of hemodynamic criteria in the diagnosis of acute right ventricular infarction. Circulation 1981;64:515–525.
12. **Lopez-Sendon J, Coma-Canella I, Viñuelas Adanez J.** Volume loading in patients with ischemic right ventricular dysfunction. Eur Heart J 1981;2: 329–338.
13. **Isner JM, Roberts WC.** Right ventricular infarction complicating left ventricular infarction secondary to coronary heart disease. Am J Cardiol 1978;42:885–894.
14. **Wyatt HL, Forrester JS, DaLuz PL, Diamond GA, Chagrasolis R, Swan HJC.** Functional abnormalities in nonoccluded regions of myocardium after experimental coronary occlusion. Am J Cardiol 1976;37:366–372.
15. **Maurer G, Nanda NC.** Two-dimensional echocardiographic evaluation of exercise-induced left and right ventricular asynergy: correlation with thallium scanning. Am J Cardiol 1981;48:720–727.
16. **Ramanathan K, Bodenheimer MM, Banka VS, Helfant RH.** Natural history of contractile abnormalities after acute myocardial infarction in man: severity and response to nitroglycerin as a function of time. Circulation 1981;63: 731–738.
17. **Holman BL, Wynne J, Idoine T, Neill RT.** Disruption in the temporal sequence of regional ventricular contraction. Circulation 1980;61:1075–1083.
18. **Erhardt LR, Sjögren A, Wahlberg I.** Single right-sided precordial lead in the diagnosis of right ventricular involvement in inferior myocardial infarction. Am Heart J 1976;91:571–576.
19. **Coma-Canella I, Lopez-Sendon J, Oliver J.** Premature pulmonic valve opening and inverted septal convexity in acute ischemic right ventricular dysfunction. Am Heart J 1981;101:684–685.
20. **Candell Riera J, Gutierrez Palau L, Valle Tudela V, Rius-Garriga J.** Estudio ecocardiográfico del infarto agudo de miocardio inferiór propagado a ventriculo derecho. Rev Esp Cardiol 1980;33:403–408.
21. **Lopez-Sendon J, Coma-Canella I, Lombera F, Benito F.** Diagnosis of ischemic right ventricular dysfunction by M-mode echocardiography. Eur Heart J 1982;3:230–237.

Truth flourishes where the students' lamp has shone, and there above. . .

W. B. Yeats

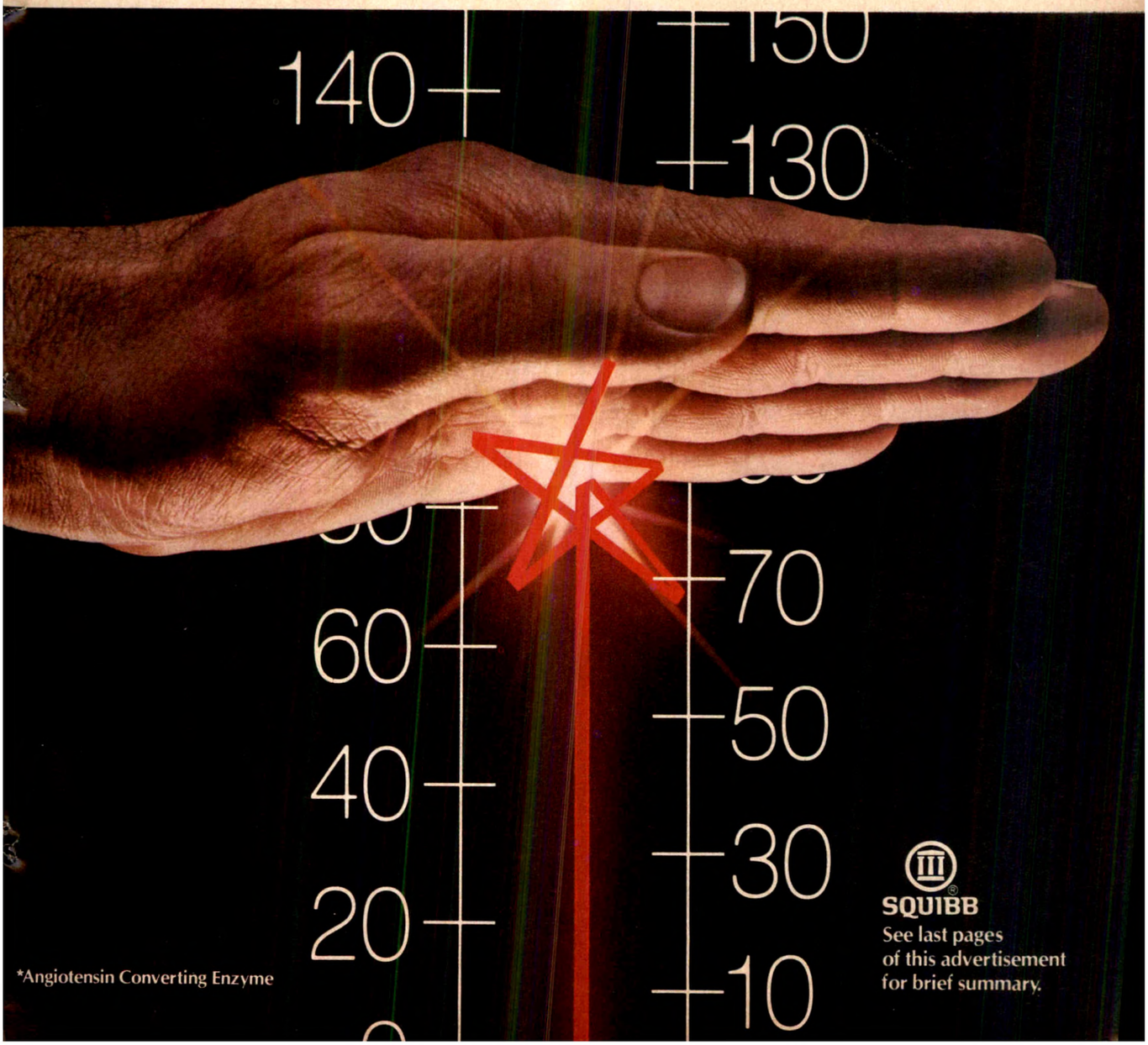
# Designed to achieve your therapeutic goals in hypertension

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# CAPOTEN® (captopril tablets)

For hypertensive patients

- **Who experience unacceptable side effects with beta blockers, antiadrenergic agents, or vasodilators**
- **In whom standard multidrug regimens are ineffective in controlling blood pressure**
- **Who have concomitant conditions contraindicating use of other antihypertensive agents**



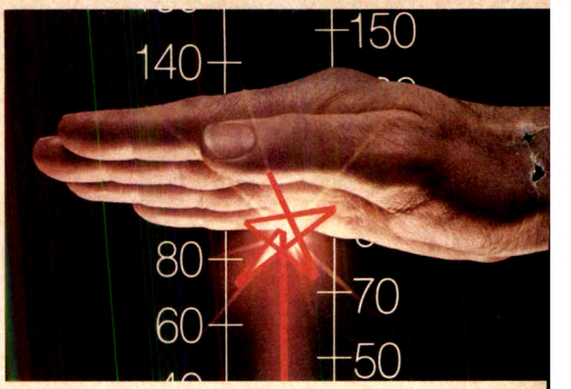

*Angiotensin Converting Enzyme

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ACE* INHIBITOR

# CAPOTEN®
# (captopril tablets)




## CAPOTEN controls blood pressure without the following usual antihypertensive side effects†:

- No cardiac depression
- No glucose intolerance
- No bradycardia
- No mental depression
- No sleep disturbances
- No nasal congestion
- No hypokalemia
- Rare impotence/loss of libido
- Rare bronchospasm
- Rare tachycardia
- Rare fatigue



## CAPOTEN is appropriate therapy when coexisting disorders complicate hypertension management

Unlike some other antihypertensive agents, CAPOTEN is appropriate for use in the presence of a wide range of cardiovascular and metabolic disorders that often coexist with hypertension.

- Bronchospastic disease
- Cardiac arrhythmias
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- Diabetes mellitus
- Hepatic disease

## CAPOTEN is effective in controlling many kinds of hypertension when conventional multidrug regimens have proven inadequate

- Essential hypertension
- Hypertension resistant to standard triple therapy (STT)
- Hypertension associated with low, normal, and high plasma renin levels
- Renovascular hypertension

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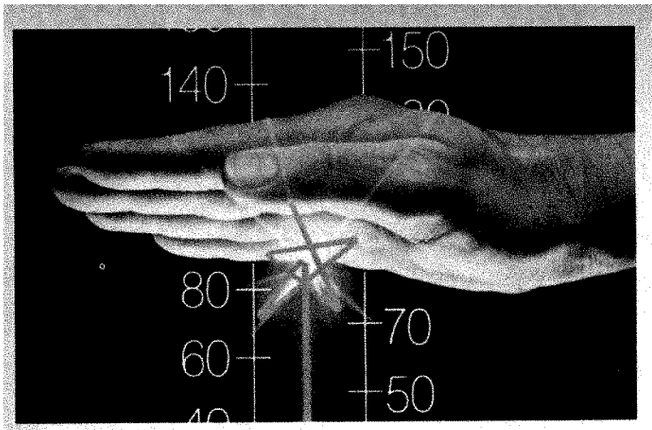
# CAPOTEN®

## (captopril tablets)

*Angiotensin Converting Enzyme

† Please see brief summary of prescribing information on the last pages of this advertisement for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.






ACE* INHIBITOR

# CAPOTEN®

## (captopril tablets)

**CAPOTEN has been associated with the development of neutropenia, agranulocytosis, or proteinuria.† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.**

**The following precautionary guidelines are recommended for all patients receiving CAPOTEN:**

- **Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.**
- **Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.**
- **Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.**
- **The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.**

SQUIBB®

*Angiotensin Converting Enzyme

†Please see brief summary of prescribing information, for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

**CAPOTEN® TABLETS**
**Captopril Tablets**

**INDICATIONS: Hypertension** — Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.
**Heart Failure:** CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.
**WARNINGS: Proteinuria** — Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine — the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

**Neutropenia/Agranulocytosis** — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

**Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.**

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.
**Hypotension** — Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

**BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.**
**PRECAUTION: General:** *Impaired Renal Function,* Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.
*Surgery/Anesthesia* — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.
**Drug Interactions:** *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.
*Agents Having Vasodilator Activity:* In heart failure patients vasodilators should be administered with caution.
*Agents Causing Renin Release* — Captopril's effect will be augmented by

(Continued on next page.)

(continued from preceding page)

antihypertensive agents that cause renin release.

*Agents Affecting Sympathetic Activity* — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

*Agents Increasing Serum Potassium* — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

**Drug/Laboratory Test Interaction:** Captopril may cause a false-positive urine test for acetone.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

**Usage in Pregnancy:** There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

**Nursing Mothers:** Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

**Pediatric Use:** Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

**ADVERSE REACTIONS:** Reported incidences are based on clinical trials involving about 4000 patients.

*Renal* — One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

*Hematologic* — Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

*Dermatologic* — Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients — reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

*Cardiovascular* — Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

*Dysgeusia* — About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

**Altered Laboratory Findings:** Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

**OVERDOSAGE:** Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

**DOSAGE AND ADMINISTRATION:** CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

**Consult package insert before prescribing CAPOTEN (captopril).**

**HOW SUPPLIED:** Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

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# Dialog of the Hearts –by Hemingway:

"And she smiled and from no distance said, 'Hello, my Inglés.'

'I'm not an Inglés', he said very lazily.

'Oh yes, you are', she said. 'You're my Inglés', and reached and took hold of both his ears and kissed him on the forehead.

'There', she said. 'How is that? Do I kiss thee better?'

Then they were walking along the stream together and he said, 'Maria, I love thee and thou art so lovely and so wonderful and so beautiful and it does such things to me to be with thee that I feel as though I wanted to die when I am loving thee'.

'Oh', she said. 'I die each time. Do you not die?'

'No. Almost. But did thee feel the earth move?'

'Yes. As I died. Put thy arm around me, please'.

'No. I have thy hand. Thy hand is enough".

The Dialogue of Robert Jordan and Maria from "For Whom the Bell Tolls".

**Another Dialog soon to appear—by Siemens.**

82219

MG/5830-018

# Variable Threshold Exertional Angina in Patients With Transient Vasospastic Myocardial Ischemia

## Repeat Exercise Test Results and Therapeutic Implications

STEFANO DE SERVI, MD, GIUSEPPE SPECCHIA, MD, COLOMBA FALCONE, MD, ANTONELLO GAVAZZI, MD, ANTONIO MUSSINI, MD, LUIGI ANGOLI, MD, EZIO BRAMUCCI, MD, DIEGO ARDISSINO, MD, LAURA VACCARI, MD, JORGE SALERNO, MD, and PIERO BOBBA, MD

**Thirty-five of 70 patients with vasospastic angina at rest complained of chest pain during exercise or during usual daily activity. In 22, the angina threshold was described as variable during exercise: that is, the amount of exertion that induced angina was not always the same. In 12 patients with variable threshold exertional angina, 3 exercise tests performed in the morning on different days yielded different results, because chest pain and ischemic electrocardiographic changes occurred at different work loads with a wide range in heart rate-systolic pressure product. Two patients, in whom great cardiac vein flow was measured during exercise before and after taking nifedipine, tolerated heavier work loads after receiving the drug, with a more marked increase in flow during exercise. It is concluded that variable threshold exertional angina can be objectively demonstrated by repeat exercise tests in patients with vasospastic angina. Variability of the angina threshold may be due to a functional mechanism that causes myocardial ischemia in addition to the increased myocardial metabolic requirements provoked by exercise. Because in such patients fluctuations in coronary arterial tone play an important role in determining the response to exercise, calcium antagonistic drugs, which lower coronary tone and prevent the occurrence of coronary spasm, are effective in increasing exercise capacity.**

Patients with vasospastic angina at rest may also have chest pain during exercise or during usual daily activity.[1,2] In these patients the angina threshold may vary from time to time; a few patients have recently been described[3-5] in whom repeated exercise tests induced myocardial ischemia at different values of heart rate-systolic blood pressure product, an index of myocardial oxygen consumption.[6] However, the incidence of this phenomenon is not yet appreciated, and it is not clear whether the clinical suspicion of variable threshold exertional angina can always be confirmed by repeated exercise tests.

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This study describes the results of repeated exercise tests in patients with vasospastic angina presenting with this clinical manifestation. We believe that the recognition of variable threshold exertional angina may have important therapeutic implications.

### Methods

**Patients: Criteria of selection:** Between October 1979 and October 1981 we observed 70 patients with vasospastic angina at rest without evidence of previous transmural myocardial infarction. Coronary vasospasm was considerd responsible for the occurrence of chest pain at rest on the basis of the following criteria: Sixty patients showed transient S-T segment elevation during at least 1 episode of chest pain at rest,[7] whereas the remaining 10 patients showed S-T segment depression repeatedly during chest pain as well as after the administration of intravenous ergonovine maleate in the coronary care unit.[14,15] Thirty-five patients also complained of chest pain during exercise or usual daily activity. In 22 of these patients the angina threshold was described as variable dur

**TABLE I Results of Repeated Exercise Tests in 12 Patients With Variable Threshold Exertional Angina**

| | First Exercise Test | | | | Second Exercise Test | | | |
|---|---|---|---|---|---|---|---|---|
| Case | Work Load | End-point | RPP | ECG Changes | Work Load | End-point | RPP | ECG Changes |
| 1 | 50 W × 1 min | Ang | 128 | ↓S-T 3 mm $V_2$-$V_6$ | 125 W × 3 min | Ang | 260 | ↓S-T 1 mm $V_4$-$V_6$ |
| 2 | 50 W × 3 min | Ang | 176 | ↓S-T 1 mm II, III, aVF | 125 W × 3 min | Exh | 259 | — |
| 3 | 50 W × 1 min | ↑S-T | 143 | ↑S-T II, III, aVF | 125 W × 1 min | Exh | 300 | — |
| 4 | 125 W × 1 min | Ang | 364 | ↑S-T $V_1$-$V_2$ | 175 W × 1 min | Exh | 285 | ↓S-T 1 mm $V_5$-$V_6$ |
| 5 | 75 W × 3 min | Ang | 304 | ↑S-T $V_1$-$V_2$ | 125 W × 1 min | Ang | 286 | ↑S-T $V_1$-$V_3$ |
| 6 | 100 W × 1 min | Exh | 246 | ↓S-T 1,5 mm $V_3$-$V_6$ | 50 W × 1 min | Ang | 189 | ↓S-T 2,5 mm $V_3$-$V_6$ |
| 7 | 100 W × 1 min | Ang | 158 | ↓S-T 2 mm $V_4$-$V_6$ | 100 W × 1 min | Exh | 145 | — |
| 8 | 75 W × 2 min | Ang | 240 | ↓S-T 2,5 mm $V_3$-$V_6$ | 75 W × 1 min | Ang | 271 | ↓S-T 1 mm $V_3$-$V_6$ |
| 9 | 50 W × 3 min | Ang | 163 | ↓S-T 1,5 mm II, III, aVF, $V_5$-$V_6$ | 75 W × 3 min | Ang | 213 | ↓S-T 1,5 mm II, III, aVF, $V_5$-$V_6$ |
| 10 | 125 W × 3 min | Exh | 176 | ↓S-T 1 mm $V_3$-$V_6$ | 125 W × 1 min | Exh | 209 | — |
| 11 | 50 W × 1 min | Ang | 140 | ↓S-T 4 mm $V_3$-$V_6$ | 50 W × 3 min | Ang | 163 | ↓S-T 3 mm $V_3$-$V_6$ |
| 12 | 100 W × 1 min | Ang | 162 | ↓S-T 1,5 mm $V_3$-$V_6$ | 50 W × 1 min | Ang | 143 | ↓S-T 4 mm $V_3$-$V_6$ |

Ang = angina; ECG = electrocardiographic; Exh = exhaustion; RPP = heart rate-systolic pressure product, mm Hg × beats/min × $10^{-2}$; ↑S-T = S-T segment elevation; ↓ST = S-T segment depression; — = no electrocardiographic changes.

exercise; these patients could not recognize a critical amount of exertion they could perform before experiencing angina but the level of activity that determined the symptoms varied from time to time. Twelve of these 22 patients were selected for this study. The selection was not done in a random fashion but depended on the clinical characteristics of the patients. We excluded patients with more than 3 episodes of chest pain at rest per day or with severe ventricular arrhythmias or left ventricular failure during anginal attacks.[16] In the 12 patients studied, drug therapy consisting of nitrates and nifedipine could be suspended 12 hours before exercise tests without any manifestation of withdrawal phenomena, such as accelerated angina or other coronary events. No patient was receiving beta-adrenergic blocking agents or digitalis.

**Exercise testing:** The 12 patients selected performed 3 bicycle exercise tests in the morning (8:30 to 11:00 A.M.) on different days during hospitalization. The mean interval between the first and the third exercise test was 7.8 ± 6 days. Two of these patients were described recently.[3] The exercise tests were performed in the supine position with an initial work load of 50 W and subsequent increments of 25 W every 3 minutes. Exercise was stopped when angina, dyspnea, exhaustion, S-T segment elevation ≥2 mm, or S-T segment depression >3 mm occurred. A 12-lead electrocardiogram was taken before and at the end of exercise, and every minute during recovery; leads $V_4$, $V_5$, and $V_6$ were monitored during exercise. Cuff blood pressure was measured at 3-minute intervals. The criteria for a positive exercise test were a horizontal or downsloping S-T segment depression ≥1 mm for 0.08 second compared with the resting tracing and S-T segment elevation ≥1 mm at 0.04 second after the J point compared with *the baseline* electrocardiogram. An estimate of myocardial oxygen consumption was made from the double product, obtained by multiplying systolic arterial pressure and heart rate.[6]

**Coronary arteriography:** The 12 patients studied underwent coronary arteriography using the Sones technique after premedication with 10 mg of diazepam. Left ventriculography was performed in the right anterior oblique projection before arteriography. Narrowing >50% of 1 or more coronary arteries was considered evidence of significant coronary artery disease. When a significant lesion was noted, the vessel was filmed again after sublingual administration of nitroglycerin.

**Coronary flow study:** In 2 patients with isolated left anterior descending artery disease, exercise tests were performed before and 20 minutes after sublingual administration of 20

**TABLE II Electrocardiographic (ECG) Changes During Chest Pain at Rest and Coronary Arteriographic Findings**

| Case | Age (yr) & Sex | ECG Changes (Spontaneous Angina) | Coronary Arteriographic Findings |
|---|---|---|---|
| 1 | 54M | ↓↑S-T ant | LAD 75% |
| 2 | 48M | ↑S-T inf | Normal |
| 3 | 38M | ↑S-T inf | RCA 90% |
| 4 | 54M | ↑S-T ant | LAD 90%, cfx 75% |
| 5 | 55M | ↑S-T ant | LAD 75%, cfx 75% |
| 6 | 44M | ↑S-T inf | Cfx 90% |
| 7 | 61M | ↓S-T ant | Normal |
| 8 | 44F | ↓S-T ant | LAD 75% |
| 9 | 62M | ↑S-T inf | RCA 90%, cfx 75% |
| 10 | 53M | ↑S-T ant | LAD 75% |
| 11 | 55M | ↑S-T ant | LAD 90% |
| 12 | 59M | ↓S-T ant | LAD 90% |

ant = anterior leads; cfx = circumflex branch; inf = inferior leads; LAD = left anterior descending artery; RCA = right coronary artery; ↑S-T = ST-T segment elevation; ↓S-T = ST-T segment depression.

**TABLE I (Continued)**

| Case | Third Exercise Test: Work Load | End-point | RPP | ECG Changes |
|---|---|---|---|---|
| 1 | 75 W × 3 min | Ang | 225 | ↓S-T 2 mm $V_3$-$V_6$ |
| 2 | 125 W × 3 min | Ang | 260 | ↓S-T 2 mm II, III, aVF |
| 3 | 150 W × 3 min | Exh | 391 | — |
| 4 | 150 W × 2 min | Exh | 250 | — |
| 5 | 125 W × 2 min | ↓S-T | 300 | ↓S-T 4 mm $V_4$-$V_6$ |
| 6 | 150 W × 3 min | Exh | 278 | ↓S-T 2,5 mm $V_3$-$V_6$ |
| 7 | 125 W × 1 min | Exh | 184 | ↓S-T 1 mm $V_4$-$V_6$ |
| 8 | 75 W × 1 min | Ang | 232 | ↓S-T 1 mm $V_3$-$V_6$ |
| 9 | 75 W × 3 min | Exh | 209 | ↓S-T 1,5 mm II, III, aVF, $V_5$-$V_6$ |
| 10 | 125 W × 3 min | Ang | 176 | ↓S-T 1 mm $V_3$-$V_6$ |
| 11 | 75 W × 3 min | Exh | 221 | ↓S-T 1 mm $V_4$-$V_6$ |
| 12 | 75 W × 2 min | Ang | 213 | ↓S-T 3 mm $V_3$-$V_6$ |

mg of nifedipine; the tests were done with the patient in the supine position with an initial work load of subsequent increments of 25 W every 3 minutes. A triple thermistor thermodilution catheter (Wilton Webster Laboratories, Altadena, California) was inserted into the coronary sinus with the tip advanced to the great cardiac vein, so that the flow recorded was entirely from the great cardiac vein.[17] Its position was confirmed with fluoroscopy and frequently checked throughout the procedure. Flow measurements were obtained in basal conditions and at peak exercise[15,18] by injecting physiologic saline solution at 24° per 30 seconds using a pump at a rate of 56 ml/min. The left brachial artery was punctured to measure intraarterial pressure.

An interval of 30 minutes was allowed to elapse between the end of the first exercise test and the administration of nifedipine. Great cardiac vein flow (GCVF) was calculated using the following formula: $GCVF = V_i \times [(T_b - T_i)/(T_b - T_m) - 1] \times 1.08$, where $V_i$ represents the volume of injectate (ml/min) and $T_b$, $T_i$, and $T_m$ the temperatures of blood, injectate, and mixture of blood and injectate; 1.08 is a constant of the saline solution.

Informed consent was obtained from all patients before each test. No complications were observed during the procedures.

## Results

**Clinical features:** Eleven patients were men and 1 a woman, with an average age of 52.7 years (range 38 to 62). In 8 patients, anginal attacks at rest were associated with S-T segment elevation, occurring in the anterior leads in 4 patients and in the inferior leads in 4, whereas 1 patient had episodes associated with either S-T segment elevation or depression in the anterior leads. Three patients showed S-T segment depression in the anterior leads during chest pain at rest. In 6 patients, angina was of recent onset (<3 months).

**Exercise tests (Table I):** Four patients (Cases 2, 4, 7, and 10) had 1 negative test and 2 positive tests; 1 patient (Case 3) had 2 negative tests and 1 positive test. Seven patients had all 3 positive tests. Chest pain occurred during all 3 exercise tests in 3 patients, while 8 patients had at least 1 exercise test ended because of exhaustion. In 1 patient the end point was angina in 2 tests and S-T segment depression >3 mm without angina in the third test.

S-T segment elevation was observed in 2 patients (Cases 3 and 4) during 1 exercise test and in 1 patient (Case 5) during 2 tests. In 6 patients (Cases 1, 6, 8, 9, 11, and 12) all 3 exercise tests induced S-T segment depression. In 5 of these patients, S-T segment depression occurred at different work loads with a wide range of values of double product. One illustrative case is shown in Figure 1. In 1 patient (Case 8) exercise tolerance did not change substantially during the 3 tests; however S-T depression was more marked during the first than during the second exercise test although a higher value of double product was attained during the latter.

**Angiographic features:** No patient had akinetic or dyskinetic areas of the left ventricle. The average ejection fraction was 59 ± 7 and the average left ventricular end-diastolic pressure was 12.5 ± 5 mm Hg. Coronary

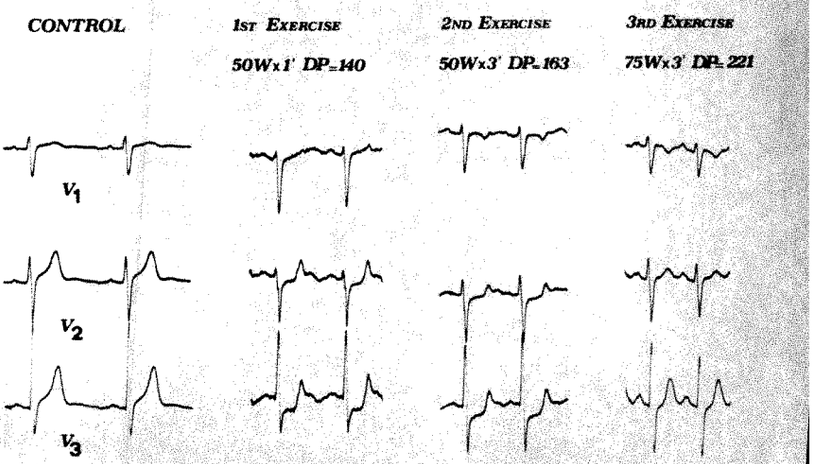



**FIGURE 1.** Case 11. Three exercise tests performed in the morning on different days yielded different results. The first and second tests induced chest pain and S-T segment depression, whereas the third test was negative despite a higher double product. DP = double product (mm Hg × beats/min × $10^{-2}$).

**TABLE III Great Cardiac Vein Flow During Exercise Tests Before and After Administration of Nifedipine**

| | Work Load | End-point | ECG Changes | Double Product (mm Hg beats/min $10^{-2}$) | GCVF (ml/min) |
|---|---|---|---|---|---|
| Case 11 | | | | | |
| Control | | | | | 72 |
| Peak exercise | 75 W × 3 min | Ang | ↓S-T 1 mm $V_4$-$V_6$ | 208 | 152 |
| After nifedipine | | | | | 64 |
| Peak exercise | 100 W × 2 min | Exh | — | 269 | 194 |
| Case 12 | | | | | |
| Control | | | | | 103 |
| Peak exercise | 25 W × 2 min | Ang | ↓S-T 4 mm $V_3$-$V_6$ | 131 | 105 |
| After nifedipine | | | | | 116 |
| Peak exercise | 75 W × 2 min | Ang | ↓S-T 4 mm $V_3$-$V_6$ | 183 | 164 |

Ang = angina; ECG = electrocardiographic; Exh = exhaustion; GCVF = great cardiac vein flow; ↓S-T = S-T segment depression; — = no electrocardiographic changes.

arteriography (Table II) showed normal coronary arteries in 2 patients. Seven patients had single-vessel disease with involvement of the left anterior descending artery in 5, of the right coronary artery in 1 and of the circumflex branch in 1.

Three patients had 2-vessel disease. During the procedure, 2 patients exhibited a spontaneous spasm of the right coronary artery and 1 of the left anterior descending artery. One patient had an ergonovine-induced spasm of the left anterior descending artery.

**Great cardiac vein flow measurements (Table III):** Both patients showed an increase in flow at peak exercise. After administration of nifedipine they tolerated heavier work loads than before and attained higher values of double product. Despite that, electrocardiographic signs of ischemia did not appear in 1 patient and occurred at far greater values of double product in the other. The increase in flow in the great cardiac vein at peak exercise was more marked after than before administration of nifedipine (Fig. 2).

## Discussion

**Variability of angina threshold during exercise:** Stable exertional angina is caused by increased myocardial oxygen consumption in the presence of fixed stenoses of the large coronary arteries. The concept that coronary lesions are fixed implies that myocardial ischemia occurs reproducibly at a given level of myocardial oxygen consumption. Epstein and Talbot[19] recently challenged this concept, because it does not explain several clinical characteristics often observed in patients with angina pectoris. For instance, "... it does not explain why angina threshold should vary markedly during different times of the day, different times of the week, or different seasons of the year."[19] This lack of reproducibility and predictability has been reported in classic descriptions of angina of effort.[20,21] Friedberg,[20] observing that some patients have only occasional seizures at intervals of days, weeks, or months, comments that "these intervals depend to some extent on avoidance of the factors which elicit the anginal attacks."

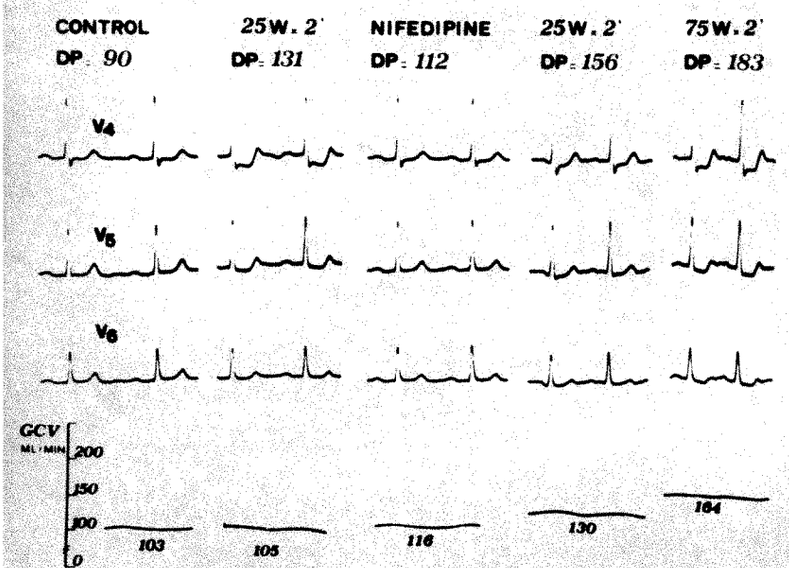



**FIGURE 2.** Case 12. In this patient with disease of an isolated left anterior descending artery, measurements of great cardiac vein flow were performed during exercise, before and after administration of nifedipine. After the drug, the patient tolerated a greater work load and attained a higher value of double product. This beneficial effect was achieved by an increase in great cardiac vein flow. DP = double product (mm Hg × beats/min × $10^{-2}$); GCVF = great cardiac vein flow measurements (ml/min).

a proved hypothesis. Am J Cardiol 1976;37:938–940.
9. **Hillis LD, Braunwald E.** Coronary-artery spasm. N Engl J Med 1978;299: 695–702.
10. **Maseri A, Pesola A, Marzilli M, de Servi S, Parodi O, L'Abbate A, Ballestra AM, Maltini G, De Nes M, Biagini A.** Coronary vasospasm in angina pectoris. Lancet 1977;1:713–717.
11. **de Servi S, Specchia G, Angoli L, Bramucci E, Mussini A, Marinoni GP, Salerno J, Bobba P.** Coronary arterial spasm in angina at rest associated with transient ST-segment changes. Clin Cardiol 1980;3:54–60.
12. **Bertrand ME, Lablanche JM, Tilmant PY.** Treatment of Prinzmetal's variant angina. Role of medical treatment with nifedipine and surgical coronary revascularization combined with plexectomy. Am J Cardiol 1981;47: 174–178.
13. **Antman E, Muller J, Goldberg S, MacAlpin R, Rubenfire M, Tabaznick B, Liang CS, Heupler F, Achuff S, Reichek N, Geltman E, Kerin NZ, Neff RK, Braunwald E.** Nifedipine therapy for coronary-artery spasm: experience in 127 patients. N Engl J Med 1980;302:1269–1273.
14. **Waters DD, Théroux P, Szlachcic J, Dauwe F, Crittin J, Bonan R, Mizgala HF.** Ergonovine testing in coronary care unit. Am J Cardiol 1980;46: 922–930.
15. **Specchia G, de Servi S, Falcone C, Bramucci E, Angoli L, Mussini M, Marinoni GP, Montemartini C, Bobba P.** Significance of exercise-induced ST-segment elevation in patients without myocardial infarction. Circulation 1981;63:46–53.
16. **de Servi S, Falcone C, Gavazzi A, Mussini A, Bramucci E, Curti MT, Vecchio C, Specchia G, Bobba P.** The exercise test in variant angina. Results in 114 patients. Circulation 1981;64:684–688.
17. **Pepine CJ, Mehta J, Webster WW, Nichols WW.** In vivo validation of a thermodilution method to determine regional left ventricular blood flow in patients with coronary artery disease. Circulation 1978;58:795–802.
18. **Ferguson RJ, Côté P, Gauthier P, Bourassa MG.** Changes in exercise coronary sinus blood flow with training in patients with angina pectoris. Circulation 1978;58:41–47.
19. **Epstein SE, Talbot TL.** Dynamic coronary tone in precipitation, exacerbation and relief of angina pectoris. Am J Cardiol 1981;48:797–803.
20. **Friedberg CK.** Diseases of the Heart. 3rd ed. Philadelphia: WB Saunders, 1966:708.
21. **Braunwald E.** Heart Disease. A Textbook of Cardiovascular Medicine. Philadelphia: WB Saunders, 1980:1390.
22. **Ellestad MH, Allen W, Wan MCK, Kemp GL.** Maximal treadmill stress testing for cardiovascular evaluation. Circulation 1969;39:517–522.
23. **Fabian J, Stoltz I, Janota M, Rohac J.** Reproducibility of exercise tests in patients with symptomatic ischaemic heart disease. Br Heart J 1975;37: 785–789.
24. **Robinson BF.** Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. Circulation 1967;35:1073–1083.
25. **Gobel FL, Nordstrom LA, Nelson RR, Jorgensen CR, Wang Y.** The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 1978;57:549–556.
26. **Redwood DR, Rosing DR, Goldstein RE, Beiser GD, Epstein SE.** Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris. Circulation 1971;43:618–628.
27. **Specchia G, de Servi S, Falcone C, Bramucci E, Angoli L, Mussini A, Marinoni GP, Montemartini C, Bobba P.** Coronary arterial spasm as a cause of exercise-induced ST-segment elevation in patients with variant angina. Circulation 1979;59:948–954.
28. **Waters DD, Chaitman BR, Dupras G, Théroux P, Mizgala HF.** Coronary artery spasm during exercise in patients with variant angina. Circulation 1979;59:580–585.
29. **Yasue H, Omote S, Takizawa A, Nagao M, Miwa K, Tanaka S.** Circadian Variation of exercise capacity in patients with Prinzmetal's variant angina: role of exercise-induced coronary arterial spasm. Circulation 1979;59: 938–948.
30. **Waters DD, Szlachcic J, Bourassa MG, Scholl JM, Théroux P.** Exercise testing in patients with variant angina: results, correlation with clinical and angiographic features and prognostic significance. Circulation 1982;65: 265–274.
31. **Gunther S, Green L, Muller JE, Mudge GH, Grossman W.** Inappropriate coronary vasoconstriction in patients with coronary artery disease: a role for nifedipine? Am J Cardiol 1979;44:793–797.
32. **de Servi S, Mussini A, Specchia G, Bramucci E, Gavazzi A, Falcone C, Ardissino D, Guagliumi G, Bobba P.** Effects of nifedipine on coronary blood flow and coronary resistance during cold pressor test and isometric exercise in patients with coronary artery disease. Eur Heart J 1980;1 Suppl B:43–47.
33. **Freedman B, Dunn RF, Richmond DR, Kelly DT.** Coronary artery spasm during exercise: treatment with verapamil. Circulation 1981;64:68–75.
34. **Yasue H, Omote S, Takizawa A, Nagao M, Miwa K, Tanaka S.** Exertional angina pectoris caused by coronary arterial spasm: effects of various drugs. Am J Cardiol 1979;43:647–652.

Braunwald[21] ascribes this unpredictability to a "complex interplay of factors relating to the physiological and emotional set of a patient." However, a good reproducibility of exercise test results, repeated at short- or long-term intervals, has been shown in patients with stable exertional angina.[22,23] Moreover, when occasional patients showing a variation in their exercise tolerance were studied,[24] angina always occurred at a constant level of heart rate-systolic pressure product, an indirect index of myocardial oxygen consumption.

All 12 patients in our study had vasospastic angina at rest and clinical evidence of variable threshold exertional angina. Repeat exercise testing objectively demonstrated the variation in exercise tolerance and the variable occurrence of angina that was not dependent on the achievement of a critical level of heart rate-systolic pressure product. Other determinants of myocardial oxygen consumption not reflected by the double product, such as contractility or left ventricular size, may be operative in producing the variation in exercise tolerance in our patients. However the double product is well correlated with myocardial oxygen consumption during exercise,[25] and in patients with stable effort angina chest pain occurs when a critical level of double product is achieved.[24,26] Thus, there is no reason to assume that changes in other factors, not included in the double product, could play a major role in determining the wide variation in exercise capacity observed in our patients with vasospastic angina.

**Role of dynamic coronary tone in exertional angina:** Variability of the angina threshold may be due to a functional mechanism that causes myocardial ischemia in addition to the increased myocardial metabolic requirements provoked by exercise. It has been shown by us[15,27] and others[28,29] that in patients with variant angina, exercise-induced S-T segment elevation is caused by coronary spasm. Recently, Yasue et al[29] reported a circadian variation of exercise capacity in patients with variant angina. These investigators showed that the treadmill exercise test induced repeated attacks in the early morning but not in the afternoon of the same day, even though the exercise was heavier in the afternoon than in the morning. In their patients, coronary angiography revealed that the diameter of the coronary vessels was smaller in the morning than in the afternoon. Under conditions of increased coronary tone, exercise can readily induce spasm and result in an attack. Furthermore, it has been demonstrated that the exercise test is frequently positive in patients with active variant angina[16,30] but may become negative if the patient is in a latent phase of his disease. Thus, the fluctuating susceptibility of the coronary vessels to vasoconstriction may be responsible for the large variability of responses to the same exertion. Epstein and Talbot[19] recently developed the hypothesis that subtle alterations in coronary tone may account for the spontaneous changes in angina threshold during exercise. They developed the concept that there is a spectrum of coronary tone in dynamic large vessels that can significantly alter angina threshold. We believe that our results support this hypothesis. When coronary tone is low, patients can perform heavy exercise because myocardial oxygen supply is impaired only by the eventual presence of organic coronary stenoses. On the contrary, when coronary tone is high, oxygen supply is decreased and even moderate physical activities may induce chest pain and myocardial ischemia. In some patients, exercise-induced coronary spasm may supervene, as in patients showing S-T segment elevation during exercise and probably in those showing unexpected S-T segment depression at very light work loads.

**Clinical implications:** Our data show that variable threshold exertional angina is clinically observed in about one third of patients with vasospastic angina and can be objectively demonstrated by repeat exercise testing. In this study we did not test patients with a fixed limitation of exercise tolerance or without effort angina. Thus, it is not possible to establish in those patients a correlation between the clinical history and the repeat exercise test results.

Coronary tone changes seem the most likely explanation for the variable occurrence of chest pain and myocardial ischemia during exercise in patients with vasospastic angina. In such patients, calcium-channel blocking agents, which lower coronary tone[31,32] and prevent the occurrence of coronary spasm,[33] may have beneficial effects, whereas propranolol may be ineffective and even detrimental, as demonstrated by Yasue et al.[34] An increase in exercise capacity was observed in 2 of our patients to whom nifedipine was administered. After drug administration, both patients tolerated heavier work loads. Ischemic electrocardiograpic changes were no longer observed in 1 patient and occurred at higher values of double product in the other patient. We documented that this salutary effect was achieved by an increase in coronary flow during exercise. These results lend further support to the hypothesis that changes in coronary tone may account for the variability of angina threshold observed during exercise in some patients with vasospastic angina. Further studies should also focus on the recognition of this clinical manifestation in patients without vasospastic angina, and should assess the role of dynamic coronary tone in stable exertional angina.

## References


1. **Maseri A, Severi S, De Nes M, L'Abbate A, Chierchia S, Marzilli M, Ballestra AM, Parodi O, Biagini A, Distante A.** Variant angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia. Am J Cardiol 1978;42:1019–1035.
2. **de Servi S, Specchia G, Ardissino D, Falcone C, Mussini A, Angoli L, Bramucci E, Marinoni GP, Gavazzi A, Bobba P.** Angiographic demonstration of different pathogenetic mechanisms in patients with spontaneous and exertional angina associated with S-T segment depression. Am J Cardiol 1980;45:1285–1291.
3. **de Servi S, Specchia G, Curti MT, Falcone C, Gavazzi A, Bramucci E, Mussini A, Angoli L, Salerno J, Bobba P.** Variable threshold of angina during exercise: a clinical manifestation of some patients with vasospastic angina. Am J Cardiol 1981;48:188–192.
4. **Brunelli C, Lazzari M, Simonetti I, L'Abbate A, Maseri A.** Variable threshold of exertional angina: a clue to a vasospastic component. Eur Heart J 1981;2:155–161.
5. **Shimokawa H, Matsuguchi T, Koiwaya Y, Fukuyama T, Orita Y, Nakamura M.** Variable exercise capacity in variant angina and greater exertional thallium-201 myocardial defect during vasospastic ischemic ST segment elevation than with ST depression. Am Heart J 1982;103:142–145.
6. **Braunwald E.** Control of myocardial oxygen consumption. Physiologic and clinical considerations. Am J Cardiol 1971;27:416–432.
7. **Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N.** Angina pectoris. I. A variant form of angina pectoris. Am J Med 1959;27:375–388.
8. **Meller J, Pichard A, Dack S.** Coronary arterial spasm in Prinzmetal's angina:

**TABLE III Great Cardiac Vein Flow During Exercise Tests Before and After Administration of Nifedipine**

| | Work Load | End-point | ECG Changes | Double Product (mm Hg beats/min $10^{-2}$) | GCVF (ml/min) |
|---|---|---|---|---|---|
| Case 11 | | | | | |
| Control | ... | ... | ... | ... | 72 |
| Peak exercise | 75 W × 3 min | Ang | ↓S-T 1 mm $V_4$-$V_6$ | 208 | 152 |
| After nifedipine | ... | ... | ... | ... | 64 |
| Peak exercise | 100 W × 2 min | Exh | — | 269 | 194 |
| Case 12 | | | | | |
| Control | ... | ... | ... | ... | 103 |
| Peak exercise | 25 W × 2 min | Ang | ↓S-T 4 mm $V_3$-$V_6$ | 131 | 105 |
| After nifedipine | ... | ... | ... | ... | 116 |
| Peak exercise | 75 W × 2 min | Ang | ↓S-T 4 mm $V_3$-$V_6$ | 183 | 164 |
| | | | | ... | ... |

Ang = angina; ECG = electrocardiographic; Exh = exhaustion; GCVF = great cardiac vein flow; ↓S-T = S-T segment depression; — = no electrocardiographic changes.

arteriography (Table II) showed normal coronary arteries in 2 patients. Seven patients had single-vessel disease with involvement of the left anterior descending artery in 5, of the right coronary artery in 1 and of the circumflex branch in 1.

Three patients had 2-vessel disease. During the procedure, 2 patients exhibited a spontaneous spasm of the right coronary artery and 1 of the left anterior descending artery. One patient had an ergonovine-induced spasm of the left anterior descending artery.

**Great cardiac vein flow measurements (Table III):** Both patients showed an increase in flow at peak exercise. After administration of nifedipine they tolerated heavier work loads than before and attained higher values of double product. Despite that, electrocardiographic signs of ischemia did not appear in 1 patient and occurred at far greater values of double product in the other. The increase in flow in the great cardiac vein at peak exercise was more marked after than before administration of nifedipine (Fig. 2).

## Discussion

**Variability of angina threshold during exercise:** Stable exertional angina is caused by increased myocardial oxygen consumption in the presence of fixed stenoses of the large coronary arteries. The concept that coronary lesions are fixed implies that myocardial ischemia occurs reproducibly at a given level of myocardial oxygen consumption. Epstein and Talbot[19] recently challenged this concept, because it does not explain several clinical characteristics often observed in patients with angina pectoris. For instance, "... it does not explain why angina threshold should vary markedly during different times of the day, different times of the week, or different seasons of the year."[19] This lack of reproducibility and predictability has been reported in classic descriptions of angina of effort.[20,21] Friedberg,[20] observing that some patients have only occasional seizures at intervals of days, weeks, or months, comments that "these intervals depend to some extent on avoidance of the factors which elicit the anginal attacks."

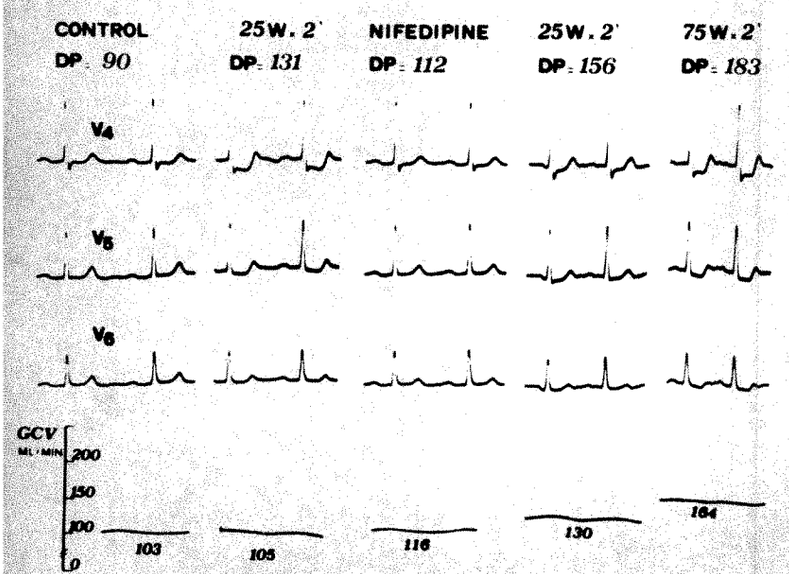



**FIGURE 2.** Case 12. In this patient with disease of an isolated left anterior descending artery, measurements of great cardiac vein flow were performed during exercise, before and after administration of nifedipine. After the drug, the patient tolerated a greater work load and attained a higher value of double product. This beneficial effect was achieved by an increase in great cardiac vein flow. DP = double product (mm Hg × beats/min × $10^{-2}$); GCVF = great cardiac vein flow measurements (ml/min).

**TABLE I (Continued)**

| Case | Third Exercise Test: Work Load | End-point | RPP | ECG Changes |
|---|---|---|---|---|
| 1 | 75 W × 3 min | Ang | 225 | ↓S-T 2 mm $V_3$-$V_6$ |
| 2 | 125 W × 3 min | Ang | 260 | ↓S-T 2 mm II, III, aVF |
| 3 | 150 W × 3 min | Exh | 391 | — |
| 4 | 150 W × 2 min | Exh | 250 | — |
| 5 | 125 W × 2 min | ↓S-T | 300 | ↓S-T 4 mm $V_4$-$V_6$ |
| 6 | 150 W × 3 min | Exh | 278 | ↓S-T 2,5 mm $V_3$-$V_6$ |
| 7 | 125 W × 1 min | Exh | 184 | ↓S-T 1 mm $V_4$-$V_6$ |
| 8 | 75 W × 1 min | Ang | 232 | ↓S-T 1 mm $V_3$-$V_6$ |
| 9 | 75 W × 3 min | Exh | 209 | ↓S-T 1,5 mm II, III, aVF, $V_5$-$V_6$ |
| 10 | 125 W × 3 min | Ang | 176 | ↓S-T 1 mm $V_3$-$V_6$ |
| 11 | 75 W × 3 min | Exh | 221 | ↓S-T 1 mm $V_4$-$V_6$ |
| 12 | 75 W × 2 min | Ang | 213 | ↓S-T 3 mm $V_3$-$V_6$ |

mg of nifedipine; the tests were done with the patient in the supine position with an initial work load of subsequent increments of 25 W every 3 minutes. A triple thermistor thermodilution catheter (Wilton Webster Laboratories, Altadena, California) was inserted into the coronary sinus with the tip advanced to the great cardiac vein, so that the flow recorded was entirely from the great cardiac vein.[17] Its position was confirmed with fluoroscopy and frequently checked throughout the procedure. Flow measurements were obtained in basal conditions and at peak exercise[15,18] by injecting physiologic saline solution at 24° per 30 seconds using a pump at a rate of 56 ml/min. The left brachial artery was punctured to measure intraarterial pressure.

An interval of 30 minutes was allowed to elapse between the end of the first exercise test and the administration of nifedipine. Great cardiac vein flow (GCVF) was calculated using the following formula: $GCVF = V_i \times [(T_b - T_i)/(T_b - T_m) - 1] \times 1.08$, where $V_i$ represents the volume of injectate (ml/min) and $T_b$, $T_i$, and $T_m$ the temperatures of blood, injectate, and mixture of blood and injectate; 1.08 is a constant of the saline solution.

Informed consent was obtained from all patients before each test. No complications were observed during the procedures.

## Results

**Clinical features:** Eleven patients were men and 1 a woman, with an average age of 52.7 years (range 38 to 62). In 8 patients, anginal attacks at rest were associated with S-T segment elevation, occurring in the anterior leads in 4 patients and in the inferior leads in 4, whereas 1 patient had episodes associated with either S-T segment elevation or depression in the anterior leads. Three patients showed S-T segment depression in the anterior leads during chest pain at rest. In 6 patients, angina was of recent onset (<3 months).

**Exercise tests (Table I):** Four patients (Cases 2, 4, 7, and 10) had 1 negative test and 2 positive tests; 1 patient (Case 3) had 2 negative tests and 1 positive test. Seven patients had all 3 positive tests. Chest pain occurred during all 3 exercise tests in 3 patients, while 8 patients had at least 1 exercise test ended because of exhaustion. In 1 patient the end point was angina in 2 tests and S-T segment depression >3 mm without angina in the third test.

S-T segment elevation was observed in 2 patients (Cases 3 and 4) during 1 exercise test and in 1 patient (Case 5) during 2 tests. In 6 patients (Cases 1, 6, 8, 9, 11, and 12) all 3 exercise tests induced S-T segment depression. In 5 of these patients, S-T segment depression occurred at different work loads with a wide range of values of double product. One illustrative case is shown in Figure 1. In 1 patient (Case 8) exercise tolerance did not change substantially during the 3 tests; however S-T depression was more marked during the first than during the second exercise test although a higher value of double product was attained during the latter.

**Angiographic features:** No patient had akinetic or dyskinetic areas of the left ventricle. The average ejection fraction was 59 ± 7 and the average left ventricular end-diastolic pressure was 12.5 ± 5 mm Hg. Coronary

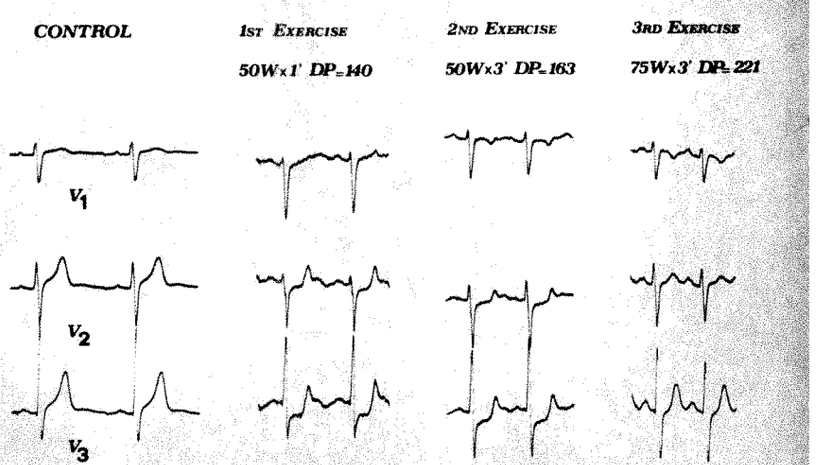



**FIGURE 1.** Case 11. Three exercise tests performed in the morning on different days yielded different results. The first and second tests induced chest pain and S-T segment depression, whereas the third test was negative despite a higher double product. DP = double product (mm Hg × beats/min × $10^{-2}$).

# Cardiovascular Disease in the Very Elderly

## Analysis of 40 Necropsy Patients Aged 90 Years or Over

BRUCE F. WALLER, MD and WILLIAM C. ROBERTS, MD

**Clinical and necropsy observations are described in 40 patients (29 women) aged 90 years and older. The majority (21 patients [57%]) died during the 4 coldest months, and 12 (30%), during the 4 warmest months. At necropsy, 39 had ≥1 major cardiac abnormalities, the most frequent being calcific deposits in the major epicardial coronary arteries in 37 (92%). In 28 patients (70%), 1 or more of the 4 major arteries was narrowed 76 to 100% in cross-sectional area (XSA) by atherosclerotic plaques, an average of 1.9/4.0 per patient: the 12 patients with clinical events compatible with myocardial ischemia (angina pectoris or myocardial infarction) had an average of 2.2/4 and the other 28 patients an average of 1.0/4.0. In 36 patients, a histologic section was examined from each 5 mm long segment from each of the 4 major coronary arteries: of the 1,789 segments, only 6 (<1%) were narrowed 96 to 100% in XSA by plaques; 147 (8%), 76 to 95%; 339 (19%), 51 to 75%; 930 (52%), 26 to 50%, and 367 (21%), 0 to 25%. The average amount of XSA narrowing for the 1,789 segments was about 42%. In 10 patients with clinical evidence of myocardial ischemia, the average amount of narrowing per segment was approximately 55%; in the 26 patients without clinical ischemia, the average was about 38%. Of the 40 patients, 18 (45%) had left ventricular transmural foci of fibrosis or necrosis or both. Of 14 patients with transmural scars, only 1 had a clinical event compatible with acute myocardial infarction; of the 10 with acute myocardial infarction at necropsy, only 4 had typical clinical features of infarction.**

**Calcific deposits were present in ≥1 aortic valve cusps in 22 patients (55%), causing aortic valve stenosis in 2, and in the mitral anulus in 19 (47%), probably causing mitral valve stenosis in 1.**

**Amyloid deposits were present in the heart in at least 9 patients; they were grossly visible and caused fatal cardiac dysfunction in 4, and microscopically visible only in 5, causing no cardiac dysfunction. Eight patients (20%) had chronic congestive heart failure; 27 of 39 (69%) had either a history of systemic hypertension or blood pressure >140/90 mm Hg during their final year of life. Precordial murmurs were recorded in 25 (62%) patients—systolic only in 24 and both systolic and diastolic in 1. Data from electrocardiograms were available in 30 patients: 12 (40%) had atrial fibrillation; 12 (40%), abnormal axis; 12, complete bundle branch block; 1, criteria for left ventricular hypertrophy (despite increased cardiac mass in 67%); and 1, low voltage.**

**All patients had fairly extensive atherosclerosis of the aorta, with aneurysmal formation in 5 with fatal rupture in 3. Five had strokes, which were fatal in 4. At least 5 had leg claudication. Two had massive pulmonary emboli superimposed on chronic obstructive pulmonary disease.**

**Thus, cardiovascular disease was present at necropsy in 39 of our 40 patients, but frequently it was not diagnosed clinically.**

Although the average age at death has increased dramatically during this century, the maximal length of life has not changed.[1] The percentage of individuals surviving for 90 years and beyond, however, is increasing.[2] In 1980, about 1% of the population in the United States was aged 90 years or older.[2] Very few necropsies are performed in patients dying after age 90 years (frequency about 4%)[3] and, therefore, little attention has been focused on the clinical and morphologic frequencies and types of cardiovascular disease observed in these very elderly persons. This report describes the types of cardiovascular disease found at necropsy in 40 patients aged 90 years or over.

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### Patients

**General observations:** Clinical and morphologic observations in the 40 patients are detailed in Table I. The patients died and underwent necropsy at 12 different hospitals (10 in the Washington, D.C. area [37 patients]); subsequently the heart and frequently the aortas were examined in all 40 patients by 1 of us (WCR). The year of death in 37 patients was between

**TABLE I Clinical and Morphologic Observations in 40 Necropsy Patients Aged 90 to 103 Years**

| Case | Age (yr) & Sex | Race | CP | AP | AMI | AD | CCHF | DM | Hx SH | SAP (mm Hg) | Electrocardiogram | | | | | | TC (mg/100 ml) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | BBB | | QRS Axis | | |
| | | | | | | | | | | | S | AF | R | L | R | L | |
| 1 | 90F | W | + | 0 | + | 0 | 0 | 0 | + | 145/70 | 0 | + | 0 | + | 0 | + | – |
| 2 | 90F | W | + | + | + | 0 | 0 | + | 0 | 120/80 | 0 | 0 | – | – | – | – | – |
| 3 | 90M | B | + | 0 | + | + | 0 | 0 | + | 140/70 | 0 | + | 0 | + | 0 | 0 | 236 |
| 4 | 90M | B | 0 | 0 | 0 | + | + | 0 | 0 | 110/70 | 0 | + | 0 | + | 0 | + | 250 |
| 5 | 90F | W | + | 0 | + | + | 0 | + | + | 118/80 | 0 | + | 0 | + | 0 | 0 | – |
| 6 | 90F | W | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 118/70 | 0 | 0 | 0 | 0 | 0 | 0 | – |
| 7 | 90F | W | 0 | 0 | 0 | 0 | 0 | 0 | + | 170/90 | 0 | 0 | 0 | 0 | 0 | 0 | 223 |
| 8 | 90F | W | 0 | 0 | 0 | 0 | 0 | 0 | + | 80/60 | 0 | 0 | 0 | 0 | 0 | 0 | – |
| 9 | 91F | B | 0 | 0 | 0 | 0 | 0 | + | + | 84/– | 0 | 0 | 0 | 0 | 0 | 0 | – |
| 10 | 91M | B | 0 | 0 | 0 | 0 | 0 | 0 | + | 140/90 | 0 | + | 0 | 0 | 0 | 0 | – |
| 11 | 91F | B | 0 | 0 | 0 | 0 | 0 | 0 | + | 95/60 | 0 | 0 | 0 | 0 | 0 | 0 | – |
| 12 | 91M | W | 0 | 0 | 0 | 0 | 0 | 0 | + | 116/85 | + | + | 0 | 0 | 0 | 0 | – |
| 13 | 91F | W | + | 0 | + | + | 0 | 0 | + | 120/60 | 0 | – | – | – | – | – | 283 |
| 14 | 92F | W | + | + | 0 | + | + | 0 | 0 | 110/70 | 0 | + | + | 0 | + | 0 | – |
| 15 | 92F | W | 0 | 0 | 0 | 0 | 0 | 0 | + | 230/110 | 0 | 0 | 0 | 0 | 0 | + | – |
| 16 | 92F | W | + | 0 | + | 0 | 0 | 0 | 0 | . . . | 0 | – | – | – | – | – | – |
| 17 | 92F | W | 0 | 0 | 0 | + | + | 0 | + | 100/50 | 0 | + | 0 | 0 | 0 | 0 | – |
| 18 | 93F | W | 0 | 0 | 0 | + | 0 | 0 | + | . . . | 0 | – | – | – | – | – | – |
| 19 | 93M | W | + | 0 | + | + | 0 | 0 | + | 170/60 | 0 | – | – | – | – | – | – |
| 20 | 93F | B | + | 0 | + | + | 0 | + | + | 135/60 | 0 | – | – | – | – | – | 243 |
| 21 | 93F | W | 0 | 0 | 0 | + | + | 0 | + | 120/70 | 0 | 0 | 0 | + | 0 | + | – |
| 22 | 93F | W | 0 | 0 | + | + | + | 0 | + | 125/80 | 0 | – | – | – | – | – | 273 |
| 23 | 95F | W | + | 0 | + | + | 0 | 0 | 0 | 110/70 | 0 | – | – | – | – | – | – |
| 24 | 95F | W | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 140/60 | 0 | 0 | 0 | 0 | 0 | 0 | – |
| 25 | 95F | W | + | 0 | 0 | 0 | 0 | + | + | 125/100 | 0 | 0 | 0 | 0 | 0 | + | – |
| 26 | 95M | B | + | 0 | 0 | + | 0 | 0 | + | 120/115 | 0 | + | + | 0 | + | + | – |
| 27 | 96M | W | 0 | 0 | 0 | + | + | 0 | + | 90/70 | 0 | + | + | 0 | 0 | + | – |
| 28 | 95M | W | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 130/70 | 0 | 0 | 0 | + | 0 | + | 181 |
| 29 | 95F | W | 0 | 0 | 0 | 0 | 0 | 0 | + | . . . | 0 | + | + | 0 | + | 0 | 235 |
| 30 | 96F | B | 0 | 0 | 0 | + | +† | 0 | + | 140/90 | + | – | – | – | – | – | 108 |
| 31 | 97F | W | 0 | 0 | 0 | 0 | 0 | 0 | + | 118/75 | + | + | 0 | 0 | 0 | 0 | – |
| 32 | 97F | W | 0 | 0 | 0 | + | 0 | 0 | 0 | 140/60 | 0 | 0 | 0 | 0 | 0 | 0 | – |
| 33 | 97F | W | 0 | 0 | 0 | 0 | 0 | 0 | 0 | . . . | + | 0 | 0 | 0 | 0 | 0 | – |
| 34 | 97M | W | 0 | 0 | 0 | + | + | 0 | + | . . . | 0 | 0 | 0 | 0 | 0 | 0 | – |
| 35 | 98F | W | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 130/85 | 0 | 0 | 0 | 0 | 0 | 0 | – |
| 36 | 98F | W | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 170/80 | 0 | 0 | 0 | + | 0 | + | 165 |
| 37 | 99M | W | + | + | 0 | 0 | 0 | 0 | + | 130/85 | + | 0 | 0 | 0 | 0 | 0 | – |
| 38 | 100F | W | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 170/80 | 0 | – | – | – | – | – | – |
| 39 | 100M | W | 0 | 0 | 0 | 0 | 0 | 0 | 0 | . . . | 0 | 0 | 0 | 0 | 0 | 0 | – |
| 40 | 103F | B | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 110/70 | 0 | 0 | + | 0 | 0 | + | – |
| Total or mean | (94) | | 13 (32%) | 3 (7%) | 10 (25%) | 17 (42%) | 7 (17%) | 5 (12%) | 25 (62%) | . . . . . | 4 (10%) | 12 (40%) | 5 (17%) | 7 (23%) | 3 (7%) | 10 (33%) | 220 . . . |

* Aortic valve stenosis.

† Idiopathic dilated cardiomyopathy.

A = cardiac amyloidosis (++ = massive, grossly visible deposits; + = minute, visible on microscope only); AD = abnormal dyspnea; AF = atrial fibrillation; AMI = acute myocardial infarction clinically; AP = angina pectoris; AV = aortic valve cusp; BBB = bundle branch block; BW = body weight; C = cardiac; CA = coronary artery; CCHF = chronic congestive heart failure; CP = chest pain; DM = diabetes mellitus; F = fibrosis; FAAA = fusiform abdominal aortic aneurysm; HW = heart weight; Hx = history; L = left; LAD = left anterior descending; LC = left circumflex; LV = left ventricular; MCS = mean coronary score; MVA = mitral valve anulus; N = necrosis; O = other; PHD = pericardial heart disease; R = right; S = stroke; SAP = systemic arterial pressure; SH = systemic hypertension; TC = total serum cholesterol; V = vascular.

**TABLE I (continued)**

| Case | Mode of Death | | | BW (kg) | HW (g) | Calcific Deposits | | | (%) 5 mm Segments Narrowed to Various Degrees | | | | MCS | Transmural LV | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C | V | O | | | CA | MVA | AV | 0–25 | 26–50 | 51–75 | 76–100 | | N | F | A | PHD | FAAA |
| 1 | + | 0 | 0 | 55 | 550 | 3+ | 3+ | 4 + a | 0 | 17(39) | 21(49) | 5(12) | 2.72 | + | 0 | 0 | 0 | 0 |
| 2 | + | 0 | 0 | 41 | 340 | 2+ | 0 | 0 | . . . | . . . | . . . | . . . | . . . | + | 0 | 0 | 0 | 0 |
| 3 | + | 0 | 0 | 50 | 450 | 2+ | 0 | 2+ | 9(18) | 16(31) | 12(24) | 13(27) | 2.58 | + | + | 0 | 0 | 0 |
| 4 | + | 0 | 0 | – | 520 | 1+ | 3+ | 1+ | 29(53) | 24(44) | 2(3) | 0 | 1.51 | 0 | 0 | ++ | 0 | 0 |
| 5 | + | 0 | 0 | 45 | 400 | 2+ | 2+ | 1+ | 16(26) | 24(39) | 11(18) | 10(17) | 2.25 | + | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | + | 45 | 220 | 1+ | 1+ | 2+ | 16(37) | 13(30) | 11(26) | 3(7) | 1.89 | 0 | 0 | 0 | 0 | 0 |
| 7 | 0 | 0 | + | 47 | 270 | 1+ | 0 | 1+ | 6(16) | 25(68) | 5(13) | 1(3) | 2.03 | 0 | 0 | 0 | 0 | 0 |
| 8 | 0 | + | 0 | 50 | 505 | 2+ | 0 | 0 | 0 | 19(40) | 15(32) | 12(28) | 2.85 | 0 | + | 0 | 0 | + |
| 9 | 0 | 0 | + | 60 | 480 | 2+ | 0 | 0 | . . . | . . . | . . . | . . . | . . . | 0 | 0 | + | 0 | 0 |
| 10 | 0 | + | 0 | – | 490 | 1+ | 0 | 1+ | 33(72) | 13(28) | 0 | 0 | 1.28 | 0 | 0 | 0 | 0 | 0 |
| 11 | 0 | + | 0 | 46 | 375 | 4+ | 4+ | 0 | 9(14) | 40(64) | 12(19) | 2(3) | 2.11 | 0 | 0 | 0 | 0 | 0 |
| 12 | + | 0 | 0 | 65 | 390 | 2+ | 0 | 1+ | 16(26) | 24(39) | 11(18) | 10(17) | 2.25 | 0 | + | 0 | 0 | 0 |
| 13 | + | 0 | 0 | – | 520 | 2+ | 0 | 0 | 11(17) | 24(37) | 16(25) | 13(21) | 2.48 | + | + | 0 | 0 | + |
| 14 | + | 0 | 0 | 49 | 380 | 1+ | 1+ | 1+ | 10(25) | 17(43) | 8(20) | 5(12) | 2.20 | 0 | + | 0 | + | 0 |
| 15 | 0 | 0 | + | 50 | 400 | 1+ | 1+ | 1+ | 19(33) | 39(67) | 0 | 0 | 1.67 | 0 | 0 | 0 | 0 | 0 |
| 16 | + | 0 | 0 | 85 | 280 | 2+ | 3+ | 1+ | 0 | 30(70) | 8(18) | 5(12) | 2.42 | + | 0 | 0 | 0 | 0 |
| 17 | + | 0 | 0 | 55 | 525 | 2+ | 4+ | 4+* | 3(7) | 37(80) | 6(13) | 0 | 2.07 | 0 | 0 | 0 | 0 | 0 |
| 18 | 0 | 0 | + | – | 500 | 3+ | 1+ | 2+ | 15(23) | 46(72) | 2(3) | 1(2) | 1.83 | 0 | + | 0 | 0 | 0 |
| 19 | + | 0 | 0 | 66 | 470 | 2+ | 0 | 1+ | 6(14) | 14(33) | 15(35) | 8(18) | 2.58 | + | + | 0 | 0 | 0 |
| 20 | + | 0 | 0 | – | 510 | 1+ | 0 | 0 | 0 | 18(24) | 18(42) | 18(34) | 3.08 | + | + | 0 | 0 | 0 |
| 21 | + | 0 | 0 | – | 380 | 1+ | 0 | 0 | 22(48) | 20(43) | 4(9) | 0 | 1.61 | 0 | 0 | ++ | 0 | 0 |
| 22 | + | 0 | 0 | 67 | 560 | 3+ | 3+ | 2+ | 7(15) | 12(26) | 14(31) | 12(28) | 2.69 | + | + | 0 | 0 | 0 |
| 23 | + | 0 | 0 | – | 490 | 1+ | 0 | 0 | . . . | . . . | . . . | . . . | . . . | + | + | 0 | 0 | 0 |
| 24 | 0 | 0 | + | 58 | 350 | 1+ | 4+ | 1+ | 3(6) | 31(65) | 12(25) | 2(4) | 2.27 | 0 | 0 | 0 | 0 | 0 |
| 25 | 0 | + | 0 | – | 460 | 2+ | 0 | 0 | 18(49) | 19(51) | 0 | 0 | 1.51 | 0 | 0 | 0 | 0 | + |
| 26 | 0 | + | 0 | 47 | 580 | 2+ | 0 | 0 | 5(8) | 36(59) | 19(31) | 1(2) | 2.26 | 0 | 0 | 0 | 0 | 0 |
| 27 | + | 0 | 0 | 50 | 660 | 3+ | 2+ | 2+ | 9(12) | 44(59) | 15(20) | 7(9) | 2.27 | 0 | + | ++ | 0 | 0 |
| 28 | 0 | 0 | + | – | 385 | 2+ | 0 | 1+ | 12(19) | 32(52) | 16(26) | 2(3) | 2.13 | 0 | 0 | 0 | 0 | 0 |
| 29 | 0 | 0 | + | 52 | 440 | 2+ | 2+ | 1+ | 2(3) | 48(69) | 15(22) | 4(6) | 2.30 | 0 | + | + | 0 | 0 |
| 30 | + | 0 | 0 | 50 | 630 | 0 | 0 | 0 | 15(31) | 33(69) | 0 | 0 | 1.69 | 0 | 0 | 0 | 0 | 0 |
| 31 | 0 | + | 0 | 45 | 300 | 2+ | 4+ | 1+ | 11(29) | 17(45) | 9(24) | 1(2) | 2.00 | 0 | 0 | 0 | 0 | 0 |
| 32 | 0 | 0 | + | 55 | 360 | 2+ | 3+ | 0 | 19(36) | 29(55) | 3(5) | 2(4) | 1.77 | 0 | 0 | 0 | 0 | 0 |
| 33 | 0 | + | 0 | 41 | 320 | 2+ | 3+ | 0 | 8(18) | 29(66) | 7(16) | 0 | 1.98 | 0 | 0 | 0 | 0 | 0 |
| 34 | + | 0 | 0 | 68 | 600 | 3+ | 1+ | 1+ | 2(5) | 24(62) | 8(20) | 5(13) | 2.41 | 0 | 0 | ++ | + | + |
| 35 | 0 | 0 | + | 53 | 360 | 0 | 0 | 0 | . . . | . . . | . . . | . . . | . . . | 0 | 0 | 0 | 0 | 0 |
| 36 | 0 | 0 | + | 52 | 320 | 1+ | 0 | 0 | 8(27) | 21(70) | 1(3) | 0 | 1.77 | 0 | 0 | 0 | 0 | 0 |
| 37 | + | 0 | 0 | 50 | 510 | 2+ | 0 | 0 | 5(11) | 22(47) | 15(32) | 5(10) | 2.43 | 0 | + | 0 | 0 | 0 |
| 38 | 0 | + | 0 | 45 | 280 | 4+ | 2+ | 2+ | 0 | 23(58) | 12(30) | 4(12) | 2.51 | 0 | 0 | + | 0 | 0 |
| 39 | 0 | 0 | + | – | 335 | 2+ | 0 | 1+ | 18(32) | 21(37) | 16(28) | 2(3) | 2.04 | 0 | + | + | 0 | 0 |
| 40 | 0 | 0 | + | 55 | 345 | 0 | 0 | 0 | 5(11) | 41(89) | 0 | 0 | 1.89 | 0 | 0 | + | 0 | 0 |
| Total (Mean) | 19 (47%) | 8 (20%) | 13 (32%) | (53) . . . | 431 . . . | 37 (92%) | 19 (47%) | 22 (55%) | 367 (21%) | 930 (52%) | 339 (19%) | 153 (8%) | 2.15 . . . | 10 (25%) | 14 (35%) | 4 (10%) | 2 (5%) | 4 (10%) |

1967 and 1982; the other 3 patients had been studied both clinically and at necropsy at the National Institutes of Health in 1954, 1966, and 1967, respectively. The month of death was known in 37 patients: death occurred during 4 cold months (November to February) in 21 (57%); during 4 warm months (June to September) in 11 (30%), and during intermediate weather months in 5 (13%) ($p < 0.05$). (The data throughout this study were analyzed using the $t$ test for paired and unpaired data and linear regression tests to determine correlation coefficients.) The ages of death in the 40 patients ranged from 90 to 103 (mean 94); 29 (72%) were women and 11 (28%) were men; 31 (78%) were white and 9 (22%) were black.

**TABLE II Morphologic Cardiac Observations in 40 Necropsy Patients Aged 90 to 103 Years**

| | Patients | |
|---|---|---|
| | n | % |
| Coronary arterial disease | | |
| Calcium | 37 | 92 |
| Luminal narrowing 76 to 100% in XSA by atherosclerotic plaques of ≥1 major coronary arteries | 28 | 70 |
| Acute myocardial infarction | 10 | 25 |
| Healed myocardial infarction | 14 | 35 |
| Aortic valve disease | | |
| Calcium | 22 | 55 |
| Stenosis | 2 | 5 |
| Mitral anular disease | | |
| Calcium | 19 | 47 |
| Cardiac amyloidosis (fatal) | 4 | 10 |
| Dilated cardiomyopathy | 1 | 3 |
| Obliterative pericardial disease | | |
| Idiopathic | 1 | 5 |
| Iatrogenic | 1 | 5 |

*Heart weights and body weights:* The weight of the heart was increased (>350 g in women and >400 g in men) in 27 (67%) patients. The hearts in the 29 women ranged from 220 to 630 g (mean 408), and those in the 11 men, from 335 to 660 g (mean 490). The body weights in the 23 women ranged from 41 to 85 kg (mean 52) and the heart weight-body weight ratio, from 0.003 to 0.013 (mean 0.007). Thus, the mean heart weight was 0.7% of the body weight (normal value for younger women is approximately 0.4%[4]). The body weights in 7 men ranged from 47 to 68 kg (mean 50) and the heart weight-body weight ratios, from 0.006 to 0.013 (mean 0.009). Thus, the mean heart weight was 0.6% of the mean body weight (the normal value for younger men is approximately 0.45%[4]).

**Necropsy observations (Table II):** *Coronary arterial calcification (Fig. 1 to 6):* Calcific deposits within atherosclerotic plaques were observed grossly in the epicardial coronary arteries in 37 (92%) patients. In 28 patients, radiograms of the heart or of the excised coronary arteries were performed; all patients had calcific deposits in the coronary arteries: 23 (82%), in the left anterior descending, left circumflex, and right coronary arteries, and the other 5 patients, in 2 of these 3 major

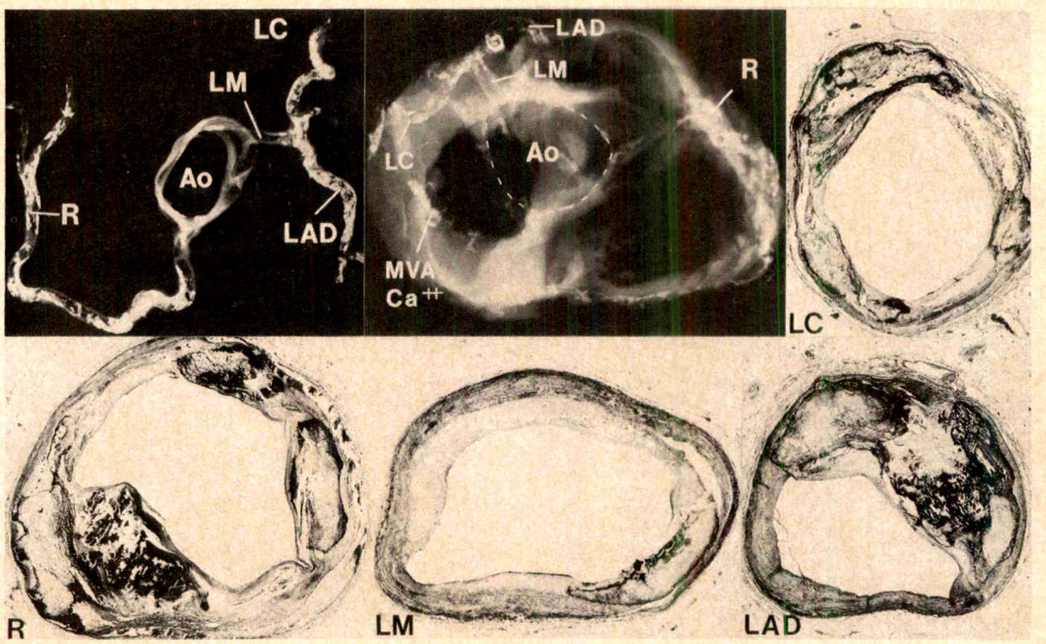



**FIGURE 1.** Patient 29 (SH #A80-74). Tortuous and heavily calcified coronary arteries in a 95-year-old woman who never had symptoms of cardiac dysfunction and who died from a perforated gastric ulcer. **Top left,** postmortem radiogram of the excised right (R), left main (LM), left anterior descending (LAD), and left circumflex (LC) coronary arteries. **Top center,** radiogram of a portion of the heart after removing the walls of the atria and most of the walls of the ventricles. MVA = mitral valve anulus. **Top right and lower panels,** photomicrographs of coronary arteries at sites of maximal narrowing by calcified atherosclerotic plaques. (Movat stains; magnification ×17, reduced 40%.) This case illustrates extensive calcific deposits in the coronary arteries without significant luminal narrowing.

coronary arteries. In 23 of the 28 patients, the left main coronary artery was studied radiographically: 18 (78%) had calcific deposits. Thus, of 112 major epicardial coronary arteries studied radiographically in 28 patients, 97 (87%) were seen to contain calcific deposits. Of the 37 patients with demonstrated calcific deposits in the epicardial coronary arteries, 26 (70%) also had calcific deposits in either aortic valve cusps or mitral anulus or both. Of the 3 patients without calcium in the coronary arteries, none had calcific deposits in either aortic valve cusps on mital anulus (Fig. 7 and 8).

*Coronary arterial atherosclerosis (qualitative studies):* At necropsy, 39 of the 40 patients had ≥1 significant cardiac conditions on *gross* examination. One or more of the 4 major (right, left main, left anterior descending, left circumflex) epicardial coronary arteries was narrowed 76 to 100% in XSA by atherosclerotic plaques in 28 (70%) patients; 37 (92%) had grossly palpable calcific deposits in ≥1 major coronary arteries. None of the 28 patients had significant (>75% in XSA) narrowing in the left main coronary artery. Of the other 3 major coronary arteries, 1 was significantly narrowed in 8 patients (29%), 2 were narrowed 76 to 100% by plaques in 15 patients (53%), and 3 arteries were so narrowed in 5 patients (18%). Of the 112 major coronary arteries in these 28 patients, 53 were significantly narrowed, an average of 1.9/4 major coronary arteries per patient. Of the 160 major coronary arteries in the 40 patients, the average number narrowed per patient was 1.3.

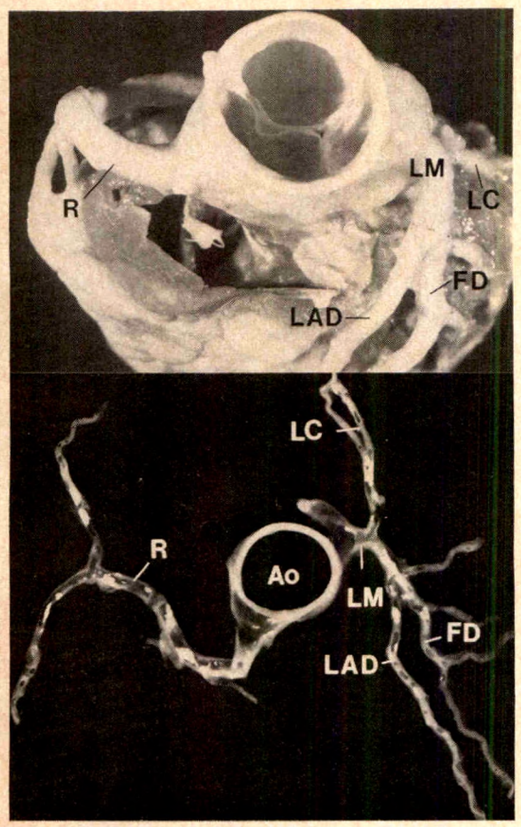



**FIGURE 2.** Patient 28 (SH #A79-77). Coronary arteries in a 95-year-old man who never had symptoms of cardiac dysfunction and who died from cancer. **Top,** aorta and coronary arteries from above. **Bottom,** radiograms of aortic root (Ao) and excised coronary arteries which contain calcific deposits. FD = first diagonal; LAD = left anterior descending; LC = left circumflex; LM = left main; R = right.

Of the 12 patients *with clinical evidence of myocardial ischemia* (angina pectoris or a clinical event diagnosed as or compatible with acute myocardial infarction or both), at least 1 of the 4 major coronary arteries was narrowed 76 to 100% in XSA by plaques: in 10 patients, 2 arteries (right, left anterior descending, or left circumflex) were so narrowed and in the other 2 patients, 3 arteries. Thus, of the 48 major coronary arteries (4 per patient) in these 12 patients, 26 arteries were significantly narrowed, an average of 2.2/4.0 per patient.

Of the 28 patients *without clinical evidence of myocardial ischemia*, at least 1 of the 4 major coronary arteries was narrowed 76 to 100% in XSA by atherosclerotic plaques in 16 patients (57%): in 8 patients, only 1 artery was so narrowed; in 5 patients, 2 arteries; and in 4 patients, 3 arteries. In 12 patients (43%), none of the 4 major coronary arteries was significantly narrowed. Thus, of the 112 major coronary arteries in these 28 patients, 27 (24%) were significantly narrowed, an average of 1.0/4.0 per patient.

*Coronary arterial atherosclerosis (quantitative studies):* In 36 patients, including 26 of the 28 in whom 1 or more of the 4 major coronary arteries were significantly narrowed and in 10 of the 12 in whom none of the 4 arteries was significantly narrowed, each of the 4 major coronary arteries was decalcified and cut into 5 mm long segments. Each segment was processed in alcohols and xylene, and imbedded in paraffin. At least 1 histologic section was cut and stained by the Movat method from each segment. Of the 1,789 5 mm segments from the 36 patients (an average of 49 segments per patient [range 30 to 75]), 6 (<1%) were narrowed 96 to 100% in XSA by atherosclerotic plaques; 147 (8%), 76 to 95%; 339 (19%), 51 to 75%; 930 (52%), 26 to 50%; and 367 (21%), 0 to 25%.

*A scoring system* was utilized to indicate the severity of the coronary narrowing. Every 5 mm long segment was assigned a score of 1 to 4 based on the amount of XSA narrowing by atherosclerotic plaques as follows: 1 = 0 to 25%, 2 = 26 to 50%, 3 = 51 to 75%, and 4 = 76 to 100% narrowing. A total score was obtained for each patient. The mean score per 5 mm segment was then calculated by dividing the total score per patient by the number of segments examined. The total scores for the 36 patients ranged from 53 to 170 (average 107) and the mean score per 5 mm segment, from 1.28 to 3.08 (average 2.15) (Fig. 9). This mean score indicates that each of the 1,789 5 mm segments was narrowed on an average of about 42% in XSA (Fig. 9).

Of the 40 patients, 12 had clinical evidence of myocardial ischemia. Of these 12 patients, the 4 major epicardial coronary arteries were available in their entirety for quantitative studies in 10. Of 467 5 mm coronary segments in these 10 patients, 2 (<1%) were narrowed 96 to 100% in XSA by atherosclerotic plaques; 90 (19%), 76 to 95%; 135 (29%), 51 to 75%; 198 (43%), 26 to 50%;

and 42 (9%), 0 to 25% (Fig. 10). The total score for each of the 10 patients ranged from 88 to 159 (average 120) and the mean score per 5 mm segment of coronary artery, from 2.20 to 3.08 (average 2.59), indicating that each 5 mm segment was narrowed an average of approximately 55% in XSA.

Of the 28 patients without clinical evidence of myocardial ischemia, the 4 major coronary arteries were available for quantitative studies in 26. Of 1,322 5 mm coronary segments examined in these patients, 4 (<1%) were narrowed 96 to 100% in XSA by atherosclerotic plaques; 63 (5%) were narrowed 76 to 95%; 206 (16%), 51 to 75%; 727 (55%), 26 to 50%; and 322 (24%), 0 to 25% (Fig. 10). The total score for each patient ranged from 53 to 170 (average 98) and the mean score per 5 mm segment, from 1.28 to 2.85 (average 2.01) (Fig. 9), indicating that each of the 1,322 5 mm segments was narrowed an average of about 38% in XSA. Of these 26 patients, ≥1 of the 4 major coronary arteries was significantly narrowed in 16. Of the 857 5 mm coronary segments examined in the 26 patients, 4 segments (<1%) had lumens narrowed 96 to 100% in XSA by plaques; 63 (7%), 76 to 95%; 183 (22%), 51 to 75%; 464 (54%), 26 to 50%; and 143 (17%), 0 to 25%. The total score for each of the 16 patients ranged from 56 to 170 (average 111) and the mean score per 5 mm segment, from 1.77 to 2.85 (mean 2.20). Thus, each of the 857 5 mm segments was narrowed an average of approximately 44% in XSA. In

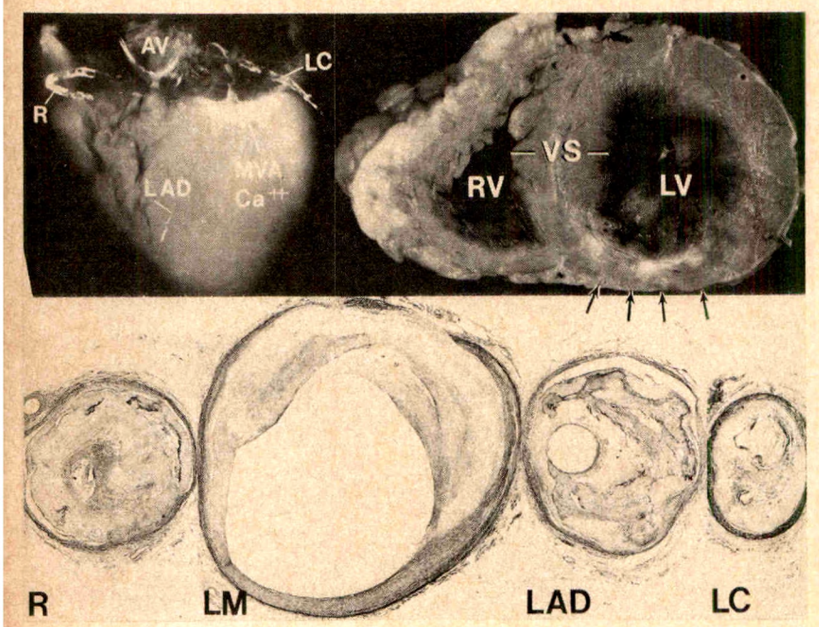



**FIGURE 3.** Patient 22 (LRC #5). Heart and coronary arteries in a 93-year-old woman who was hospitalized with worsening chronic congestive heart failure. **Top left,** postmortem radiogram showing calcific deposits in the right (R), left anterior descending (LAD), and left circumflex (LC) coronary arteries and in the mitral valve anulus (MVA) and aortic valve. **Top right,** view of right (RV) and left (LV) ventricles and ventricular septum (VS) showing a transmural scar (**arrows**). **Bottom,** coronary arteries at sites of maximal narrowing. LM = left main. (Movat stains; magnification ×17, reduced 40%.)

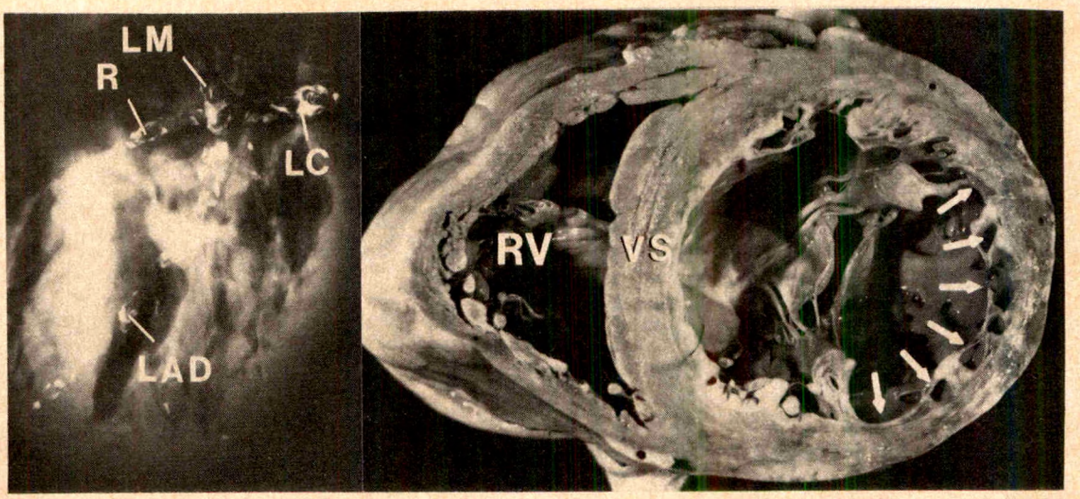



**FIGURE 4.** Patient 13 (LRC #3). This 91-year-old woman had a "typical" clinical acute myocardial infarct, which was fatal. **Left,** postmortem radiogram showing calcific deposits in the right (R), left main (LM), left anterior descending (LAD), and left circumflex (LC) coronary arteries. **Right,** view of left and right (RV) ventricles showing transmural necrosis and fibrosis (**arrows**) and dilated ventricles. VS = ventricular septum.

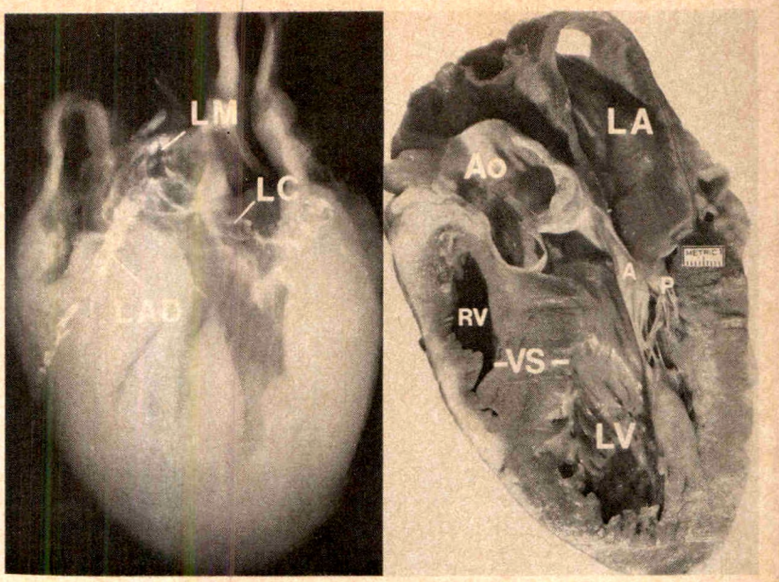



**FIGURE 5.** Patient 8 (SH #A82-1). This 90-year-old woman had no symptoms of cardiac dysfunction and died from a ruptured fusiform abdominal aortic aneurysm. **Left,** postmortem radiogram of the entire heart showing calcific deposits in the left anterior descending (LAD), left circumflex (LC), and left main (LM) coronary arteries. **Right,** view of heart cut in an anteroposterior fashion (M-mode or long-axis 2-dimensional echocardiographic view) showing a dilated left atrium (LA) and left ventricle (LV). A and P = anterior and posterior mitral valve leaflets; Ao = aorta; RV = right ventricle; VS = ventricular septum.

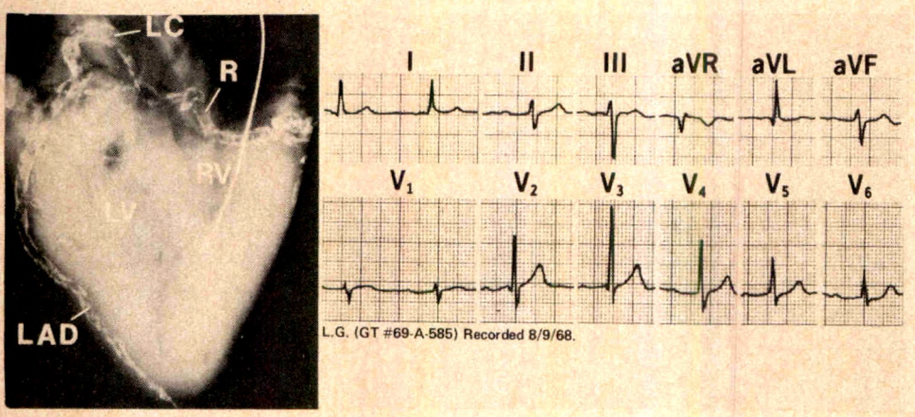



**FIGURE 6.** Patient 34 (GT #69A-585). This 97-year-old man had complete heart block and had a pacemaker inserted when he was 91 years old. **Left,** radiogram of heart at necropsy showing calcific deposits in the left anterior descending (LAD), left circumflex (LC), and right (R) coronary arteries, and a pacemaker wire in the right ventricle (RV). LV = left ventricle. **Right,** electrocardiogram.

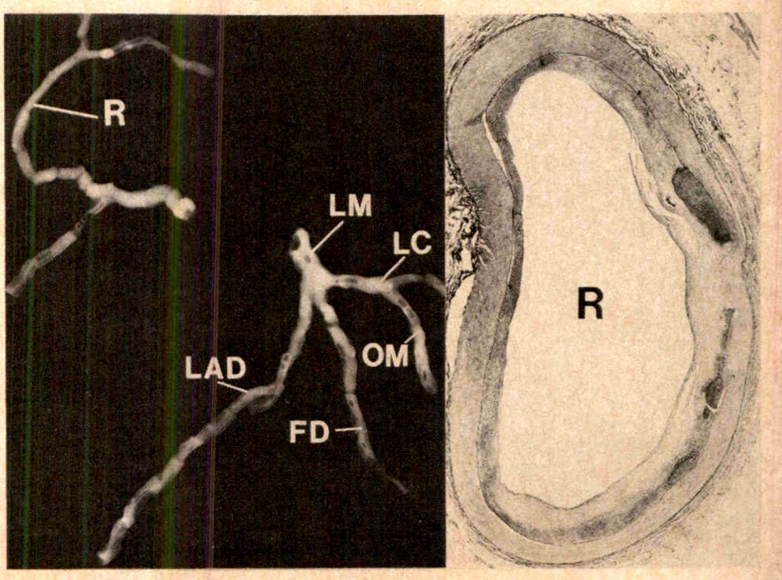



**FIGURE 7.** Patient 30 (DCGH #68A80). This 96-year-old woman had chronic congestive heart failure from dilated cardiomyopathy. Her total serum cholesterol level was 108 mg/dl. **Left,** postmortem radiogram of the right (R), left main (LM), left anterior descending (LAD), left circumflex (LC), first diagonal (FD), and left obtuse marginal (OM) coronary arteries showing no calcific deposits. **Right,** right coronary artery section devoid of calcium or narrowing. (Movat stain; magnification ×16, reduced 23%.)

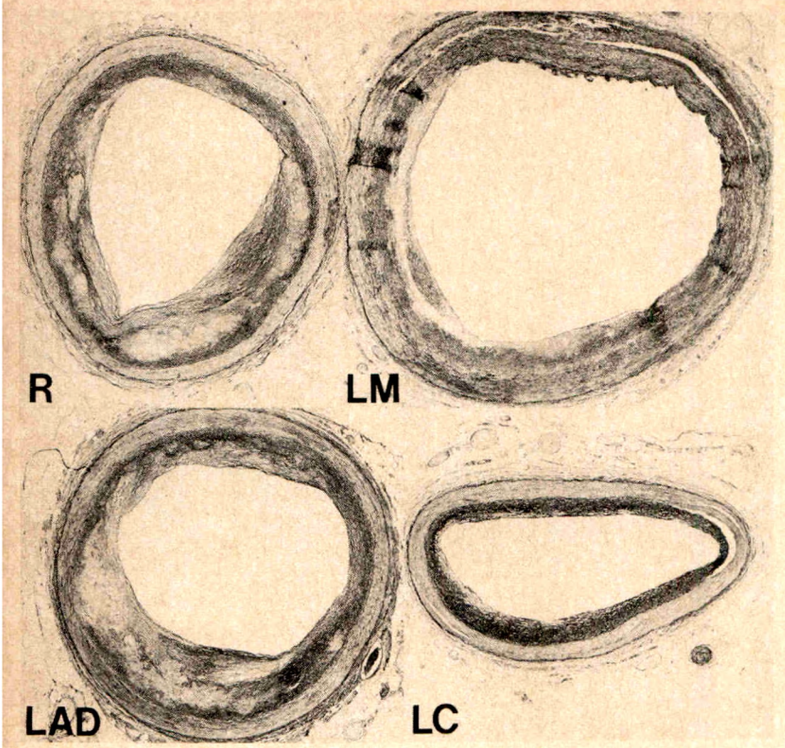



**FIGURE 8.** Patient 40 (GT #70A301). Right (R), left main (LM), left anterior descending (LAD), and left circumflex (LC) coronary arteries at sites of maximal narrowing in a 103-year-old woman. She never had evidence of cardiac dysfunction and died from complications of a duodenal ulcer. The coronary arteries are devoid of calcium and of significant narrowing. (Elastic van Gieson's stain; magnification ×16, reduced 31%.)

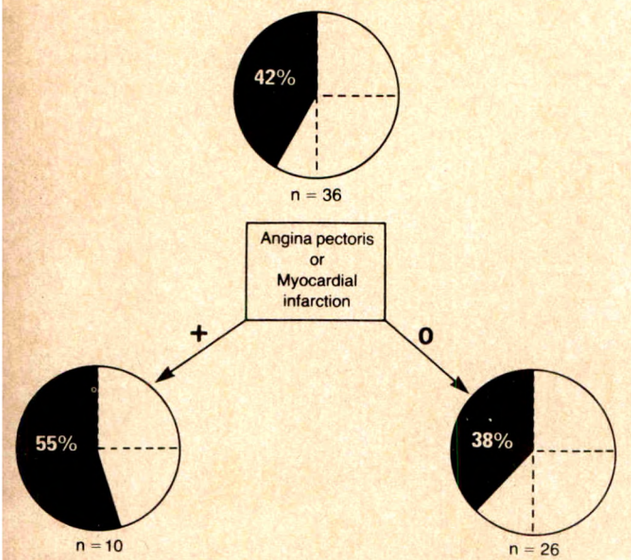



**FIGURE 9.** Mean percent cross-sectional area narrowing by atherosclerotic plaques in 1,789 5 mm segments of the 4 major epicardial coronary arteries in 36 necropsy patients aged 90 years and older, 10 of whom had angina pectoris or acute myocardial infarction or both and 26 of whom did not. The mean percentage of narrowing for each 5 mm segment differs significantly in the group with clinical evidence of myocardial ischemia (55%) and the group without such evidence ($p < 0.05$).

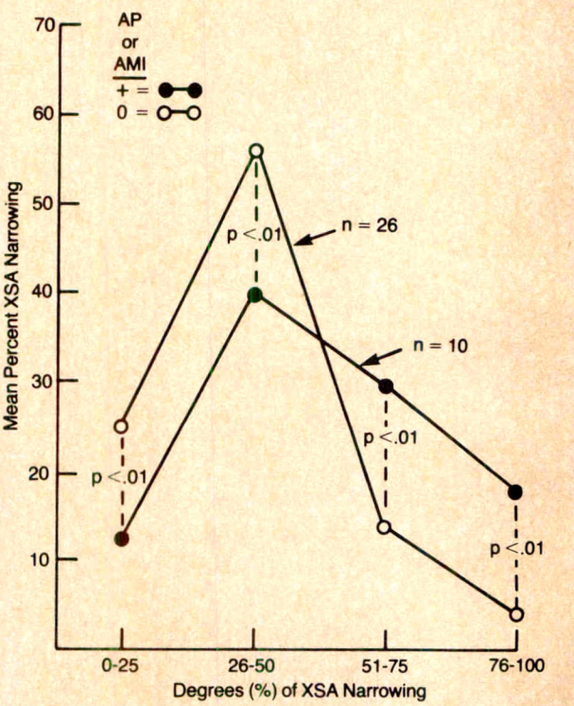



**FIGURE 10.** Mean percent cross-sectional area (XSA) narrowing by atherosclerotic plaques in the 5 mm segments of the right, left main, left anterior descending, and left circumflex coronary arteries in the 36 patients in whom the 4 major coronary arteries in their entirety were available for examination. The 36 patients were classified into 10 with and 26 without clinical evidence of myocardial ischemia. For each of the 4 categories of narrowing, a highly significant ($p < 0.01$) difference in the amount of narrowing was observed.

the 10 patients without significant narrowing, 465 5 mm segments were examined: 23 (5%) were narrowed 51 to 75% in XSA by plaque; 263 (57%), 26 to 50%; and 179 (38%) ≤25%. The total score for each of these 10 patients ranged from 53 to 138 (average 85) and the mean score per 5 mm segment, from 1.28 to 2.07 (average 1.66). Thus, each of the 465 segments was narrowed an average of approximately 29%.

*Left ventricular fibrosis or necrosis or both:* Of the 40 patients, 18 (45%) had ≥1 grossly visible foci of transmural (involvement of all the inner one half and a portion of or all of the outer one half of left ventricular wall) sites of necrosis or fibrosis or both (Fig. 3 and 4). Of the 18 patients, 5 had foci of transmural necrosis only, 8 had transmural scars only, 4 had transmural foci of necrosis and fibrosis, and 1 had transmural fibrosis and subendocardial (involvement of less than the inner one half of the left ventricular wall) necrosis. Of the 23 transmural infarcts in 18 patients, 11 (2 acute, 11 healed [10 patients]) were "small"; 9 (7 acute, 2 healed [8 patients]) were "large"; and 2 (both healed [2 patients]) were "intermediate" in size. All 18 patients had narrowing of 76 to 100% in XSA by atherosclerotic plaque of ≥1 of the 4 major epicardial coronary arteries. None of the 10 patients with fatal acute myocardial infarction had a thrombus in a major coronary artery at necropsy.

*Valvular and anular calcification* (Fig. 11 to 16): Grossly visible calcific deposits were present in ≥1 of the 3 aortic valve cusps (on their aortic surfaces) in 22 patients (55%): in 20 patients, the amount of calcium on the cusps was mild (graded 1+ or 2+/4+) and valvular function was considered normal; in the other 2 patients (Cases 1 and 17) (Fig. 11), the cuspal calcific deposits were extensive (4+/4+) and cuspal mobility was limited, and the orifice in each appeared severely stenotic.[5]

Of the 40 patients, 19 (47%) had grossly visible *mitral anular calcific deposits:* graded 1+ in 5 patients (26%), 2+ in 5 (26%), 3+ in 5 (26%), and 4+ in 4 (22%).[6] In 1 of the 4 patients with 4+ mitral anular calcium (Patient 11), the mitral orifice appeared stenotic (Fig. 13). Of the 40 patients, 26 (65%) had calcific deposits in the aortic valve or mitral anulus or both: in both aortic valve and mitral anulus in 16 (62%), in aortic valve only in 7 (27%), and in mitral anulus only in 3 (11%).

*Cardiac amyloidosis* (Fig. 17): Four patients had extensive amyloid deposits detected grossly in the walls of all 4 cardiac chambers and in many other body organs.[8] The extent of the deposits in each patient produced symptoms and signs of cardiac dysfunction,

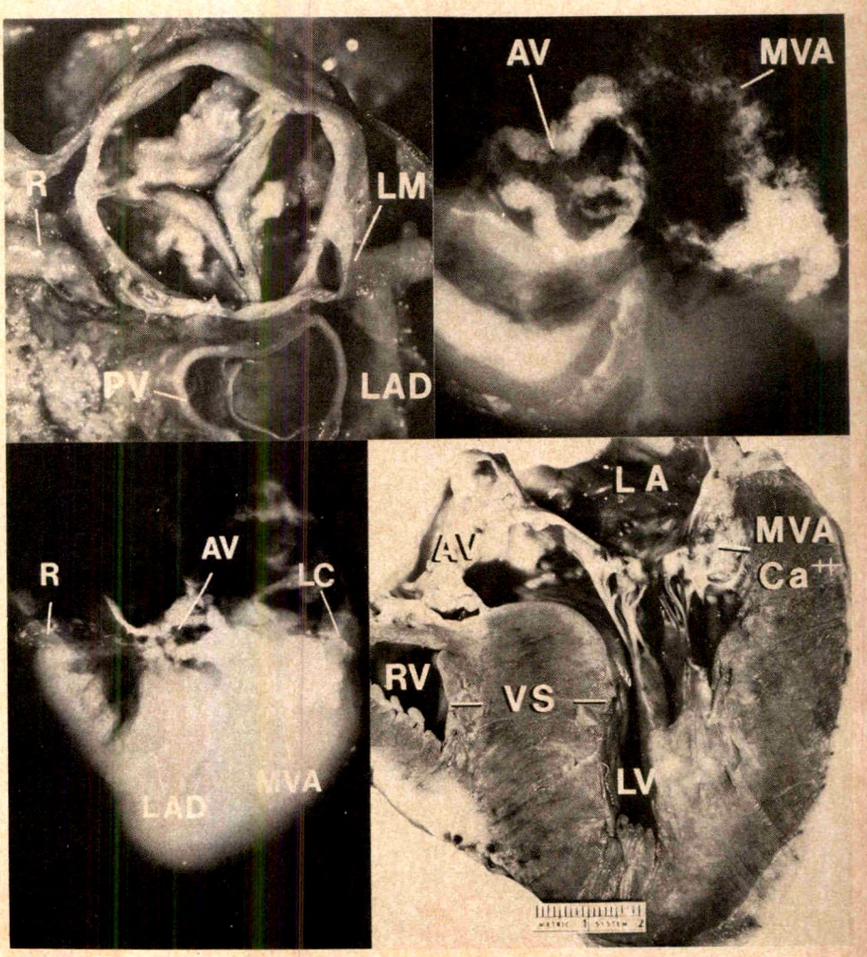



**FIGURE 11.** Patient 17 (GT #78A58). A 92-year-old woman with clinically recognized and eventually fatal aortic valve stenosis. **Top left,** stenotic aortic valve from above. PV = pulmonic valve; R = right; LM = left main; LAD = left anterior descending coronary arteries. **Top right,** postmortem radiogram showing heavy calcific deposits in the aortic valve (AV) and in mitral valve anular (MVA) region. **Bottom left,** radiogram of the heart at necropsy showing calcific deposits in the coronary arteries, in the aortic valve, and in the mitral anular region. **Bottom right,** long-axis view of heart (M-mode or 2-dimensional long-axis view) showing a small left ventricular (LV) cavity, a thickened and "sigmoid-shaped" ventricular septum (VS), and the stenotic aortic valve just above the right ventricular (RV) outflow tract. LA = left atrium.

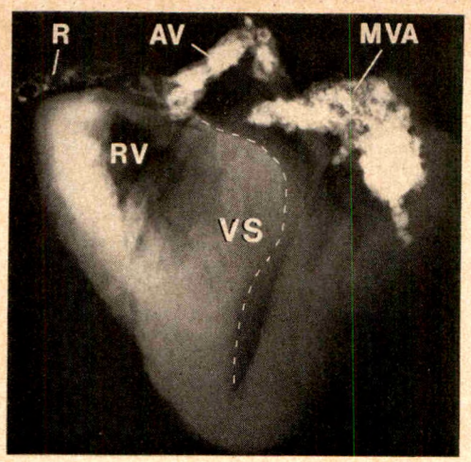



**FIGURE 12.** Patient 31 (GT #68A-367). Radiogram of the heart showing heavy calcific deposits in the aortic valve (AV), mitral valve anulus (MVA), and right (R) coronary artery. The ventricular septum (VS) has a *S* or sigmoid shape (**dashed line**). RV = right ventricle.

manifested primarily by chronic congestive cardiac failure. The presence of extensive amyloidosis was confirmed by histologic examination. At least 5 other patients also had amyloid deposits. The extent of the cardiac amyloid deposits in these 5 patients, however, was minimal and detectable only by histologic examination. Among the 40 patients, histologic sections (1 to 8 per patient [mean 3]) of left ventricular myocardium extending from endocardium to epicardium were examined in 37: 9 of the 37 patients (24%) had amyloid deposits, which were "massive" in 4 and minimal in 5.

*Idiopathic dilated cardiomyopathy:* One patient (Case 30) had a large heart (700 g), dilated ventricular cavities without foci of myocardial fibrosis or necrosis, normal valves and pericardia, epicardial coronary arteries virtually free of atherosclerotic plaques, and chronic congestive heart failure. Although a history of systemic hypertension was absent, the blood pressure in the last month of life was recorded as 140/90 mm Hg. The kidneys, however, were near normal. This patient, therefore, fulfills criteria for diagnosis of idiopathic dilated cardiomyopathy. The patient apparently had habitually consumed excessive quantities of alcohol.

*Obliterative "pericarditis":* Two patients (Cases 14 and 34) had obliterated space between visceral and parietal pericardia by adhesions, some calcified. One (Patient 14) had had talcum powder sprinkled on the epicardium 29 years before death at operation (Beck procedure) for relief of angina pectoris.[9] This patient was the only 1 of the 40 who had undergone a cardiovascular operation. The cause of the obliterative pericardial disease in the other patient was not determined.

*Disease of aorta:* In 34 of the 40 patients, the status of the aorta was known. In all 34, the aorta was dilated in both its transverse and longitudinal dimensions. The latter produced varying degrees of tortuosity. Some degree of atherosclerotic plaquing was present in the aorta in all 34 patients. The most extensive plaquing involved the abdominal portion. Three patients (Cases 8, 13, and 34) had atherosclerotic fusiform abdominal aortic aneurysms with intraaneurysmal thrombus; death in 1 (Patient 8) was secondary to aneurysmal rupture. One patient (Case 25) had an atherosclerotic fusiform aneurysm of the descending thoracic aorta which ruptured, and 1 patient (Case 11) had a dissection limited to descending thoracic aorta; death was due to rupture of the aneurysm into the esophagus.[10]

*Cerebrovascular disease:* Extensive cerebral arterial atherosclerosis was described in the necropsy reports in each of the 4 patients (Cases 30, 31, 33, and 38) with clinical strokes.

*Pulmonary embolism:* Massive pulmonary embolism, that is, thromboembolic material in 1 or both major right and left main pulmonary arteries, was observed at necropsy in 2 patients (Cases 10 and 26). Both had underlying chronic obstructive pulmonary disease.

**Clinical observations:** *Evidence of coronary heart disease:* Of the 40 patients, 12 (30%) had definite or probable clinical evidence of coronary heart disease as manifested by angina pectoris or acute myocardial infarction or both: 1 patient (Case 14) had angina only, 1

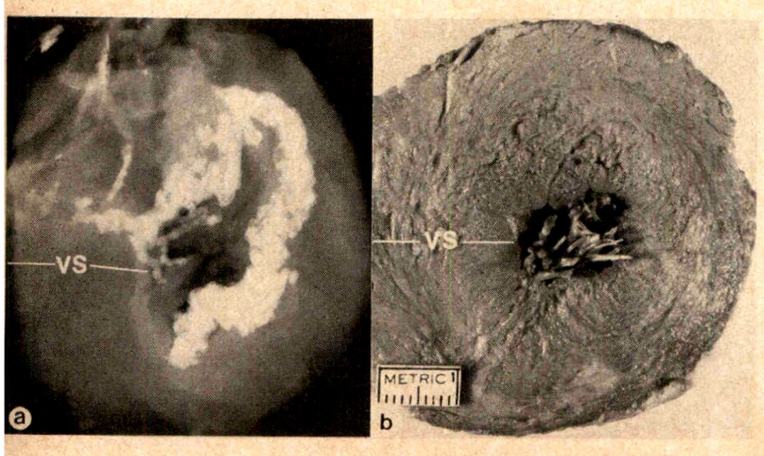



**FIGURE 13.** Patient 11 (GT #80-A-126). A 90-year-old woman with heavy mitral valve anular calcific deposits which reduced the mitral valve orifice to <1 cm in diameter (**a**). The unusual feature of the mitral calcium in this patient was that it not only was located behind the posterior mitral leaflet (mitral anular region) but it also extended across the anterior mitral leaflet nearly producing a letter *O*, as has been described previously.[7] She died from rupture of a descending thoracic aortic aneurysm. VS = ventricular septum. **b,** view of the left ventricle at the level of the tips of the mitral leaflets showing a very small cavity.

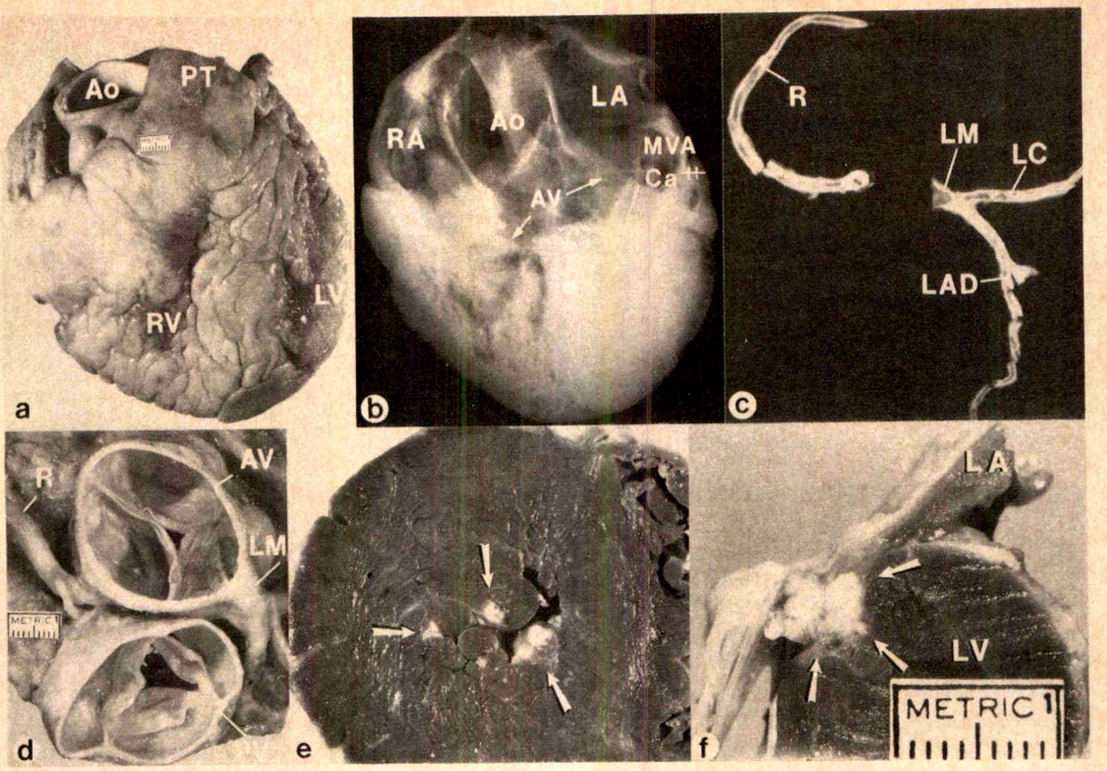



**FIGURE 14.** Patient 32 (SH #A81-62). A 97-year-old woman who never had clinical evidence of cardiac dysfunction and who died from cancer. **a,** external view of anterior surface of the heart showing an increased amount of subepicardial fat. Ao = aorta; LV = left ventricle; PT = pulmonary trunk; RV = right ventricle. **b,** postmortem radiogram showing calcific deposits in the mitral valve anulus (MVA) and aortic valve (AV). LA = left atrium; RA = right atrium. **c,** radiogram of the excised coronary arteries showing a few calcific deposits. LAD = left anterior descending; LC = left circumflex; LM = left main; R = right. **d,** view of aortic valve (AV) and pulmonic valve (PV) from above. **e,** view of left ventricle showing calcific deposits (**arrows**) in the papillary muscles. **f,** calcific deposits in mitral anular region.

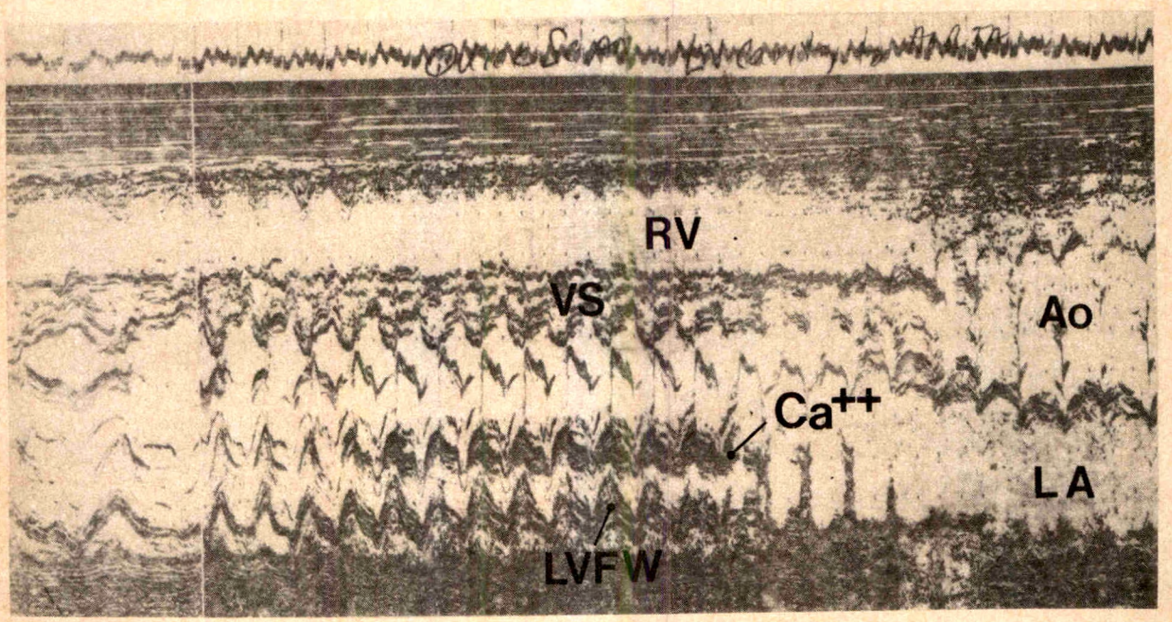



**FIGURE 15.** Patient 32 (SH #80-18). M-mode echocardiogram obtained 10 months before death from the patient whose heart is shown in Figure 14. The ascending aorta (Ao) has a larger diameter than does the left atrium (LA). The left ventricular (LV) cavity is small. Calcium is present in the mitral anular region. (We thank Dr. Robert Montgomery, Bethesda, Maryland, for allowing us to show this echocardiogram from his patient.)

(Case 37) had angina and a nonfatal acute myocardial infarct 2 years before death. (This patient died 24 hours after onset of increased dyspnea and vague chest pain but at necropsy no myocardial necrosis was visible histologically.) One patient (Case 2) had angina and a fatal acute myocardial infarct, and 9 patients had fatal acute myocardial infarcts which in each was the first one seen clinically. The clinical records regarding anginal attacks in the 3 patients are deficient in details: 2 patients (Cases 2 and 37) were stated to have had angina for "many years" and the third patient (Case 14) had angina for 29 years (since age 63). In none of the 3 patients was there information regarding the frequency of the anginal attacks and only 1 (Patient 37) was known to have taken nitroglycerin tablets.

Ten patients had deaths compatible with acute myocardial infarction. Of these 10 patients, however, only 3 (Cases 13, 16, and 23) had typical "crushing" substernal chest pain associated with typical electrocardiographic changes and enzyme elevations. The remaining 7 patients all were hospitalized because of some acute change in their status; however, acute myocardial infarction was never clearly established in these patients until necropsy. Only 5 of the 7 had chest pain, and it was atypical and not severe. Four had acute worsening of dyspnea. None had typical electrocardiographic features of acute myocardial infarction, but 5 had complete left bundle branch block at admission to the hospital. In 5 of these 7 patients in whom serum enzymes (creatine phosphokinase, lactic dehydrogenase, serum glutamic-oxaloacetic transaminase) were determined, the values were elevated in 4. Of the 14 patients with transmural left ventricular scars, only 1 had a clinical event diagnosed as acute myocardial infarction.

Chronic congestive heart failure was described in 8 patients (20%). In 4 patients (Cases 4, 21, 27, and 34) its cause, as determined initially by necropsy, was diffuse cardiac amyloidosis: in 1 patient (Case 17), its cause was aortic valve stenosis, which was diagnosed clinically; 1 patient (Case 14) had obliterative pericardial disease from the Beck procedure 25 years earlier[9]; 1 patient (Case 30) had cardiomegaly (660 g heart) of uncertain cause clinically (at necropsy the condition was considered idiopathic dilated cardiomyopathy); 1 patient (Case 22) also had congestive heart failure of uncertain cause clinically but at necropsy had a transmural left ventricular scar and severe narrowing of all 3 major epicardial coronary arteries. Of the 8 patients with chronic congestive heart failure, all had cardiomegaly at necropsy and 6 had histories of systemic hypertension during life.

*Systemic hypertension:* Information regarding "a history of hypertension" or an actual indirect systemic arterial blood pressure recording in the last year of life was available in 39 of the 40 patients: 19 (51%) had "a history" of systemic hypertension; of the 34 patients with actual blood pressure recordings, only 7 had systolic pressures >140 mm Hg or diastolic pressures >90 mm Hg. Of the 39 patients on whom information was available, 27 (69%) had either "a history of hypertension" or a recorded elevated blood pressure in the last year of life. Of the other 12 patients, only 1 (Case 23) had unequivocal cardiomegaly without explanation.

*Diabetes mellitus:* Five patients, all women, had diabetes mellitus. In 2, its duration was known: 20 years (Patient 5) and 40 years (Patient 20). One patient (Case 5) was treated with insulin; 1 (Case 9) with diet alone; 1 (Case 2) with diet plus tolbutamide; in 2 patients the type therapy received was unknown. Although 3 patients (Cases 2, 5, and 20) had transmural left ventricular scars, none had clinical events compatible with acute myocardial infarction.

*Precordial murmurs:* Of the 40 patients, 25 (62%) had had precordial murmurs. In all 25, the murmur was

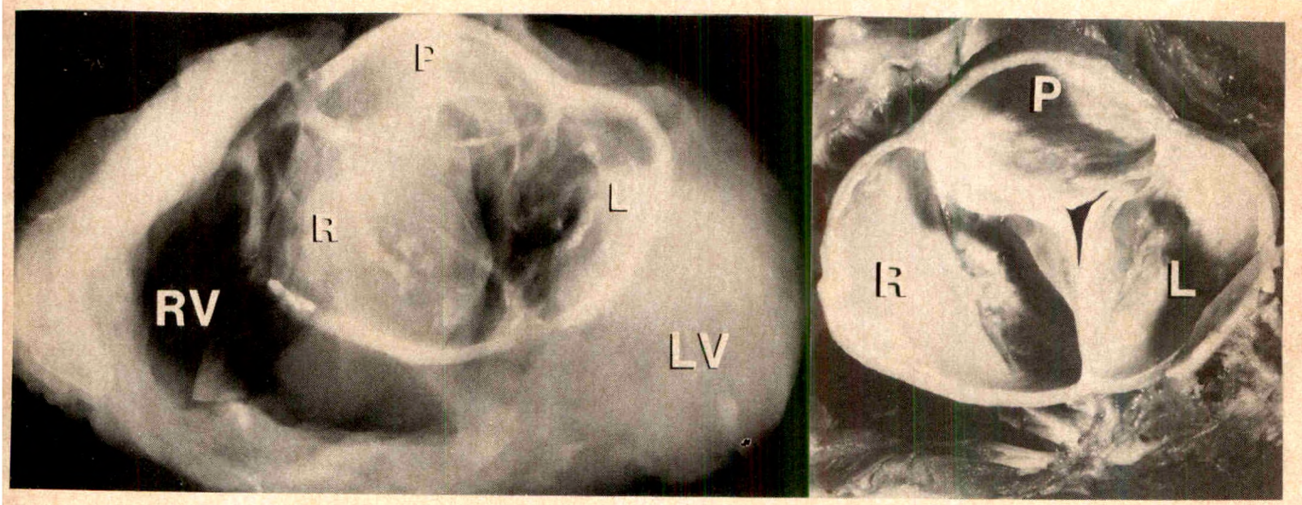



**FIGURE 16.** Patient 28 (SH #79-77). A 95-year-old man who never had symptoms of cardiac dysfunction and died from sarcoma. The coronary arteries are shown in Figure 2. **Left,** radiogram of heart at necropsy showing considerable enlargement of the aorta in comparison to the ventricles. LV = left ventricle; RV = right ventricle; R = right, L = left, and P = posterior sinuses of Valsalva. **Right,** aortic valve from above. The coronary arteries had been excised before the radiogram and photographs were taken.

described as systolic: apical only in 6; left sternal border only in 8; basal only in 2; all 3 locations in 3; and unspecified in 6. Only 1 (Case 9) of the 25 patients had both diastolic and systolic precordial murmurs. The diastolic murmur appeared to represent mild aortic regurgitation from systemic hypertension. The intensity of the murmur in the 24 patients with purely systolic murmurs was grade 1/6 in 2 patients, grade 2/6 in 5, grade 3/6 in 8, grade 4/6 in 4, and unspecified in 5. The cause of the precordial systolic murmurs was variable and often unclear. Of the 24 patients, 17 (71%) had calcific deposits in either the mitral valve anulus or aortic valve cusps or both: in mitral anulus only in none, in aortic valve only in 4, and in both mitral anulus and aortic valve in 13. In only 4 of the 17 patients, however, was the extent of calcium grade 3 to 4/6. In contrast, of the 15 patients without precordial murmurs recorded, 8 (53%) had calcific deposits in either mitral anulus or aortic valve cusps or both: in 3, the extent of the calcific deposits was either grade 3 or 4/6, but 4 of these 8 patients underwent precordial examination while in severe respiratory distress (3 patients) or in coma (1 patient). The blood hematocrit level ranged from 29 to 46% (mean 39) in the 18 patients with precordial murmurs and known hematocrit values, and from 30 to 57% (mean 38) in the 10 without precordial murmurs but known hematocrit values.

*Noncardiac vascular disease:* Five patients had strokes, which were fatal in 4 (Cases 12, 31, 33, and 38) and nonfatal in 1 (Case 30). Of the 3 patients with fusiform abdominal aortic aneurysms, only the 1 (Case 8) which ruptured was diagnosed during life. Neither the patient (Case 25) with a ruptured fusiform aneurysm of thoracic aorta nor the patient (Case 11) with rupture of the descending thoracic aorta into the esophagus had the condition diagnosed during life.[10] Five patients (Cases 1, 3, 9, 20, and 25) had leg claudication, requiring amputations in 2 (Cases 3 and 9) for gangrene. In the 2 patients with massive pulmonary embolism, this condition was suspected clinically.

*Electrocardiographic data* (Fig. 18 and 19) (Tables III and IV): Information on electrocardiograms recorded at age 90 years or later was available in 30 of the 40 patients. In 24 patients, the electrocardiograms were available for reexamination but in the other 6 patients, only the electrocardiographic reports were available. Of the 30 patients, 3 (Cases 1, 3, and 5) had electrocardiograms recorded during the acute illness (recordings 4, 9, and 7 days, respectively, before death). The illnesses, although not diagnosed clinically, were seen at necropsy

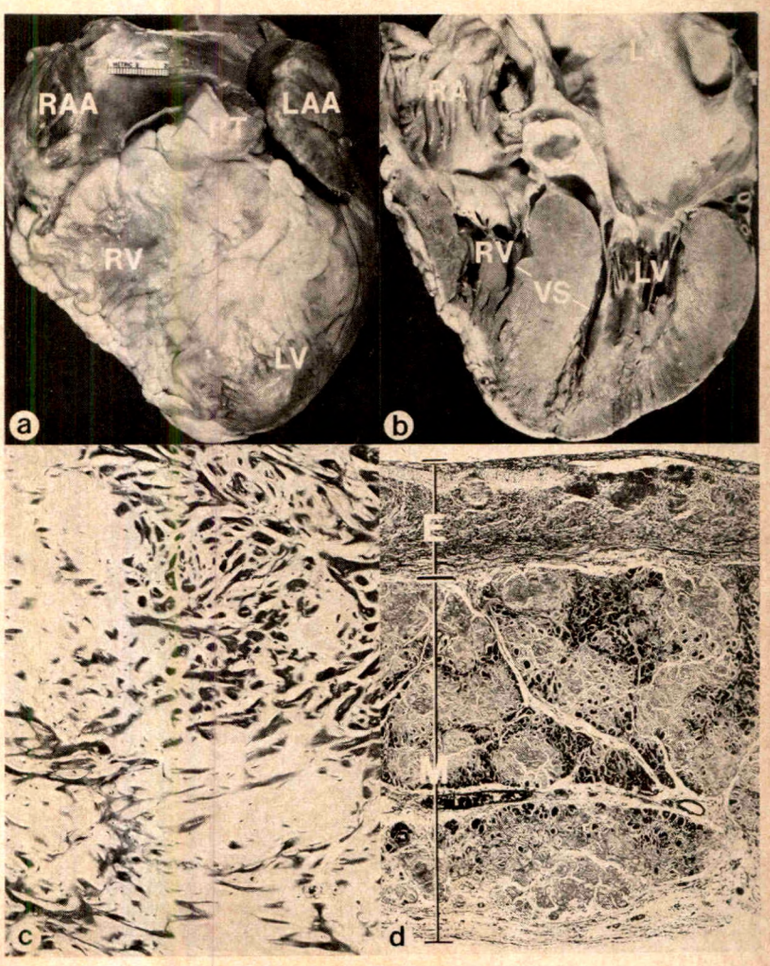



**FIGURE 17.** Patient 4 (DCGH #69A391), a 90-year-old man with chronic, eventually fatal congestive heart failure from clinically unrecognized cardiac amyloidosis. **a,** external view of the heart showing a prominent left ventricle (LV) and left atrial appendage (LAA). PT = pulmonary trunk; RAA = right atrial appendage; RV = right ventricle. **b,** right-to-left longitudinal cut of the heart (4-chamber, 2-dimensional echocardiographic view) showing thickened ventricular walls and dilated right (RA) and left (LA) atria. VS = ventricular septum. **c,** photomicrograph of a portion of the left ventricle showing extensive amyloid deposits. **d,** photomicrograph of LA wall showing amyloid deposits in endocardium (E) and in myocardium (M). (Hematoxylin-eosin stains; magnification ×100 (**c**) and ×25 (**d**), both reduced 35%.)

to clearly result from acute myocardial infarction. The electrocardiograms in all 3, however, disclosed only atrial fibrillation and complete left bundle branch block and these findings in all 3 patients were known to be present before the fatal acute myocardial infarction. The electrocardiograms in the other 27 patients were not recorded during periods of acute myocardial ischemia. Of the 30 patients on whom electrocardiographic information was available, 8 had clinical evidence of heart disease and 22 did not; the findings are summarized in Table III.

The QRS voltage in all 12 leads in each of 24 patients is summarized in Table IV (Fig. 19). The total 12-lead QRS voltage ranged from 82 to 251 mm (mean 151) (10 mm = 1 mV). In the 19 women, the total voltage ranged from 82 to 251 mm (mean 158), and in the 5 men, from 105 to 154 mm (mean 101) ($p < 0.05$). The total 12-lead QRS voltage did not correlate with either heart ($r = -0.01$) or body weight ($r = -0.2$). The 24 patients in whom the total 12-lead QRS voltage was measured were separated into 2 groups: 8 patients in whom clinical evidence of cardiac dysfunction was present (coronary heart disease in 5, massive cardiac amyloid in 2, aortic valve stenosis in 1) and 16 patients without such evidence. Comparison of the total QRS voltage in the 8 patients with and in the 16 patients without clinical evidence of heart disease disclosed no significant difference (mean 147 mm versus mean 152 mm). Breakdown on the 8 patients with cardiac dysfunction did show some differences: the total 12-lead QRS voltage in the 5 patients with angina pectoris or acute myocardial infarction (Patients 1, 3, 5, 14, and 37) ranged from 123 to 163 mm (mean 143); in the 2 patients with massive cardiac amyloidosis (Patients 21 and 27) it was 102 and 117 mm (mean 109); and in the 1 patient with aortic valve stenosis (Patient 17) it was 238 mm.

Of 29 patients on whom information was available, 18 (62%) received *digitalis* and only 2 appeared to have evidence of digitalis toxicity.

*Blood hematocrit levels* in the last month of life, known in 29 patients, ranged from 29 to 57% (mean 38).

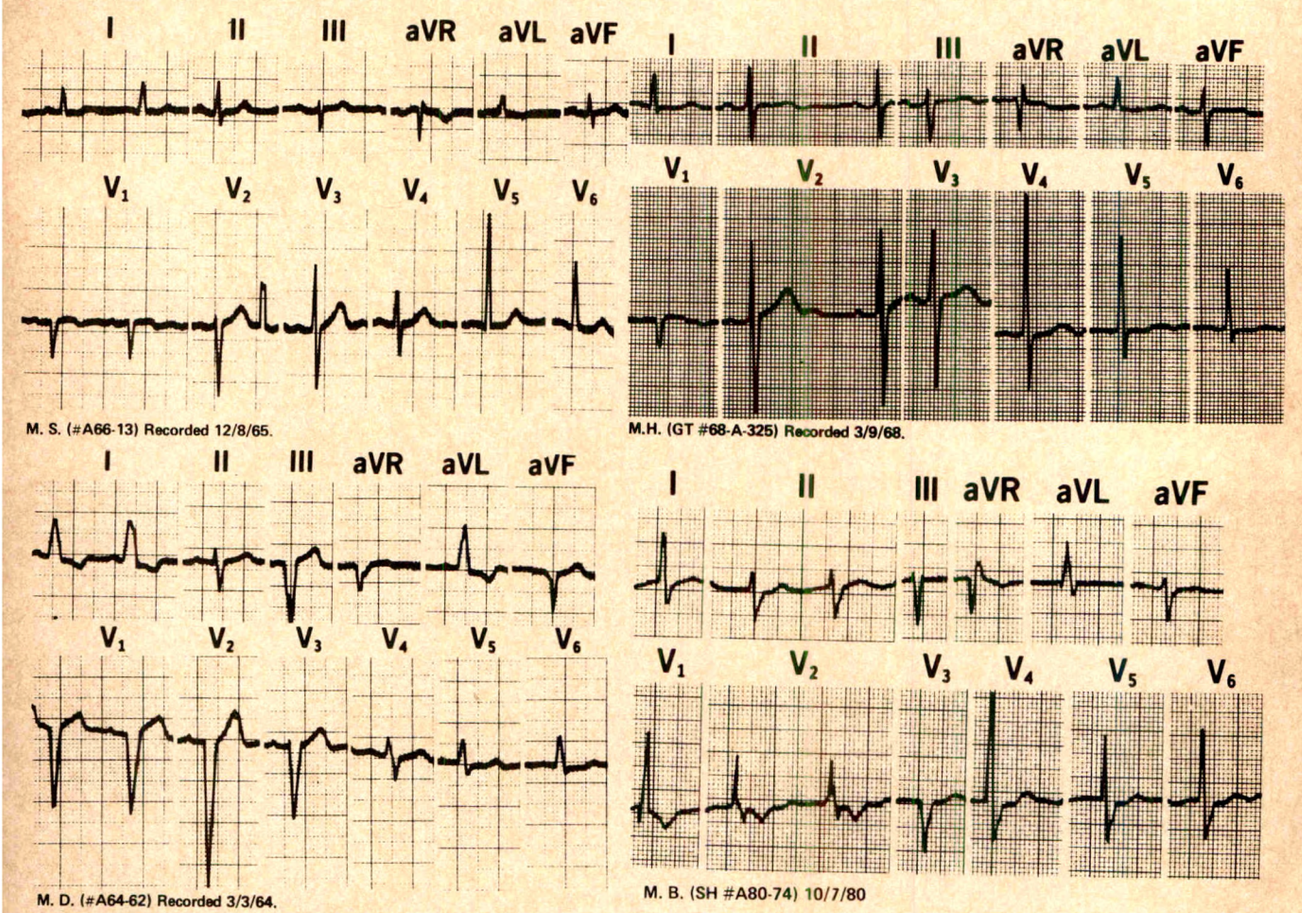



**FIGURE 18.** Electrocardiograms in 4 patients, each recorded at age 90 years or older. None ever had symptoms of cardiac dysfunction and each died from noncardiac conditions. **Top left,** Patient 7 (A66-13). The electrocardiogram was recorded 43 days before death and it is normal (heart weight 270 g). **Top right,** Patient 15 (GT #68A325). The electrocardiogram was recorded 11 days before death and it shows left QRS axis deviation and a slightly prolonged P-R interval (heart weight 400 g). **Bottom left,** Patient 36 (A64-62). This electrocardiogram was recorded 28 days before death and it shows left-axis deviation and complete left bundle branch block (heart weight 320 g). **Bottom right,** Patient 29 (SH #A80-74). This electrocardiogram was recorded 128 days before death and it shows atrial fibrillation, left-axis deviation, and complete right bundle branch block (heart weight 440 g).

*Total serum cholesterol levels* recorded at age 90 years or older, available in 10 patients, ranged from 108 to 283 mg/100 ml (mean 220).

*Total serum protein values*, available in 18 patients, ranged from 5.2 to 8.1 g/100 ml (mean 6.8). Serum albumin values, available in 19 patients, ranged from 2.0 to 4.5 g/100 ml (mean 3.3).

*Blood urea nitrogen values*, available in 27 patients, ranged from 7 to 70 g/100 ml (mean 33). Most values were obtained during the last month of life and some patients were clearly dehydrated at the time.

*Modes of death:* Of the 40 patients, 18 (45%) appeared to have died from consequences of cardiac disease, 7 (17%) from noncardiac but vascular problems, and 15 (38%) from noncardiac and nonvascular problems.

Of the 18 patients with cardiac causes of death, 10 had acute transmural myocardial infarcts, 1 (Case 14) had chronic congestive cardiac failure after healing of acute transmural myocardial infarcts, and 1 (Case 37) died in ventricular fibrillation after 24 hours of chest pain and at necropsy was shown to have severe coronary atherosclerosis without myocardial necrosis. Fatal congestive heart failure was due to aortic valve stenosis in 1 (Patient 17), to cardiac amyloidosis in 4 (Patients 4, 21, 27, and 34), and to idiopathic dilated cardiomyopathy in 1 (Patient 30). Of the 7 patients with noncardiac and nonvascular causes of death, 4 (Patients 12, 31, 33, and 38) died from complications of strokes, and the other 3, from rupture of aortic aneurysms (Patients 8, 11, and 25). Of the 15 patients with noncardiac and nonvascular causes of death, 7 (Cases 6, 7, 9, 28, 32, 35, and 36) died from various malignant neoplasms; 3 from nonneoplastic gastrointestional problems (bowel obstruction from adhesions in 1 [Patient 15], perforated gastric ulcer in 1 [Patient 29], and active duodenal ulcer in 1 [Patient 40]); 2 (Patients 24 and 39) from complications of bone fractures after falls; 2 (Patients 10 and 26) from massive pulmonary emboli superimposed on chronic obstructive pulmonary disease; and 1 (Patient 18) from uncertain cause. Of the 7 patients with fatal malignant neoplasms, 3 (Cases 6, 7 and 28) had 2 neoplasms and 4 (Cases 9, 32, 35, and 36) had 1 neoplasm.

## Discussion

As in any body organ or tissue, certain changes take place in the cardiovascular system as life progresses. Some of these changes allow easy identification of the very elderly heart when examining cardiac specimens as unknowns. The "normal" elderly heart has relatively small ventricular cavities and relatively large atria and great arteries (Fig. 20). The ascending aorta and left atrium, in comparison with the relatively small left ventricular cavity, appear particularly large. The cor-

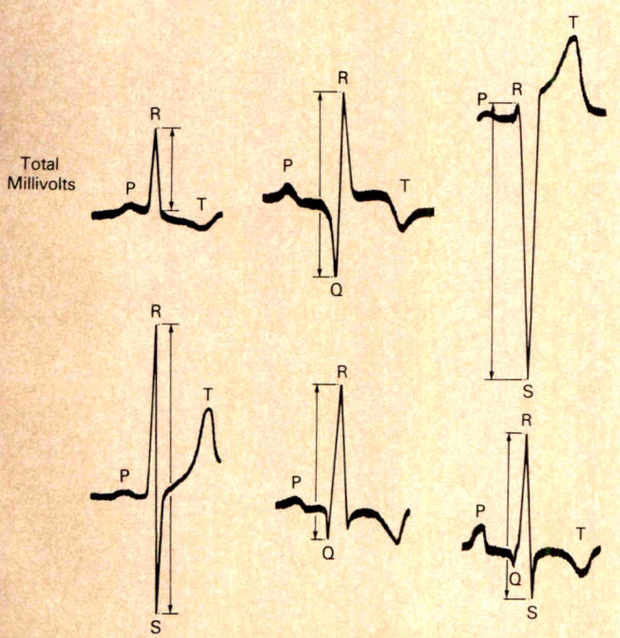



**FIGURE 19.** Various QRS complexes, and how each was measured. (Reproduced with permission from Siegel RJ, Roberts WC: Electrocardiographic observations in severe aortic valve stenosis: correlative necropsy study to clinical, hemodynamic, and ECG variables demonstrating relation of 12-lead QRS amplitude to peak systolic transaortic pressure gradient. Am Heart J 1982;103:210–221.)

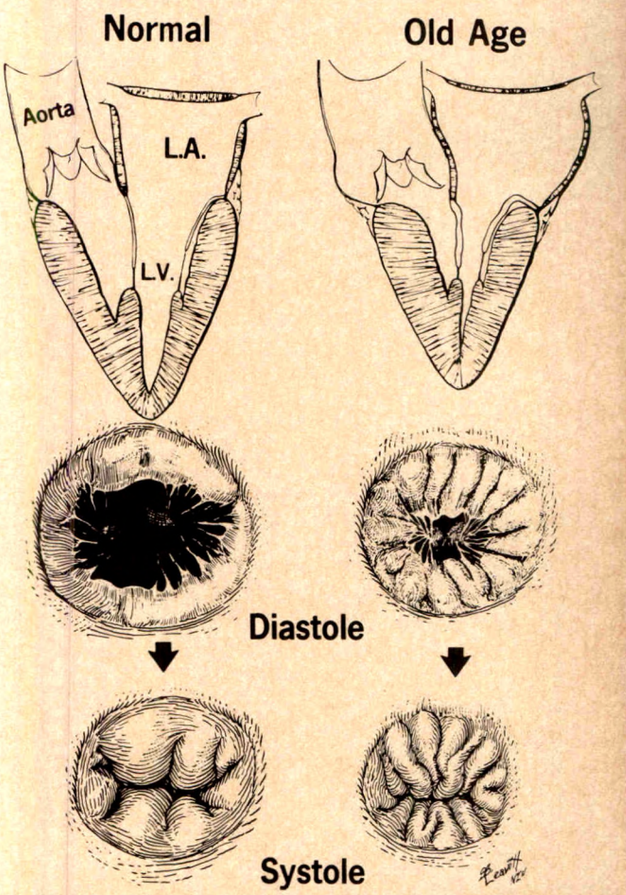



**FIGURE 20.** Diagram summarizing cardiac changes in the very elderly. The left atrial (LA) cavity enlarges and the left ventricular (LV) cavity becomes smaller. The amount of space available for the mitral leaflets decreases with aging, and consequently the number of scallops in the leaflets appears to increase.

onary arteries increase in both length and width and the former, particularly in association with the decreasing sizes of the cardiac ventricles, results in tortuosity. (The young river is straight and the old one, winding.) The subepicardial adipose tissue increases in amount with aging. The leaflets of each of the 4 cardiac valves thicken with age, particularly the atrioventricular valves, which have a smaller area to occupy in the ventricles because of the diminishing size of the latter. Histologic examination discloses large quantities of lipofuscin pigment in myocardial cells; some contain mucoid deposits ("mucoid degeneration"). These changes appear to affect all population groups of elderly individuals irrespective of where they reside on this earth and irrespective of their level of serum lipids. An elevated systemic arterial pressure appears to both accelerate and amplify these "normal" expected aging cardiac changes.

Both the aorta and its branches and the major pulmonary arteries and their branches enlarge with age. Because the enlargement is in both longitudinal and transverse dimensions, the aorta, like the coronary arteries, tends to become tortuous. This process also is amplified as the vertebral bodies become smaller and the height, somewhat shorter. The major pulmonary arteries appear to be too short and to have too low a pressure to dilate longitudinally.

Although several reports have described cardiovascular finding at necropsy in aged persons, old age was defined as >55,[11] >65,[12] or >75[13] years, and consequently findings in those aged 90 years and over could not be separated from those occurring in the "younger" older persons. The present study appears to be the first to focus entirely on a group of necropsy patients aged 90 years or older. A major finding in our study is the high frequency of calcific deposits in the heart. Of the 40 patients, 37 (92%) had calcific deposits in the epicardial coronary arteries. In most, the deposits were extensive. Although the calcific deposits were located entirely in atherosclerotic plaques, which are located in the intima, the presence of calcific deposits in the coronary arteries in this very elderly population did not necessarily indicate the presence of significant (>75% XSA) luminal narrowing. In contrast, the presence of calcific deposits in epicardial coronary arteries in persons aged <65 years generally indicates the presence of significant luminal narrowing.[14] The calcific deposits tended to occur in each of the 4 major (right, left main, left anterior descending, and left circumflex) epicardial arteries and were always larger in the proximal than in the distal halves of the right, left anterior descending, and left circumflex arteries or, if small, limited to their proximal halves.

Calcific deposits occurred with near equal frequency (55% and 47%) in the aortic valve cusps and in the mitral anular region. The deposits in the aortic valve were located on the aortic aspects of 1 or more of the 3 cusps and usually were unassociated with commissural fusion. The presence or absence of aortic valve stenosis was determined by the quantity of calcium deposited. In 2 patients, the extent of the calcific deposits imparted an immobility to the cusps resulting in aortic valve stenosis. The mitral "anular" calcific deposits, of course, were not limited to the anulus but included the space between the ventricular aspect of the posterior mitral leaflet and the mural endocardium of left ventricular free wall behind posterior mitral leaflet. Often this "anular" calcium extended into the adjacent left ventricular myocardium. Most patients with aortic valve calcium had mitral "anular" calcium and vice versa and all with aortic valvular or mitral "anular" calcium had coronary arterial calcific deposits.

The presence of calcium in the 3 locations in the heart, namely the coronary artery, the aortic valve, and

**TABLE III Electrocardiographic Observations in 30 Patients Aged 90 to 103 Years**

| Abnormality | Clinical Heart Disease | | Total | |
|---|---|---|---|---|
| | Present* (n = 8) | Absent (n = 22) | n | % |
| Atrial fibrillation | 5 | 7 | 12 | 40 |
| Abnormal QRS axis | | | 12 | 40 |
| Left (−30 to −90°) | 4 | 6 | | |
| Right (+111 to +210°) | 1 | 1 | | |
| Complete (QRS ≥0.12 second) BBB | | | 12 | 40 |
| Left | 6 | 1 | | |
| Right | 1 | 4 | | |
| Ventricular premature complexes | 4 | 6 | 10 | 33 |
| Atrial premature complexes | 1 | 2 | 3 | 10 |
| Heart Block | | | 8 | 27 |
| P-R interval >0.20 second | 3 | 3 | | |
| Second degree | 0 | 1 | | |
| Third degree (complete) | 1† | 0 | | |
| Q-wave abnormality without BBB | | | 4 | 13 |
| Q II, III, $aV_f$ | 0 | 1 | | |
| Q-S $V_1$–$V_3$ | 0 | 1 | | |
| Both | 0 | 2 | | |
| Left ventricular hypertrophy without BBB (R in $V_5$ or $V_6$ + S in $V_1$ ≥35 mm) | 1 | 0 | 1 | 3 |
| Low voltage (QRS ≤15 mm in I + II + III) | 0 | 1 | 1 | 3 |

* Coronary heart disease = 3; cardiac amyloidosis = 4; aortic valve stenosis = 1.
† Pacemaker inserted 6 years before death.
BBB = bundle branch block.

**TABLE IV Total QRS Voltage in 24 Necropsy Patients Aged ≥90 Years: 8 With (Angina Pectoris [AP] or Acute Myocardial Infarction [AMI] in 5, Amyloid in 2, Aortic Valve Stenosis [AS] in 1) and 16 Without Symptoms of Cardiac Dysfunction**

| Pt | Age (yr) & Sex | Clinical Heart Disease | Body Wt (Kg) | Heart Wt (g) | QRS (mm) | | | | | | | | | | | | Sum 1 + 11 +111 | Sum R + L +F | Sum 1 − 111 +R − F | Sum $V_1 - V_6$ | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | I | II | III | R | L | F | $V_1$ | $V_2$ | $V_3$ | $V_4$ | $V_5$ | $V_6$ | | | | | |
| Patients (n = 8) With Symptoms of Cardiac Dysfunction | | | | | | | | | | | | | | | | | | | | | |
| 5 | 90F | AMI | 100 | 400 | 8 | 5 | 6 | 6 | 7 | 5 | 11 | 28 | 21 | 12 | 7 | 15 | 19 | 18 | 37 | 94 | 131 |
| 1 | 90F | AMI + AS | 120 | 540 | 6 | 7 | 8 | 5 | 6 | 6 | 15 | 20 | 14 | 14 | 11 | 11 | 21 | 17 | 38 | 85 | 123 |
| 3 | 90M | AMI | 110 | 450 | 5 | 8 | 9 | 5 | 6 | 10 | 12 | 24 | 26 | 19 | 11 | 10 | 22 | 21 | 43 | 102 | 145 |
| 14 | 92F | AP | 107 | 380 | 7 | 8 | 9 | 7 | 7 | 8 | 14 | 12 | 20 | 40 | 16 | 15 | 24 | 22 | 46 | 117 | 163 |
| 17 | 92F | As | 120 | 525 | 16 | 15 | 14 | 17 | 13 | 12 | 16 | 25 | 34 | 35 | 25 | 16 | 45 | 42 | 87 | 151 | 238 |
| 21 | 93F | Amyloid | ... | 380 | 10 | 6 | 12 | 5 | 10 | 10 | 9 | 10 | 11 | 14 | 14 | 6 | 28 | 25 | 53 | 64 | 117 |
| 27 | 96M | Amyloid | 126 | 660 | 6 | 5 | 11 | 2 | 8 | 8 | 7 | 18 | 12 | 11 | 9 | 5 | 22 | 18 | 40 | 62 | 102 |
| 37 | 99M | AMI | 110 | 510 | 7 | 11 | 7 | 8 | 6 | 7 | 22 | 22 | 6 | 18 | 22 | 18 | 25 | 21 | 46 | 108 | 154 |
| Range (mean) | (93) | ... | (137) | (481) | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | 19–45 (26) | 17–42 (23) | 37–87 (49) | 62–151 (98) | 102–238 (147) |
| Patients (n = 16) Without Symptoms of Cardiac Dysfunction | | | | | | | | | | | | | | | | | | | | | |
| 6 | 90F | 0 | 100 | 220 | 10 | 12 | 8 | 10 | 8 | 8 | 10 | 24 | 27 | 28 | 22 | 14 | 30 | 26 | 56 | 125 | 181 |
| 7 | 90F | 0 | 104 | 270 | 7 | 10 | 6 | 10 | 4 | 7 | 10 | 22 | 30 | 38 | 32 | 17 | 23 | 21 | 44 | 149 | 193 |
| 8 | 90F | 0 | 110 | 505 | 9 | 7 | 13 | 5 | 9 | 9 | 12 | 16 | 13 | 3 | 4 | 7 | 29 | 23 | 52 | 55 | 107 |
| 11 | 91F | 0 | 99 | 375 | 10 | 10 | 6 | 10 | 5 | 6 | 22 | 21 | 25 | 21 | 18 | 14 | 26 | 21 | 47 | 121 | 168 |
| 15 | 92F | 0 | 109 | 400 | 8 | 8 | 9 | 6 | 8 | 8 | 25 | 27 | 33 | 31 | 20 | 13 | 25 | 22 | 47 | 149 | 196 |
| 24 | 95F | 0 | 128 | 350 | 6 | 7 | 4 | 6 | 7 | 5 | 7 | 6 | 5 | 6 | 10 | 13 | 17 | 18 | 35 | 47 | 82 |
| 29 | 95F | 0 | 120 | 440 | 5 | 10 | 10 | 10 | 10 | 8 | 19 | 15 | 33 | 32 | 22 | 20 | 25 | 18 | 43 | 141 | 184 |
| 25 | 95F | 0 | ... | 460 | 14 | 11 | 12 | 6 | 12 | 10 | 12 | 17 | 18 | 15 | 5 | 4 | 37 | 28 | 65 | 71 | 136 |
| 28 | 95M | 0 | ... | 385 | 4 | 13 | 10 | 8 | 4 | 11 | 3 | 8 | 11 | 14 | 11 | 8 | 27 | 23 | 50 | 55 | 105 |
| 31 | 96F | 0 | 100 | 300 | 7 | 15 | 10 | 11 | 4 | 11 | 9 | 16 | 17 | 22 | 29 | 28 | 32 | 26 | 58 | 121 | 179 |
| 32 | 97F | 0 | 120 | 360 | 9 | 5 | 3 | 8 | 12 | 5 | 10 | 19 | 16 | 14 | 15 | 10 | 17 | 25 | 42 | 84 | 126 |
| 33 | 97F | 0 | 90 | 320 | 10 | 6 | 10 | 7 | 9 | 6 | 7 | 16 | 15 | 23 | 28 | 23 | 26 | 22 | 48 | 112 | 160 |
| 35 | 98F | 0 | 117 | 360 | 5 | 10 | 8 | 7 | 3 | 8 | 8 | 15 | 14 | 12 | 8 | 5 | 23 | 18 | 41 | 62 | 103 |
| 36 | 98F | 0 | 115 | 320 | 10 | 9 | 15 | 6 | 10 | 10 | 20 | 34 | 18 | 10 | 8 | 9 | 34 | 26 | 60 | 99 | 159 |
| 39 | 100M | 0 | ... | 335 | 6 | 6 | 1 | 6 | 2 | 3 | 14 | 11 | 2 | 24 | 24 | 12 | 13 | 11 | 24 | 87 | 111 |
| 40 | 103F | 0 | 120 | 345 | 13 | 25 | 37 | 20 | 22 | 13 | 26 | 19 | 16 | 25 | 23 | 12 | 75 | 55 | 130 | 121 | 251 |
| Range (mean) | (95) | ... | (110) | (359) | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | 13–75 (28) | 11–55 (24) | 24–130 (52) | 47–149 (100) | 82–251 (152) |

Pt = patient; Wt = weight.

the mitral "anulus," might be termed *the senile cardiac calcification syndrome* and strongly suggests that the etiology of the calcific deposits in each of the 3 locations is similar. It is well appreciated, as already mentioned, that the calcific deposits in the coronary arteries are located in atherosclerotic plaques and, therefore, that the calcific deposits in both aortic valve and mitral anular regions might be viewed as anatomic expressions of the atherosclerotic process. All 3 appear to occur only in populations where the total serum cholesterol level is >150 mg/700 ml. Of our 40 patients, total serum cholesterol levels were available in 10: in only 1 (Patient 30) was the level <150, and in 2 the level was 150 to 200 mg/100 ml. In Patient 30, whose value was 108 mg/100 ml, no calcific deposits were present in any of the 3 sites; in Patient 36 whose level was 165 mg/100 ml, minimal calcific deposits were present only in the coronary arteries; and in Patient 28, whose level was 181 mg/100 ml, small calcific deposits were present in the aortic valve (Fig. 16) and coronary arteries. In contrast, of the 7 patients in whom the total serum cholesterol level was >200 mg/100 ml, calcific deposits were present in either aortic valve or mitral anulus or both in 5 patients and in the coronary arteries in all 7 patients; in each the deposits were larger. Calcific deposits in the coronary artery, aortic valve cusp, and mitral anulus are extremely rare in populations where total serum cholesterol levels are <150 mg/100 ml and, of course, clinical evidence of coronary heart disease in these population groups is extremely rare[15] despite a high prevalence of systemic hypertension.

Of the 40 patients, 28 had narrowing of >75% in XSA of ≥1 of the 4 major epicardial coronary arteries. Of the 28 patients, 17 had transmural foci of left ventricular fibrosis or necrosis (myocardial infarction) and of the 12 with insignificant coronary narrowing, none had grossly visible acute or healed myocardial infarcts. Of the 14 patients with healed myocardial infarcts, only 1 had a clinical event compatible with acute myocardial infarction which healed. Of the 10 patients with acute myocardial infarcts at necropsy, only 3 had typical clinical features of acute myocardial infarction; the other 7 had acute changes in their clinical course and acute myocardial infarction was either suspected or compatible with the acute illness. Angina pectoris was described in 3 patients, 1 of whom was among the 10 with fatal acute myocardial infarcts, and 1 of whom had had a nonfatal acute infarct. Thus, 12 patients had clinical features compatible with coronary heart disease and each was among the 28 with significant narrowing of ≥1 of the major coronary arteries. Conversely, of the 28 patients with significant coronary narrowing at necropsy, 16 (57%) never had either angina pectoris or acute myocardial infarction. Of the total 40 patients, only 12 (30%) had clinical events compatible with coronary heart disease and only in 6 were the clinical events really typical.

In 36 of the 40 patients, each of the 4 major coronary arteries were divided into 5 mm long segments and the degree of XSA narrowing by atherosclerotic plaque was determined for each segment. Of the 1,789 5 mm segments in the 36 patients, the average amount of XSA narrowing by atherosclerotic plaques/segment was 42% (range 19 to 69). Of the 467 5 mm segments in the 10 patients with clinical evidence of coronary heart disease, the average amount of XSA narrowing/segment was 55% (range 43 to 69), and 1,322 segments in the 26 patients without clinical evidence of coronary heart disease, 38% (range 19 to 40) ($p < 0.01$). Among 129 patients aged 22 to 85 years (mean 56), the amount of XSA narrowing by atherosclerotic plaques/segment averaged 67%; in the control subjects, that is, those without symptomatic coronary heart disease, XSA narrowing averaged 32%. The mean percent of 5 mm coronary segments narrowed 76 to 100% in XSA in the 36 patients was 13% (range 2 to 89); of the 10 patients with symptomatic coronary heart disease, the mean was 19% (range 10 to 34); and of the 26 patients without symptomatic coronary heart disease, the mean was 7% (range 2 to 28) ($p < 0.05$). The mean of 19% in patients with symptomatic coronary heart disease aged ≥90 was half that observed in patients aged ≤85 years (mean 56) with fatal coronary heart disease and the mean of 8% was nearly 3 times that observed in the younger patients without fatal coronary heart disease.[16–21]

These detailed morphologic studies of the coronary arteries in these very elderly persons suggest that the degree of severe coronary narrowing necessary to have a fatal or near-fatal coronary event is considerably less than that necessary to have a coronary event in younger patients. Moreover, these studies indicate that these very elderly patients without symptoms of coronary heart disease have distinctly more coronary luminal narrowing by atherosclerotic plaques that do control subjects who are younger, (mean age 52 years).[16–21] The latter observation suggests that coronary heart disease may be underdiagnosed clinically in the very elderly.

Clinical diagnosis of cardiac and other conditions in patients aged 90 years and over appears more difficult than in younger persons. Historic information may be difficult to obtain because of impaired intellect on the part of the patient and an impaired diagnostic pursuit on the part of the physician. Physicians caring for these very elderly persons may focus primarily on the prevention of suffering and only secondarily on accurate diagnosis or longer-term therapy. Patients aged 90 years and over generally have outlived their spouses and private physicians, and often are "inherited" by nursing-home physicians who may have limited access to earlier medical records.

Angina pectoris appears particularly difficult to diagnose in the very elderly because they may not be able to describe this symptom. Acute myocardial infarction also is difficult to diagnose clinically but it is often fatal in the very elderly. Of 11 clinical acute infarcts at or after age 90 years in our patients, 10 were fatal. Only 4 of the 11 acute infarcts were clearly diagnosed clinically; most others were manifest as more dyspnea. Furthermore, the electrocardiogram is not as useful in diagnosis of acute myocardial infarction in the very elderly because left bundle branch block is frequent and it, of course, prevents the appearance of typical changes. Serial recordings of electrocardiograms also appear to be quite infrequent in the very elderly. Only

2 of our 10 patients with fatal acute myocardial infarction had as many as 2 electrocardiograms recorded during the final illness.

Physical examination in the very elderly may be both difficult and misleading. The lack of mobility may prevent proper positioning of the elderly patient for proper examining. Precordial murmurs, although very common (25 of our 40 patients), infrequently indicate significant functional abnormality. Although 22 of our 40 patients had calcific deposits in the aortic valve, only 2 appeared to have actual aortic valve stenosis. Likewise, although 19 of the 40 patients had mitral anular calcific deposits, in only 1 patient did the calcific deposits appear to actually narrow the mitral orifice.

Electrocardiographic abnormalities are common in elderly persons. Of our 30 patients with electrocardiograms available, all had ≥1 abnormalities recorded, the most frequent ones being abnormal axis, atrial fibrillation, and complete bundle branch block. Although 15 of the 30 patients had cardiomegaly (>350 g in women, >400 g in men) at necropsy, only 1 had voltage criteria for left ventricular hypertrophy shown by electrocardiography. Likewise, only 1 had low voltage. Measurement of the QRS amplitude in each of the 12 leads was performed in 24 patients; these measurements have never been recorded previously in elderly individuals. The total QRS voltage was similar in the 8 patients with and in the 16 patients without clinical evidence of cardiac disease (mean 147 mm versus mean 152 mm [10 mm = 1 mV]). Although normal amplitudes of the QRS complexes in all 12 leads in elderly patients are lacking, Simonson[22] provided data on the upper and lower limits of amplitude of the QRS complexes in each of the 12 leads in normal men and women aged 20 to 59 years (means not available). The upper and lower limits of normal for men aged 50 to 59 years was 277 and 36 mm, and for the women 248 and 27 mm, respectively.

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## References

1. **Fries JF.** Aging, natural history, and the compression of morbidity. N Engl J Med 1980;303:130–135.
2. **Siegel JS.** Recent and prospective demographic trends for the elderly population and some implications for health care. In: Haynes SG, Feinleib M, eds. Second Conference on the Epidemiology of Aging. U.S. Department of Health and Human Services, Washington DC, NIH Publication No. 80-969, 1980;293.
3. **Kohn RR.** Cause of death in very old people. JAMA 1982;247:2793–2797.
4. **Eckner FAD, Brown BW, Davidson DL, Glagov S.** Dimensions of normal hearts: after standard fixation by controlled pressure coronary perfusion. Arch Pathol Lab Med 1969;88:497–507.
5. **Roberts WC, Perloff JK, Constantino T.** Severe valvular aortic stenosis in patients over 65 years of age. A clinicopathologic study. Am J Cardiol 1971;27:497–506.
6. **Roberts WC, Perloff JK.** Mitral valve disease. A clinico-pathologic survey of the conditions causing the mitral valve to function abnormally. Ann Intern Med 1972;77:939–975.
7. **Roberts WC, Waller BF.** Mitral valve "anular" calcium forming a complete circle or "O" configuration: clinical and necropsy observations. Am Heart J 1981;101:619–621.
8. **Buja LM, Khoi NB, Roberts WC.** Clinically significant cardiac amyloidosis. Clinicopathologic findings in 15 patients. Am J Cardiol 1970;26:394–405.
9. **Beck CS.** Coronary artery disease. A report to William Harvey 300 years later. Am J Cardiol 1958;1:38–45.
10. **Roberts WC.** Aortic dissection: anatomy, consequences and causes. Am Heart J 1981;101:195–214.
11. **Surgiura M, Hiraoka K, Ohkawa S, Shimada H.** A clinicopathologic study on the heart diseases in the aged. The morphologic classification of 1,000 consecutive autopsy cases. Jpn Heart J 1975;16:526–537.
12. **Pomerance A.** Cardiac pathology in the elderly. In: Noble RJ, Rothbaum DA, eds. Geriatric Cardiology. Philadelphia: FA Davis, 1981: 9–54.
13. **Promerance A.** Pathology of the heart with and without cardiac failure in the aged. Br Heart J 1965;27:697–710.
14. **Aldrich RF, Brensike JF, Battaglini JW, Richardson JM, Loh IK, Stone NJ, Passamani ER, Ackerstein H, Seningen R, Borer JS, Levy RI, Epstein SE.** Coronary calcifications in the detection of coronary artery disease and comparison with electrocardiographic exercise testing. Results from the National Heart, Lung, and Blood Institute's Type II Coronary Intervention Study. Circulation 1979;59:1113–1124.
15. **Gelfand M.** Heart disease in the elderly African. Br Heart J 1961;23: 387–392.
16. **Roberts WC, Jones AA.** Quantitation of coronary arterial narrowing at necropsy in sudden coronary death. Analysis of 31 patients and comparison with 25 control subjects. Am J Cardiol 1979;44:39–45.
17. **Roberts WC, Virmani R.** Quantification of coronary arterial narrowing on clinically-isolated unstable angina pectoris. An analysis of 22 necropsy patients. Am J Med 1979;67:792–799.
18. **Roberts WC, Jones AA.** Quantification of coronary arterial narrowing at necropsy in acute transmural myocardial infarction: analysis and comparison of findings in 27 patients and 22 controls. Circulation 1980;61:786–790.
19. **Virmani R, Roberts WC.** Quantification of coronary arterial narrowing and of left ventricular myocardial scarring in healed myocardial infarction with chronic, eventually fatal, congestive heart failure. Am J Med 1980;68: 831–838.
20. **Cabin HS, Roberts WC.** True left ventricular aneurysm and healed myocardial infarction. Clinical and necropsy observations including quantification of degrees of coronary arterial narrowing. Am J Cardiol 1980;46:754–763.
21. **Virmani R, Roberts WC.** Non-fatal healed transmural myocardial infarction and fatal non-cardiac disease. Qualification and quantification of coronary arterial narrowing. Br Heart J 1981;45:434–441.
22. **Simonson F.** Differentiation Between Normal and Abnormal in Electrocardiography. St. Louis: CV Mosby, 1961:328.

# Hemodynamic Effects of a New Antiarrhythmic Agent, Flecainide (R-818), in Coronary Heart Disease

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**The hemodynamic effects of flecainide acetate, a new class I antiarrhythmic agent, were studied in 10 patients with coronary heart disease. The drug was injected intravenously at a dose of 2 mg/kg over 30 minutes. The mean drug plasma level achieved was 394 ng/ml (range 329 to 470). The heart rate did not change, but a significant increase ($p < 0.001$) in P-R (+17%), QRS (+15%), and Q-T (+7%) duration occurred after drug administration. Negative inotropic effects also were observed and consisted of an increase ($p < 0.01$) in pulmonary wedge pressure (+27%) and a decrease ($p < 0.01$) in stroke index (−10%), left ventricular stroke work index (−12%), and left ventricular ejection rate (−11%). No significant change in mean aortic pressure or systemic and pulmonary vascular resistance occurred. Left ventriculography performed after drug infusion revealed a significant increase ($p < 0.01$) in systolic volume (+9%) and a decrease in ejection fraction (−9%) and mean velocity of circumferential fiber shortening (Vcf) (−13%). A progressive and significant decrease of dP/dt was observed during drug infusion, but 15 minutes after the injection, dP/dt had returned to near basal values. Thus, flecainide acetate has slight, but significant negative inotropic effects, particularly conspicuous during drug infusion. The drug should be administered with caution in patients with poorly compensated heart.**

Flecainide acetate is a novel antiarrhythmic drug that has many properties of class I antiarrhythmic agents. It possesses local anesthetic properties and in preliminary clinical trials has markedly or completely suppressed ventricular arrhythmias.[1-8] Despite very promising results, better knowledge of the hemodynamic effects of flecainide is needed before its wide acceptance for clinical use. Previous studies in animals[9,10] showed a slight negative inotropic effect, whereas noninvasive studies in man yielded controversial results.[4,11]

It is particularly important to know whether flecainide has deleterious negative inotropic effects in patients with serious cardiac disorders, especially coronary heart disease. This study was undertaken to examine the hemodynamic effects of flecainide in patients with ischemic heart disease who are theoretically at special risk when this agent is administered intravenously.

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## Methods

**Patients:** Ten patients with recent acute myocardial infarction submitted to angiographic and hemodynamic evaluation constituted the study group (Table I). All required antiarrhythmic therapy because of ventricular premature beats or tachycardia. The nature of the procedure was explained to the patient and informed consent was obtained.

**Procedures:** The studies were performed in the afternoon. Four patients (Patients 2, 3, 6, and 10) were currently treated by beta blocking drugs; none received calcium antagonists. All previous therapy was withdrawn for at least 12 hours.

With the patient in the supine position, a Swan-Ganz and a pigtail catheter were introduced using the Seldinger technique and a femoral approach. Pressure was recorded from the left ventricle, aorta, right ventricle, right atrium, pulmonary artery, and pulmonary wedge by means of a Statham P23 db strain gauge on a Philips photographic recorder. The common zero reference level for all pressures was set at the mid-chest. The mean pressure values and determination of dP/dt maximum were determined electronically by an automatic catheterization system (Philips Physio Cardiopan System PC 5000). Cardiac output was determined in triplicate with thermodilution techniques using an Edwards model 9620 thermodilution cardiac output computer.

The systemic (SVR) and pulmonary (PVR) vascular resistance and total pulmonary resistance (TPR) in dynes s $cm^{-5}$ were obtained using the following formulas: SVR =

**TABLE I Patients' Characteristics**

| Case | Age (yr) & Sex | Electrocardiographic Site of Infarction | Peak CK (U/liter) | Delay From MI to Investigation (days) | Diseased Vessels (n) | Total R-818 Injected Intravenously (mg) |
|---|---|---|---|---|---|---|
| 1 | 58M | Inferior | 873 | 21 | 2 | 150 |
| 2 | 62M | Inferior | 1,063 | 43 | 1 | 165 |
| 3 | 63M | Inferoposterior | 1,340 | 40 | 3 | 140 |
| 4 | 55F | Inferior | 2,418 | 21 | 2 | 110 |
| 5 | 50M | Inferior | 970 | 26 | 2 | 160 |
| 6 | 58M | Inferolateral | 2,850 | 35 | 1 | 140 |
| 7 | 43M | Inferior | 296 | 17 | 1 | 140 |
| 8 | 55M | Inferoposterior | 1,380 | 20 | 3 | 150 |
| 9 | 40M | Inferior | 1,143 | 20 | 2 | 165 |
| 10 | 36M | Inferior | 1,503 | 20 | 1 | 180 |

CK = creatine kinase; MI = myocardial infarction.

(MBP − MRA)·1.332/CO, PVR = (MPAP − PCWP)·1.332/CO; TPR = MPAP·1.322/CO, where MBP = mean aortic blood pressure (mm Hg), MRA = mean right atrial pressure (mm Hg), MPAP = mean pulmonary artery pressure (mm Hg), PCWP = pulmonary capillary wedge pressure (mm Hg), and CO = cardiac output (ml/min).

Left ventricular stroke work index (LVSWI) in g·m/m$^2$ and mean systolic ejection rate (MSER) in ml/s·m$^2$ were calculated from the following formulas: LVSWI = SVI [MBP − LVEDP] ×13.6/100 and MSER = SVI/SEP, where SVI = stroke volume index (ml/m$^2$), MBP = mean aortic blood pressure (mm Hg), LVEDP = left ventricular end-diastolic pressure (mm Hg), and SEP = systolic ejection period (s/beat).

Left ventricular volumes were determined using the Simpson's rule by an automated program. End-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV = EDV − ESV), and ejection fraction (SV/EDV) were calculated for each patient. The mean velocity of circumferential fiber shortening (Vcf) was obtained as follows: Vcf = (dED − dES)/(dED·ejection time). In this equation, dED and dES are the left minor axes in end-diastole and end-systole obtained after determination of end-diastolic and end-systolic areas planimetered in the right anterior oblique view (D area and S area) and the corresponding left major axes (lED and lES): dED = 4 D area/$\pi$lED, and dES = 4 S area/$\pi$lES. A quantitative analysis of segmental wall motion was applied for each ventriculogram according to the technique described by Ingels et al.[12] A point located at 69% of the distance from the anterolateral edge of the aortic valve to the ventricular apex at end-systole served as a fixed reference. Using polar coordinates, regional shortening for all points along the ventricular outline was calculated and displayed by an automated system, which gives an objective and quantitative evaluation of regional contractility.

**Study protocol:** The hemodynamic variables were first measured in basal conditions. Thereafter, a left ventriculogram was obtained in a 30° right anterior oblique view followed by coronary arteriography. Ten minutes were allowed to elapse before the infusion of flecainide was started. Flecainide, 2 mg/kg, was then injected intravenously at a constant rate over 30 minutes. Fifteen minutes after the end of the infusion, hemodynamic measurements were repeated and a second ventriculogram was performed. In the last 6 patients, dP/dt was also recorded using a Millar micromanometer throughout the infusion of the drug and 15 minutes later. At least 55 minutes separated the first and second angiogram: the pharmacologic effects of contrast medium on myocardial contractility were thus most probably eliminated.[13–15]

Blood samples for determination of plasma flecainide concentration were obtained during the second hemodynamic measurements, 15 minutes after the end of the infusion. The plasma concentration of flecainide was measured by gas-liquid chromatography.[4] Averaged data are presented as mean ± standard deviation. Student's $t$ test for paired observations was used. Statistics are based on the raw data.

## Results

**Heart rate and electrocardiogram (Fig. 1):** No significant change in heart rate was observed after administration of the drug. Significant increases in P-R (+16.6%), QRS (+15.2%), and Q-T (+6.6%) ($p < 0.001$) were noted.

**Pressure and cardiac index (Fig. 2):** The mean pulmonary capillary wedge pressure (PCWP) increased in all but 1 patient ($p < 0.01$) and the stroke index decreased ($p < 0.01$) in all except 1 (in whom PCWP in-

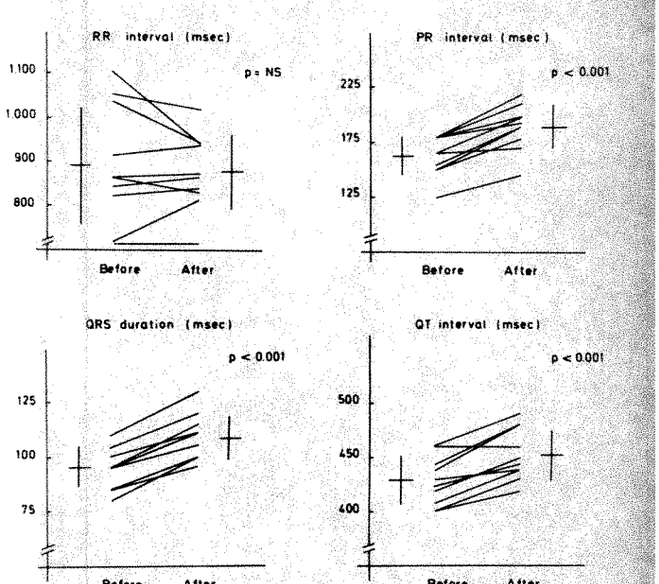



**FIGURE 1.** Diagrams showing the individual variations in R-R, P-R, QRS, and Q-T intervals. Changes induced by flecainide infusion (before = before infusion; after = after infusion). The p value indicated is the level of significance of $t$ test for paired data. NS = not significant.

**TABLE II Plasma Flecainide Concentrations and Relative Changes in Main Electrocardiographic Hemodynamic and Angiographic Variables**

| Patient | Plasma Level (ng/ml) | Change in P-R Duration (%) | Change in QRS Duration (%) | Change in PCWP (%) | Change in SI (%) | Change in LVSWI (%) | Change in LVER (%) | Change in EF (%) | Change in Mean Vcf (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 470 | +9 | +14 | +25 | −10 | −7 | −7 | −11 | −10 |
| 2 | 388 | +22 | +10 | +7 | −13 | −9 | −14 | −3 | −5 |
| 3 | 425 | +27 | +16 | +50 | −15 | −12 | −20 | −10 | −27 |
| 4 | 390 | +16 | +12 | +37 | −12 | −18 | −12 | −16 | −17 |
| 5 | 361 | +20 | +18 | 0 | −12 | −19 | −11 | −9 | −9 |
| 6 | 413 | +21 | +25 | +57 | −14 | −1 | −9 | −5 | −22 |
| 7 | 329 | +22 | +26 | +50 | +4 | −14 | +1 | +4 | −9 |
| 8 | 397 | +11 | +18 | +56 | −6 | −16 | −7 | −7 | 0 |
| 9 | 394 | +8 | +10 | −7 | −13 | −24 | −12 | −23 | −16 |
| 10 | 373 | +17 | +11 | +25 | −2 | 0 | −8 | −8 | −18 |
| Mean | 394 ± 38 | +17 | +15 | +27 | −10 | −12 | −11 | −9 | −13 |

All changes express the variation in percentage after flecainide infusion compared with the basal value. EF = ejection fraction; LVER = left ventricular ejection rate; LVSWI = left ventricular stroke work index; mean Vcf = mean velocity of circumferential fiber shortening; PCWP = pulmonary capillary wedge pressure; SI = systolic index.

creased from 12 to 18 mm Hg). No significant change in mean aortic pressure was noted. A significant increase in mean pulmonary pressure ($p < 0.001$) was also observed, whereas mean right atrial pressure did not change.

**Vascular resistance and cardiac performance index (Fig. 3):** Slight but insignificant increases in systemic and pulmonary vascular resistance were noted. The left ventricular stroke work index was reduced in 9 patients ($p < 0.01$). The left ventricular ejection rate also decreased in all but 1 patient ($p < 0.001$). The dP/dt was measured during flecainide infusion in 6 patients. Although significant changes were not demonstrated by an analysis of variance, individual variations in dP/dt showed a progressive decrease which became significant 15 minutes after the beginning of infusion as compared with basal value (paired $t$ test). Fifteen minutes after the end of the injection, dP/dt had returned to near basal values (Fig. 4).

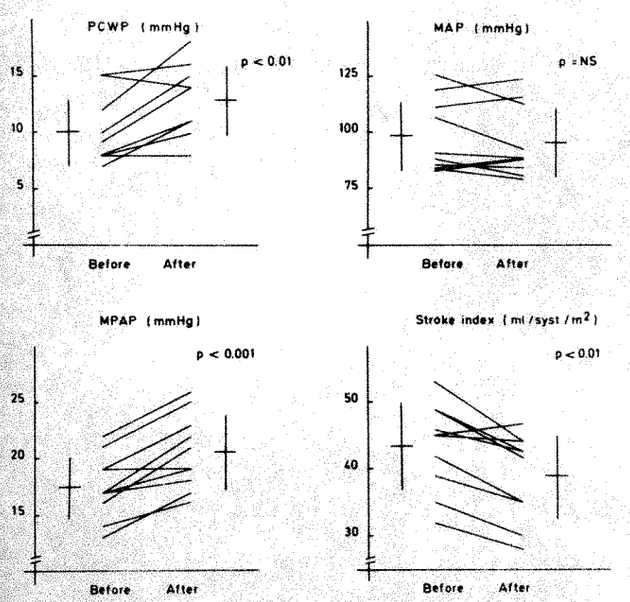



**FIGURE 2.** Diagrams showing the individual variations in pulmonary capillary wedge pressure (PCWP), mean aortic pressure (MAP), mean pulmonary arterial pressure (MPAP), and stroke index induced by flecainide infusion (before = before infusion; after = after infusion). The p value indicated is the level of significance of Student's $t$ test for paired data. NS = not significant.

**Ventricular volumes (Fig. 5):** No significant changes were noted to diastolic volume after flecainide injection. However, systolic volume increased in all patients ($p < 0.01$), causing a significant decrease in stroke volume ($p < 0.01$) and ejection fraction. Mean velocity of circumferential shortening also decreased significantly ($p < 0.001$).

**Regional wall motion:** All patients had regional disorders of left ventricular contractility. In each, the area of asynergy was supplied by a critically narrowed coronary artery and corresponded to the electrocardiographic site of infarction. After flecainide injection, segmental wall motion analysis indicated a slight diffuse decrease in wall movement with no new areas of asynergy.

**Plasma drug concentrations:** Plasma drug levels obtained 15 minutes after the infusion of 2 mg/kg of flecainide over 30 minutes varied from 329 to 470 ng/ml. Within this drug level range, there was no relation between drug concentration and changes in individual electrocardiographic, hemodynamic, and angiographic variables (Table II).

**Side effects:** Apart from the cardiac effects just described, there were no complications or patient's complaints during or after the study.

## Discussion

**Intrinsic myocardial depressant effect:** Intravenous flecainide in doses recommended for the treatment of arrhythmia (2 mg/kg) exerts mild but significant adverse hemodynamic effects in man. In our patients without overt left heart failure, stroke index and index of cardiac contractility (LVSWI and LVER) decreased 10% ($p < 0.01$). The ejection fraction, which is considered one of the most sensitive indexes of global ventricular performance, decreased 9% ($p < 0.01$). No significant

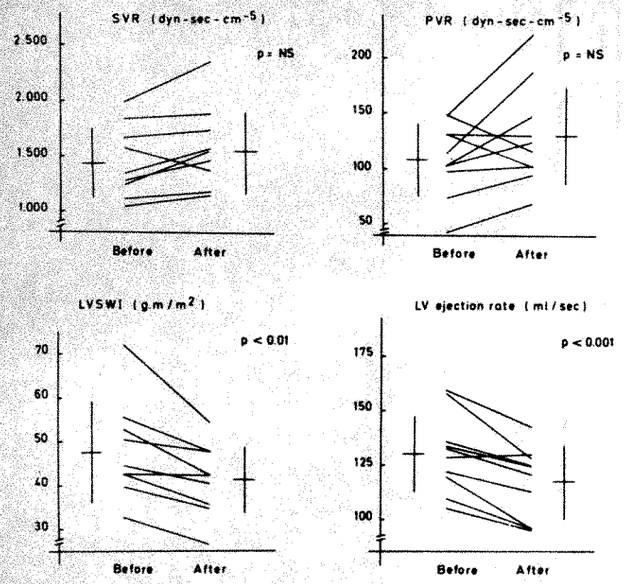



**FIGURE 3.** Diagrams showing the individual variations of systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), left ventricular stroke work index (LVSWI), and left ventricular (LV) ejection rate induced by flecainide infusion (before = before infusion; after = after infusion). The p value indicated is the level of significance of Student's *t* test for paired data. NS = not significant.

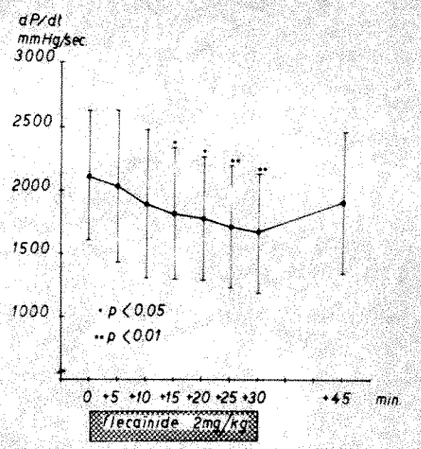



**FIGURE 4.** Mean variations in dP/dt observed during flecainide infusion and 15 minutes after the end of injection. The p value indicated is the level of significance of Student's *t* test for paired data; comparison is made with the basal values before flecainide infusion.

changes in systemic and pulmonary vascular resistance were noted, which suggests the absence of vascular effects. Pulmonary wedge pressure, mean pulmonary arterial pressure, and total pulmonary resistance significantly increased as a consequence of depressed left ventricular function. Thus, flecainide, exerted a direct negative inotropic effect on myocardial fiber but failed to exhibit any significant peripheral vasoconstrictive action.

Although similar hemodynamic side effects were reported with all class I antiarrhythmic drugs,[16] comparative studies are required to evaluate the importance of myocardial depression induced by flecainide as compared with that induced by other class I antiarrhythmic drugs. Previous hemodynamic studies showed that the negative inotropic effect produced by tocainide or encainide is comparable to that observed in our study with flecainide.[17,18]

**Dose-related myocardial depression:** The plasma concentration of flecainide in our patients ranged from 329 to 470 ng/ml, a value similar to that achieved by others after 1 to 2 mg/kg administered intravenously or orally and recognized to have antiarrhythmic effects.[2,4,19]

Interpatient comparison did not reveal any relation between plasma level and cardiac effects of the drug; however, the range of drug concentration was rather small. This observation suggests that within the therapeutic range achieved, the cardiac response to flecainide is individual and cannot be predicted from the plasma drug level.

Experimental studies in pigs have shown a dose-related negative inotropic effect during infusion of the drug.[10] The individual response of dP/dt during drug infusion in 6 of our patients confirmed those observations. As the drug was infused, the contractility index dP/dt exhibited a progressive decrease; however, improvement in myocardial contractility appeared after the end of infusion and dP/dt returned to near basal values within 15 minutes. Plasma levels were not studied throughout drug infusion; however, one may hypothesize that intravenous administration of flecainide results in high plasma levels of the drug which rapidly

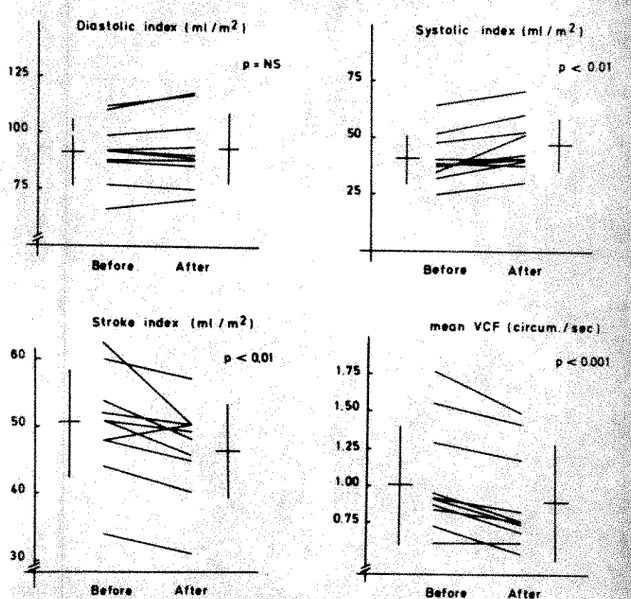



**FIGURE 5.** Diagrams showing the individual variation in diastolic volume index, systolic volume index, stroke volume index, and mean velocity of circumferential fiber shortening (VCF) induced by flecainide infusion (before = before infusion; after = after infusion). The p value indicated is the level of significance of Student's *t* test for paired data.

decrease during the first 10 minutes after administration, as shown in animal studies.[10]

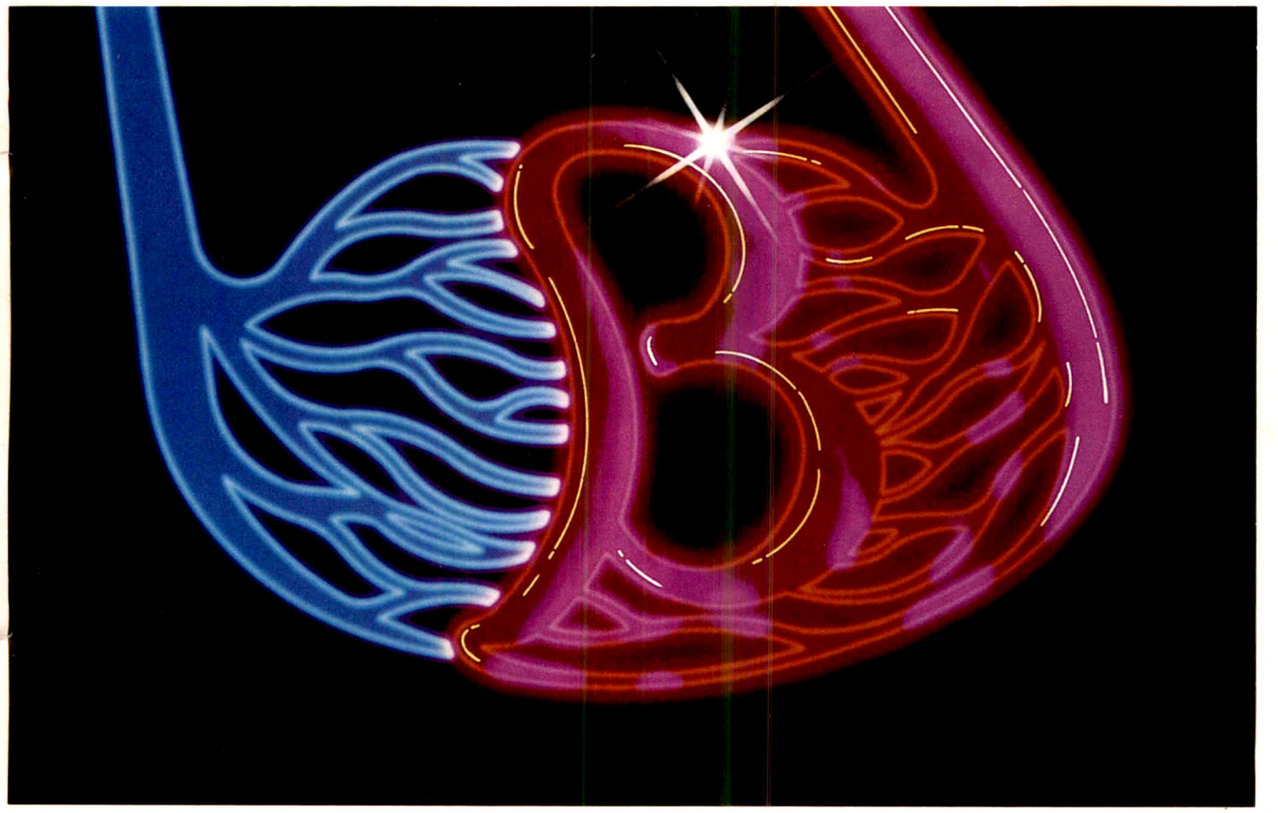
**Therapeutic implications:** Flecainide acetate administered intravenously exerts a negative inotropic effect that may be of clinical importance in patients with congestive heart failure. This effect is particularly marked during infusion. Therefore, in patients with an uncompensated or poorly compensated heart, the drug should be administered with caution and the infusion interrupted if any deterioration of cardiac function occurs. In such cases, an initial primary dose of only 1 mg/kg or slower administration over 60 minutes may be preferred.

## References


1. **Duff HJ, Roden DM, Woosley RL.** Abolition of resistant ventricular arrhythmias by twice daily dosing with flecainide (abstr). Circulation 1980; 62:Suppl III:III–81.
2. **Somani P.** Antiarrhythmic effects of flecainide. Clin Pharmacol Ther 1980;27:464–470.
3. **Hodges M, Haugland JM, Granrud G. Asinger RW, Mikell FL, Krejci J.** Flecainide acetate, a new antiarrhythmic agent: dose ranging and efficacy study (abstr). Am J Cardiol 1981;47:482.
4. **Anderson JL, Stewart JR, Perry BA, Van Hamersveld DD, Johnson TA, Conard GJ, Chang SF, Kvam DC, Pitt B.** Oral flecainide acetate for the treatment of ventricular arrhythmias. N Engl J Med 1981;305:473–477.
5. **Seipel L, Abendroth RR, Breithardt G.** Electrophysiological effects of flecainide R 818 in man (abstr). Eur Heart J 1981;2A:115.
6. **Granrud G, Krejci J, Coyne T, Hodges M.** Sustained elimination of ventricular arrhythmias during chronic flecainide dosing (abstr). Circulation 1981;64:Suppl IV:IV-316.
7. **Van Hamersveld DD, Stewart JR, Johnson TA, Anderson JL.** Oral flecainide acetate for long term treatment of ventricular arrhythmias in man (abstr). Circulation 1981;64:Suppl IV:IV-316.
8. **Campbell RWF, Henderson A, Bryson LG, Reid DS, Sheridan DJ, Rawlins MD, Julian DG.** Intravenous flecainide: pharmacokinetics and efficacy. Circulation 1981;64:Suppl IV:IV-265.
9. **Welter AN, Schmid JR, Kvam C.** Cardiovascular profile of R 818, flecainide, a new antiarrhythmic (abstr). Fed Proc 1977;36:1003.
10. **Verdouw PD, Dekers JW, Conard GJ.** Antiarrhythmic and hemodynamic actions of flecainide acetate (R 818) in the ischemic porcine heart. J Cardiovasc Pharmacol 1979;1:473–486.
11. **Hodges M, Hoback J, Graham E, Erlien D, Asinger R, Mikell F.** Cardiac function after oral dosing with flecainide acetate (abstr). Clin Pharmacol Ther 1981;29:251.
12. **Ingels NB Jr, Daughters GT, Stinson EB, Alderman EL.** Evaluation of methods of quantitative left ventricular segmental wall motion in man using myocardial markers as a standard. Circulation 1980;61:966–972.
13. **Mullins CB, Leshin SJ, Miersziak DS, Alsobrook HD, Mitchell JH.** Changes in left ventricular function produced by the injection of contrast media. Am Heart J 1972;83:373–381.
14. **Hamby RI, Aintablian A, Wilsoff BG, Hartstein ML.** Effects of contrast medium on left ventricular pressure and volume with emphasis on coronary artery disease. Am Heart J 1977;93:9–18.
15. **Fischer HW, Thomson KR.** Contrast media in coronary arteriography: a review. Invest Radiol 1978;13:450–459.
16. **Jewitt DE.** Hemodynamic effects of newer antiarrhythmic drugs. Am Heart J 1980;100:984–989.
17. **Winkle RA, Anderson F, Peters F, Meffin PG, Fowles RE, Hainson DC.** The hemodynamic effects of intravenous tocainide in patients with heart disease. Circulation 1978;57:787–792.
18. **Harrison DC, Winkle R, Sami M, Mason J.** Encainide: a new and potent antiarrhythmic agent. Am Heart J 1980;100:1046–1054.
19. **Conard GC, Carlson GL, Frost JW, Ober RE.** Human plasma pharmacokinetics of flecainide acetate (R 818), a new antiarrhythmic following single oral and intravenous dose (abstr). Clin Pharmacol Ther 1979;25:218.


Life is not easy for any of us. But what of that? We must have perseverance and above all confidence in ourselves. We must believe that we are gifted for something, and that this thing, at whatever cost, must be attained.

Marie Curie



**Pick the only beta blocker that reduces total peripheral resistance:**

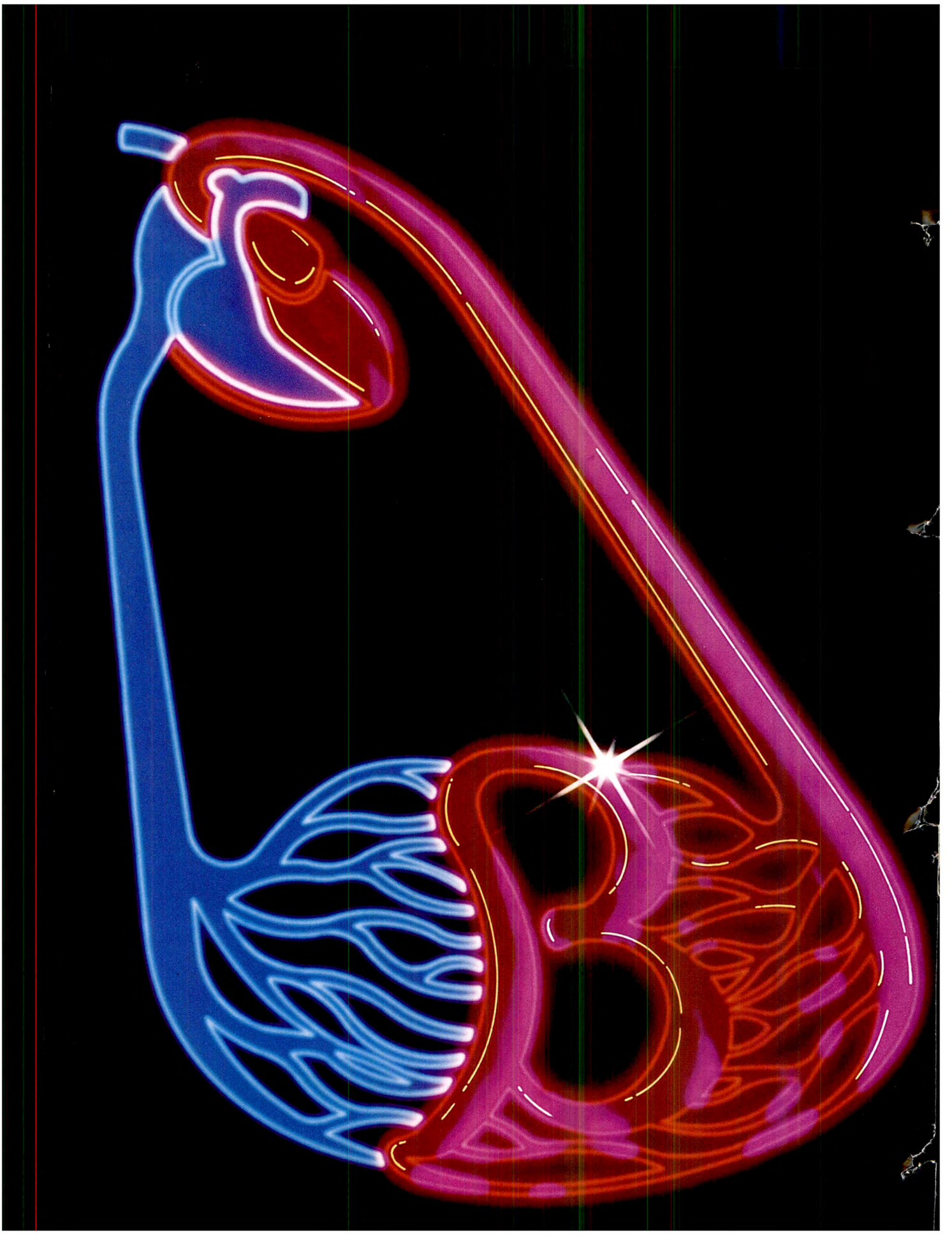
**1. Inderal®** (propranolol)

**2. Lopressor®** (metoprolol)

**3. Tenormin®** (atenolol)

**4. None of the above**

**(If you picked #4, you're right.)**



## Introducing:

# Visken® (pindolol)

## the only beta blocker that reduces blood pressure and total peripheral resistance*

# Here's the difference:

### Blood pressure

Blood pressure equals cardiac output times total peripheral resistance.

**bp=co×tpr**

### Visken (pindolol)

Visken (pindolol) is the only beta blocker that reduces blood pressure while maintaining resting cardiac output and reducing total peripheral resistance* during long-term therapy.

**bp↓=co×tpr↓**

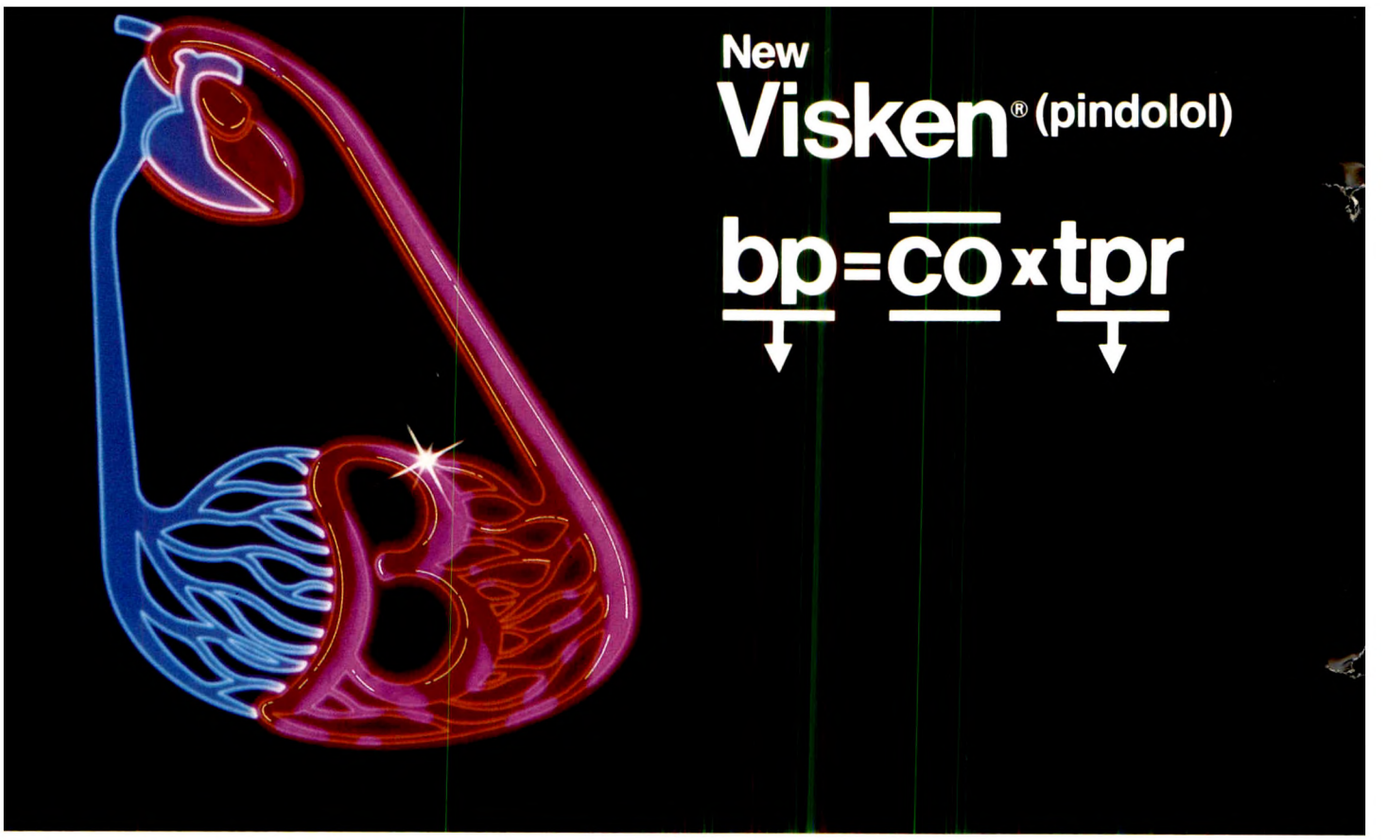
### All other beta blockers

All other beta blockers reduce blood pressure, and reduce cardiac output with an initial reflex rise in total peripheral resistance and a subsequent return to baseline in many cases.

**bp↓=co↓×tpr↑**

*The clinical significance has not been evaluated.
See clinical significance statement on fourth page of this advertisement.

Please see last page of this advertisement for brief summary of prescribing information.




# Here's the result:

## Reduced blood pressure

U.S. studies at 29 major medical centers[1] have shown that Visken (pindolol) is an effective antihypertensive. It is as effective as propranolol in normalizing blood pressure (dbp≤90 mmHg) when used alone. It is also effective when used in combination with a diuretic.

This antihypertensive effectiveness is supported by 13 years of clinical use throughout the world. In fact, Visken (pindolol) is the #2 beta blocker in the rest of the world.

## Reduced peripheral resistance*

Studies of 178 patients treated with Visken (pindolol) for at least two weeks have shown that Visken therapy reduces total peripheral resistance.[1]*

## Reduction of exercise-induced tachycardia

Like other beta blockers, Visken (pindolol) blocks stimulation by catecholamines to reduce exercise-induced increases in systolic blood pressure and heart rate.

## The clinical significance has not been evaluated

The clinical significance of maintaining resting cardiac output, resting heart rate and reduced total peripheral resistance has not been evaluated and there is no evidence or reason to believe that exercise cardiac output is less affected by Visken (pindolol) than other beta blockers.

*See clinical significance statement.

# Here's the importance:

## Visken® (pindolol) reduces blood pressure with little effect on resting cardiac output

Unlike other beta blockers, Visken (pindolol) has little effect on resting cardiac output during long-term therapy.

## Visken (pindolol) makes hemodynamic sense in the treatment of hypertension

Visken (pindolol) reduces one of the recognized components of hypertension: increased peripheral resistance.*

## Visken (pindolol) reduces blood pressure with little effect on resting heart rate

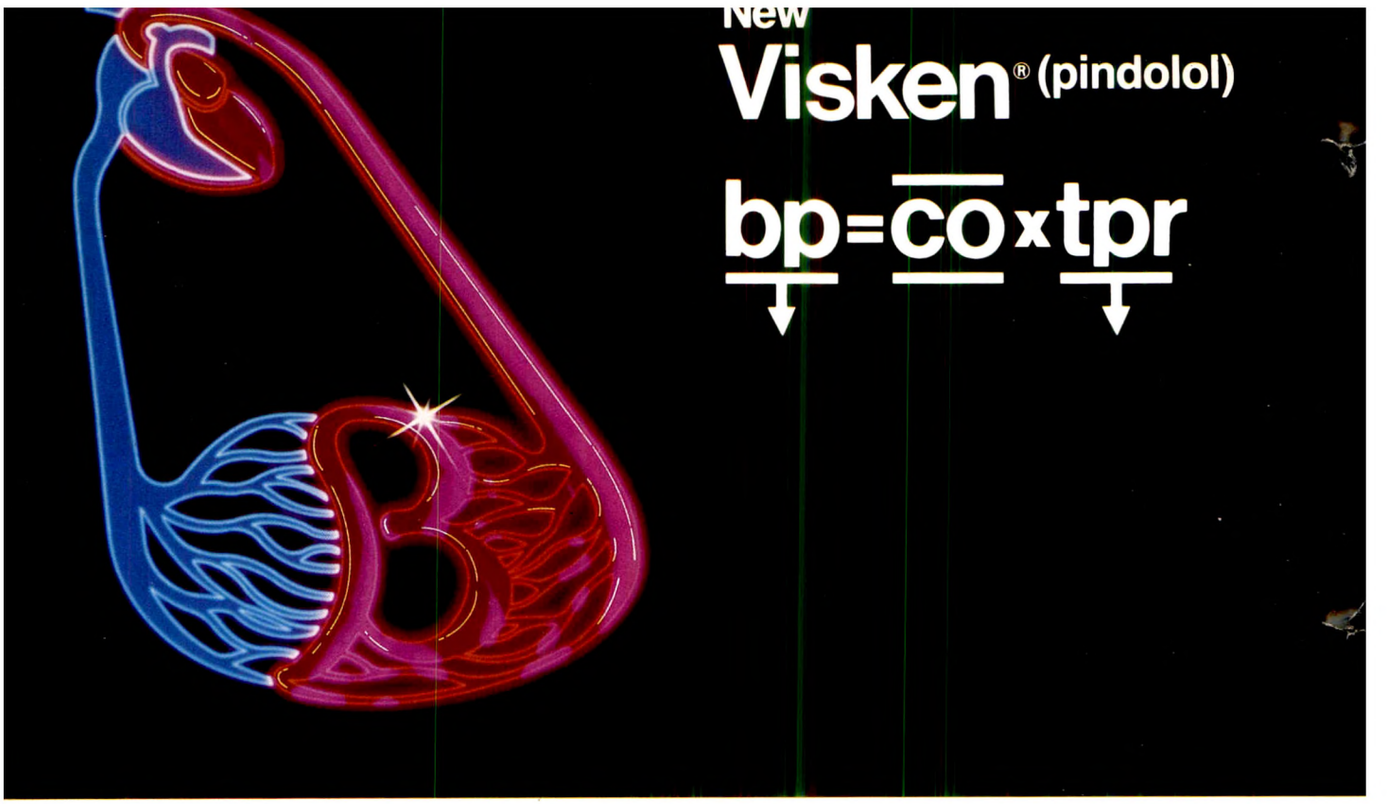
Visken (pindolol) produces minimal changes in resting heart rate. Average reduction: 4-8 beats/minute. Minimal effect on resting heart rate results in low potential for bradycardia.

## Visken (pindolol) maintains renal blood flow

Visken (pindolol) reduces supine and standing blood pressure while maintaining effective renal plasma flow and glomerular filtration rates.[2]

*See clinical significance statement on facing page of this advertisement.

See last page of this advertisement for brief summary of prescribing information.




# Here's what you can expect:

**Reduced total peripheral resistance***

**Minimal effect on resting cardiac output**

**Minimal effect on resting heart rate**

**Minimal effect on renal blood flow**

**Favorable side effect profile†**

**Low incidence of bradycardia**

**Low incidence of cold extremities**

*See clinical significance statement on fourth page of this advertisement.

†Visken (pindolol) is contraindicated in:

1) bronchial asthma
2) overt cardiac failure
3) cardiogenic shock
4) second- and third-degree heart block
5) severe bradycardia

# Prescribing information:

## Available in 5 mg and 10 mg tablets

## Convenient bid dosage

Dosage should be titrated on an individual basis. Many patients respond to 10-30 mg a day in divided doses.


**References:**

1. Data on file, Sandoz Pharmaceuticals.
2. Wilcox CS, Lewis PS, Peart WS, et al: Renal function, body fluid volumes, renin, aldosterone, and noradrenaline during treatment of hypertension with pindolol. *J Cardiovasc Pharmacol* 3:598–611, 1981.


*The clinical significance has not been evaluated. See clinical significance statement on fourth page of this advertisement.

Please see last page of this advertisement for brief summary of prescribing information.

# New Visken® (pindolol)

*Before prescribing or administering, see package circular for full product information. The following is a brief summary.*

## INDICATIONS AND USAGE
Visken (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

## CONTRAINDICATIONS
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

## WARNINGS
**Cardiac Failure:** Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

**In Patients Without A History of Cardiac Failure:** In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal:** Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers:** Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

**Major Surgery:** Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

**Diabetes and Hypoglycemia:** Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

**Thyrotoxicosis:** Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

## PRECAUTIONS
**Impaired Renal or Hepatic Function:** Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

**Information for Patients:** Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

**Drug Interactions:** Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

**Pregnancy—Category B:** Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

**Pediatric Use:** Safety and effectiveness in children have not been established.

## CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

## ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

| Body System/ Adverse Reaction | Total (Volunteered and Elicited) Visken (pindolol) (N = 322) % | Active Controls* (N = 188) % | Placebo (N = 78) % |
|---|---|---|---|
| Central Nervous System | | | |
| Anxiety | 4 | <1 | 1 |
| Bizarre or Many Dreams | 8 | 3 | 8 |
| Dizziness | 17 | 23 | 8 |
| Fatigue | 15 | 19 | 12 |
| Hallucinations | 1 | 0 | 0 |
| Insomnia | 19 | 8 | 12 |
| Lethargy | 3 | 6 | 4 |
| Nervousness | 11 | 5 | 9 |
| Weakness | 7 | 5 | 4 |
| Autonomic Nervous System | | | |
| Paresthesia | 5 | 2 | 8 |
| Visual Disturbances | 4 | 3 | 4 |
| Cardiovascular | | | |
| Dyspnea | 9 | 8 | 9 |
| Edema | 11 | 9 | 3 |
| Heart Failure | 2 | <1 | 0 |
| Palpitations | 2 | 2 | 0 |
| Weight Gain | 3 | 5 | 0 |
| Musculo-Skeletal | | | |
| Chest Pain | 5 | 3 | 5 |
| Joint Pain | 11 | 6 | 8 |
| Muscle Cramps | 8 | 2 | 0 |
| Muscle Pain | 12 | 12 | 9 |
| Gastrointestinal | | | |
| Abdominal Discomfort | 7 | 7 | 5 |
| Nausea | 7 | 4 | 1 |
| Skin | | | |
| Pruritus | 2 | <1 | 0 |
| Rash | 2 | 3 | 3 |

*Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

## POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

**Central Nervous System:** Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

**Cardiovascular:** Intensification of AV block. See CONTRAINDICATIONS.

**Allergic:** Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

**Hematologic:** Agranulocytosis; thrombocytopenic and nonthrombocytopenic purpura.

**Gastrointestinal:** Mesenteric arterial thrombosis; ischemic colitis.

**Miscellaneous:** Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

## OVERDOSAGE
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

**Excessive Bradycardia:** administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

**Cardiac Failure:** digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

**Hypotension:** administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

**Bronchospasm:** administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ≥80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

## DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 10 mg b.i.d. alone or in combination with other antihypertensive agents. Many patients will respond to 15 mg per day (5 mg t.i.d.). The antihypertensive response usually occurs within the first week of treatment. If a satisfactory reduction in blood pressure does not occur within 2-3 weeks, the dose may be adjusted in increments of 10 mg per day at 2-3 week intervals up to a maximum of 60 mg per day.

## HOW SUPPLIED
White, round, scored tablets: 5 mg and 10 mg, packages of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" on one side, and "78-73" and scored on other side (NDC 0078-0073-05). [VIS-Z2 9/1/82]

**Pharmaceutical Division**
**SANDOZ, INC.**
East Hanover, NJ 07936

VIS-1182-1

# Pindolol and Propranolol in Patients With Angina Pectoris And Normal or Near-Normal Ventricular Function

## Lack of Influence of Intrinsic Sympathomimetic Activity on Global and Segmental Left Ventricular Function Assessed by Radionuclide Ventriculography

DANTE E. MANYARI, MD, WILLIAM J. KOSTUK, MD, S. GEORGE CARRUTHERS, MD, DONALD J. JOHNSTON, MD, and PAUL PURVES, RT

**To investigate the role of intrinsic sympathomimetic activity on left ventricular (LV) function during antianginal therapy with beta-adrenoreceptor antagonists, 23 patients with chronic, exercise-induced angina pectoris and normal or near normal LV function underwent radionuclide ventriculography at rest and during exercise, during 3 randomly allocated periods: (1) treatment with oral propranolol, a drug without intrinsic sympathomimetic activity, 40 to 80 mg 4 times a day; (2) treatment with pindolol, a drug with marked intrinsic sympathomimetic activity, 5 to 10 mg 2 times a day; and (3) a control period. During the control period, the LV ejection fraction decreased from rest (58.9 ± 8.2%) to exercise (54.3 ± 10.7%), and the wall motion score decreased from 0.57 ± 1.08 at rest to 2.39 ± 2.10 during exercise, p <0.001. After propranolol, the ejection fraction did not change significantly at rest (57.2 ± 8.1%) but improved during exercise (56.8 ± 11.8%), compared with control values. After pindolol, the ejection fraction did not change at rest (57.9 ± 8.6%) but improved during exercise (56.9 ± 8.1%), compared with control values. Similarly, the wall motion score after administration of both agents did not change significantly at rest, but improved during exercise (p <0.001). The number of anginal episodes, nitroglycerin tablets consumed, and magnitude of S-T segment depression decreased significantly with both pindolol and propranolol. With both drugs, a similar improvement in exercise tolerance and a similar decrease in exercise heart rate and blood pressure were obtained. It is concluded that pindolol and propranolol, beta-adrenoreceptor antagonists with and without intrinsic sympathomimetic activity, respectively, have similar effects on global and regional LV function in patients with angina pectoris, at doses producing equal suppression of exercise heart rate and similar antianginal effect.**

Comprehensive, carefully designed studies have failed to show any significant antianginal differences between various beta-adrenoreceptor antagonists with different ancillary pharmacologic properties, when administered on a short- or long-term basis to patients with stable, exertional angina pectoris.[1,2] The influence of intrinsic sympathomimetic activity on global or regional LV function in patients with angina is not known. This investigation compared the effects of pindolol and propranolol, drugs with and without intrinsic sympathomimetic activity, respectively, on LV performance at rest and during exercise in patients with exercise-induced angina. LV function was assessed using electrocardiogram-multigated blood pool cardiac scintigraphy, a noninvasive technique which has been shown to reliably assess global and segmental LV function.[3-5]

From the Cardiac Investigation Unit, University Hospital, and the Department of Medicine, University of Western Ontario, London, Ontario, Canada. This study was supported by the Ontario Heart Foundation and Sandoz (Canada) Limited, Dorval, Quebec, Canada. Manuscript received April 12, 1982; revised manuscript received September 15, 1982, accepted September 24, 1982.

Address for reprints: William J. Kostuk, MD, Cardiac Investigation Unit, University Hospital, Box 5339, Terminal A, London, Ontario, N6A 5A5 Canada.

### Methods

**Patient group:** Twenty-six men, aged 39 to 68 years (mean 52), with exercise-induced angina pectoris were studied. The duration of angina ranged from 3 months to 6 years (average 17 months). No patient had systemic hypertension, valvular

heart disease, intermittent claudication, or any condition that could limit exercise performance. None had diabetes mellitus, obstructive airway disease, or any history of previous adverse reaction to beta-blocking agents. The cardiothoracic ratio was normal in each. There was no clinical or roengtenographic evidence of heart failure. All had sinus rhythm. Ischemic electrocardiographic changes developed during treadmill exercise in all 26. Patients seen consecutively at the outpatient clinic, who met the foregoing criteria, were selected for this study solely on the basis of their willingness to participate.

Coronary cineangiography performed within 1 year of study in 16 of the 26 patients showed evidence of 3-vessel disease in 10, 2-vessel disease in 4, and 1-vessel disease in 2. Two patients had a history of myocardial infarction with abnormal Q waves (>40 ms duration) on the electrocardiogram. Six patients were taking long-acting oral nitrates, which were kept constant during the study period.

**Study design:** This investigation assessed objective measures of LV function; thus an open crossover design was used. Each patient underwent 3 consecutive study periods: (1) a control period in which no beta-adrenoreceptor antagonists were administered; (2) treatment with oral propranolol 4 times a day; and (3) treatment with oral pindolol 2 times a day. The order of the 3 treatment periods was allocated randomly for each patient. The duration of the control period varied between 1 and 4 weeks; the duration of treatment periods with propranolol and pindolol varied from 4 to 6 weeks. The dose of propranolol was 40 mg 4 times a day and the dose of pindolol was 5 mg 2 times a day, a 16:1 ratio shown to exert similar beta-adrenergic blockade.[6] These doses were increased to 80 mg 4 times a day and 10 mg 2 times a day, respectively, in patients in whom clinical improvement did not occur (compared with the control period) or whose exercise heart rate was >120 beats/min with the initial dose, indicating that beta-adrenoreceptor blockade was inadequate. The initial doses were not increased in patients in whom clinical improvement was achieved or in whom the heart rate at peak exercise was lower than 120 beats/min. Improvement was defined by a reduction in the number of anginal attacks of at least 40% compared with that in the control stage. Patients requiring dosage increases underwent more than 3 study periods, but only data during drug treatment with the larger doses are reported. Patients kept a daily record of the number of anginal episodes and the number of therapeutic glyceryl trinitrate tablets consumed.

Change in therapy when switching from one beta-adrenoreceptor antagonist to another was made abruptly from 1 day to the next. When treatment with 1 of the 2 drugs was followed by the control period, the drug was discontinued gradually over 1 week.

At the end of each of the 3 treatment periods, all patients underwent, successively, radionuclide ventriculography at rest and during bicycle exercise 120 to 150 minutes after the morning dose of either drug or at a similar hour of the day after the control period, a treadmill exercise test 45 minutes after termination of bicycle exercise, and clinical assessment.

In the 6 patients taking long-acting nitrates, doses were kept constant throughout the entire investigation, but were withheld for 24 hours before exercise studies; the same dose was given again after clinical assessment.

The clinical assessment was made by 2 participating cardiologists. The number of anginal episodes experienced, glyceryl trinitrate tablets consumed, and adverse effects were recorded. The number of remaining tablets were counted to assess compliance. New drugs, instructions, or both were given.

The treadmill exercise test was performed using a modified Bruce protocol, with elevation of the speed and incline at 3-minute intervals.[7] All patients were exercised to angina during the control stage, and to angina or fatigue after drug treatment. An ischemic electrocardiographic response was a flat or downward sloping depression of the S-T segment of at least 0.1 mV (1 mm) in any lead, persisting for ≥0.08 second and present in 3 consecutive beats with stable isoelectric baseline. Cuff blood pressure measured over the right brachial artery and a 12-lead electrocardiogram were obtained at rest, at each exercise stage, and immediately and at 2, 4, 6, and 8 minutes after exercise. The treadmill walking time was recorded to the nearest 5-second period. Exercise heart rate was measured continuously on a cardiotachometer and the maximal heart rate was measured from 10 consecutive beats on the electrocardiogram recorded during the last 15 seconds of peak exercise. S-T segment depression was measured as the linear depression of the J point from the isoelectric line joining 2 consecutive P-R segments. Measurements were made in the lead that showed maximal S-T segment depression and were averaged over 4 consecutive complexes in which the isoelectric line was stable. The symptoms limiting exercise tolerance were recorded.

**Assessment of LV function:** Radionuclide ventriculography, to assess global and regional LV function, was performed using the electrocardiographic-multigated method described previously.[3-5] After in vivo labelling of the red blood cells with technetium-99m, blood pool cardiac scintigraphy was performed in the modified left anterior oblique projection that best separated both ventricles and atria, at rest and during graded supine bicycle ergometer exercise. Details of the exercise protocol and the instrumentation used in our laboratory have previously been described.[4] Analysis of the radionuclide studies was carried out blindly by an experienced observer. Global LV ejection fraction and semiquantitative measurements of segmental LV function (wall motion score) were obtained at rest and during peak exercise.

In our laboratory, radionuclide LV ejection fraction and wall motion analysis correlated closely with contrast studies, $r = 0.87$.[5] Inter- and intraobserver variability of ejection fraction measurements showed correlation coefficients of 0.97 and 0.92, respectively.[4,5] A radionuclide ventriculogram at rest was considered normal if ejection fraction was ≥55% and the wall motion score was equal to zero. Failure of ejection fraction to increase by at least 7% (absolute value), or any increase in wall motion score from resting values, or both was considered an abnormal LV function response to peak exercise.[4]

**Statistical methods:** Analysis of variance was used to determine the significance of changes during treatment periods. If this analysis indicated a significant difference in the mean values for a variable, then Tukey's multiple comparison procedure was performed. In addition, changes in exercise duration, electrocardiographic S-T segment depression, and wall motion score were also analyzed by a nonparametric method using Wilcoxon's rank sum test. Probability of ≤5% was considered significant.

**TABLE I Order of the Therapy Periods in 23 Patients With Angina Pectoris in This Study**

| Patients (n) | First Therapy | Second Therapy | Third Therapy |
|---|---|---|---|
| 6 | C | Pr | Pi |
| 4 | C | Pi | Pr |
| 3 | Pr | C | Pi |
| 2 | Pr | Pi | C |
| 2 | Pi | Pr | C |
| 6 | Pi | C | Pr |

C = control; Pi = pindolol; Pr = propranolol.

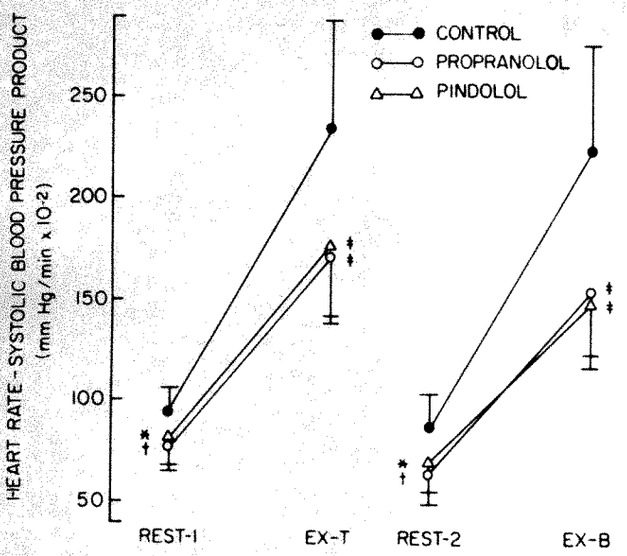



**FIGURE 1.** Comparison of the effects of propranolol and pindolol during sustained therapy in 23 patients with angina pectoris. Data represent mean ± standard deviation. REST-1 = data standing, immediately before treadmill exercise. REST-2 = data supine, just before bicycle exercise. EX-T and EX-B = data at peak exercise on the treadmill and the bicycle, respectively. * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$, versus control values.

## Results

Three of the initial 26 patients did not complete the entire investigation: 1 had hypothyroidism during the initial treatment period; 2 became asymptomatic while on treatment with the first beta-adrenoreceptor antagonist and insisted on receiving the same medication thereafter. Thus, these 3 patients were excluded, leaving a total of 23 patients who completed all phases of this study and form the basis of this report.

Random allocation of the order of treatment periods resulted in fairly even distribution of patients among the 6 possible combinations (Table I). Compliance was good because <3% (average value) of the tablets were returned.

No patient experienced adverse effects serious enough to warrant discontinuation of medications during the study period. Complaints such as fatigue, drowsiness, vivid dreams, and cold extremities were reported with similar frequency during therapy with propranolol and pindolol. Clinical improvement of similar degree was observed during propranolol therapy in 17 patients taking 40 mg 4 times a day, in 5 patients taking 80 mg 4 times a day, and during pindolol therapy in 14 patients taking 5 mg twice each day, and in 7 patients taking 10 mg twice a day. In the remaining patient taking propranolol 80 mg 4 times a day and 2 patients taking pindolol 10 mg twice a day, the frequency of angina also was reduced but by <40% despite a significant reduction in the exercise heart rate (to <120 beats/min).

**Effect of treatment on the frequency of angina, number of glyceryl trinitrate tablets consumed, and exercise duration:** During the control period, the mean number of anginal episodes reported was higher ($p < 0.001$) than those during therapy with propranolol or pindolol (19.4 ± 10.4, 7.0 ± 5.7, and 8.6 ± 6.4 anginal episodes/month, respectively). The average number of glyceryl trinitrate tablets consumed was lower ($p < 0.001$) during propranolol and pindolol therapy than during the control period (4.0 ± 3.0, 5.2 ± 5.4, and 11.0 ± 8.3 tablets of glyceryl trinitrate/month, respectively), in keeping with the number of anginal episodes reported.

Exercise duration on the treadmill (Table II) was significantly higher during therapy with both drugs than during the control period. Patients exercised for shorter periods of time on the bicycle, but the mean exercise duration showed trends similar to those of exercise on the treadmill (duration of bicycle exercise: 5.61 ± 2.08 minutes during control, 6.52 ± 1.73 minutes after propranolol, and 6.00 ± 1.81 minutes after pindolol). The treadmill walking time, frequency of angina, and number of glyceryl trinitrate tablets consumed after propranolol were similar ($p = 0.20$) to those after pindolol administration.

**Circulatory changes:** No significant differences were observed between supine and standing resting heart rates. The heart rate increased significantly ($p < 0.001$) from resting values with treadmill and bicycle exercise during the 3 study periods. Resting and exercise heart rates (Table II) were lower during treatment with both beta-adrenoreceptor antagonists when compared

**TABLE II Effects of Propranolol and Pindolol on Exercise Tolerance, S-T Segment Depression, Heart Rate, Systolic Blood Pressure, and LV Function During Sustained Therapy in Patients With Angina Pectoris**

| Drug | TWT (min) | S-T Segment Depression (mm) | Heart Rate (beats/min) | | SBP (mm Hg) | | EF (%) | | WMS | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Rest | Exercise | Rest | Exercise | Rest | Exercise | Rest | Exercise |
| Control | 6.74 ±2.30 | 2.4 ±0.9 | 78 ±12 | 137 ±25 | 128 ±12 | 169 ±24 | 59 ±8 | 54 ±11 | 0.57 ±1.08 | 2.39 ±2.10 |
| Propranolol | 7.94 ±2.70* | 1.8 ±0.8† | 65 ±11* | 113 ±20* | 122 ±10 | 151 ±21* | 57 ±8 | 57 ±12 | 0.61 ±1.16 | 1.78 ±2.15† |
| Pindolol | 7.97 ±2.31* | 1.5 ±0.8† | 70 ±12‡ | 110 ±17* | 125 ±9 | 148 ±19* | 58 ±9 | 57 ±8 | 0.70 ±1.29 | 1.61 ±2.31† |

Data expressed as mean ± standard deviation.
EF = LV ejection fraction; SBP = systolic blood pressure; TWT = treadmill walking time; WMS = left ventricular wall motion score. Data for S-T segment depression, exercise heart rate, and systolic blood pressure represent values during peak treadmill exercise. * $p < 0.001$; † $p < 0.01$; ‡ $p < 0.05$ versus control values.

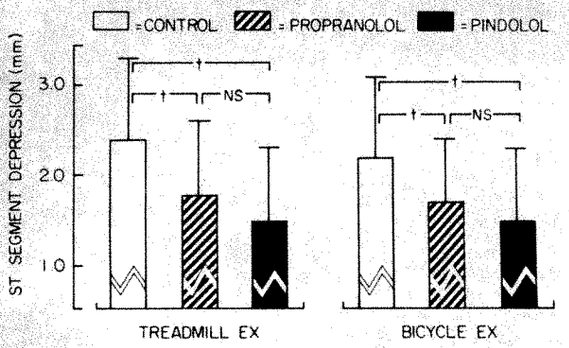



**FIGURE 2.** Comparison of the effects of propranolol and pindolol during sustained therapy in 23 patients with angina pectoris. Data represent mean ± standard deviation at peak exercise (EX) on the treadmill and the bicycle. No significant difference in S-T segment depression was observed between the 2 modes of exercise. † $p < 0.01$; NS = $p > 0.05$.

with heart rates during the control period. Both supine and standing heart rates at rest were somewhat lower during propranolol than during pindolol administration but the difference between means did not reach statistical significance. Heart rates during peak exercise were similar with the 2 drugs. Systolic blood pressure increased ($p < 0.001$) from rest to exercise during control and during administration of propranolol and pindolol (Table II). At rest, supine and standing systolic blood pressure after both beta-adrenoreceptor antagonists were similar to those during the control period. After administration of both drugs, systolic blood pressures at peak exercise, on the treadmill and the bicycle, were significantly lower ($p < 0.001$) than those during control. The differences in systolic blood pressure, at rest or during exercise, after administration of the 2 drugs were not significant.

Compared with the control period, the product of heart rate and systolic blood pressure (Fig. 1), with the patients at rest in both supine and standing positions and during peak treadmill and bicycle exercise, were lower during treatment with both drugs. The products of heart rate and systolic blood pressure were similar after administration of both propranolol and pindolol.

**Electrocardiographic changes:** An ischemic electrocardiographic response to exercise was present in all patients during the control stage, in 14 patients after propranolol, and in 10 patients after pindolol. During the control period, S-T segment depression at peak exercise was significantly greater than after propranolol or pindolol administration (Table II). The difference between mean S-T segment depression after both beta-adrenoreceptor antagonists was not statistically significant (Fig. 2).

**Effects of treatment on global LV function:** During the control stage, the LV ejection fraction at rest was normal (>55%) in 14 patients and abnormal (<55%) in 9 patients, but <50% in only 1 patient. After administration of propranolol, resting ejection fraction was found within the normal range in 14 patients and <50% in 3, whereas after administration of pindolol, the ejection fraction at rest was normal in 18 patients and <50% in the 3 (Fig. 3). There was no significant difference between the means of resting ejection fraction during the 3 study periods (Table II).

An abnormal response of ejection fraction to peak exercise, as defined in the Methods section, was observed in 22 patients during the control period, in 18 patients after propranolol, and in 21 patients after pindolol. During the control period, the mean ejection fraction during peak exercise was significantly lower ($p < 0.05$) than that at rest, whereas it was not significantly different from the resting ejection fraction after administration of both beta-adrenoreceptor antagonists (Fig. 3). The average ejection fraction at peak exercise during therapy with propranolol and pindolol was somewhat greater than during control (Table II), but the differences did not reach statistical significance. No significant differences were observed in rest or exercise mean ejection fraction between patients taking 5 and 10 mg of pindolol twice a day.

**Effects of treatment on regional LV function:** During the control period, 20 patients showed a normal or near-normal segmental LV function (wall motion score values of 0 to 1), the remaining 3 patients had wall motion score values of 2 or higher; in only 1 patient was this higher than 3. After propranolol therapy, the resting wall motion score was normal or near normal in 20 patients, higher than 1 in 3 patients, and higher than 3 in 1 patient. After pindolol, the wall motion score at rest was normal or near-normal in 18 patients, higher than 1 in 5 patients, and higher than 3 in 1 patient (Fig. 4). No significant differences during any of the 3 study periods were found between the means of wall motion score at rest (Table II).

An abnormal response of regional LV function to exercise, as defined previously, was observed in 18 patients during the control stage, in 12 patients after propranolol therapy, and in 10 patients after pindolol administration. The mean wall motion score during exercise was significantly higher ($p < 0.001$) than the respective resting values during the control period, after propranolol, and after pindolol (Fig. 4). However, the mean exercise wall motion score during the control stage was significantly higher than that during therapy with both drugs (Table II). At peak exercise, the mean wall motion score after propranolol was similar ($p = 0.30$) to that after pindolol administration. No significant differences were observed in rest or exercise mean wall motion score among patients taking 5 and 10 mg of pindolol twice a day.

**Effects of treatment in relation to the basal status of LV function:** Resting LV function during the control period was considered normal (ejection fraction >55% and wall motion score, 0) in 13 patients and below in 10 patients. In the former group, the mean ejection fraction was 64 ± 6% and the mean wall motion score was zero; those in the latter group were 52 ± 5% and 1.3 ± 1.3, respectively. In the 2 subgroups, both propranolol and pindolol produced an improvement in global and regional LV function during exercise to an extent similar to that observed in the entire group.

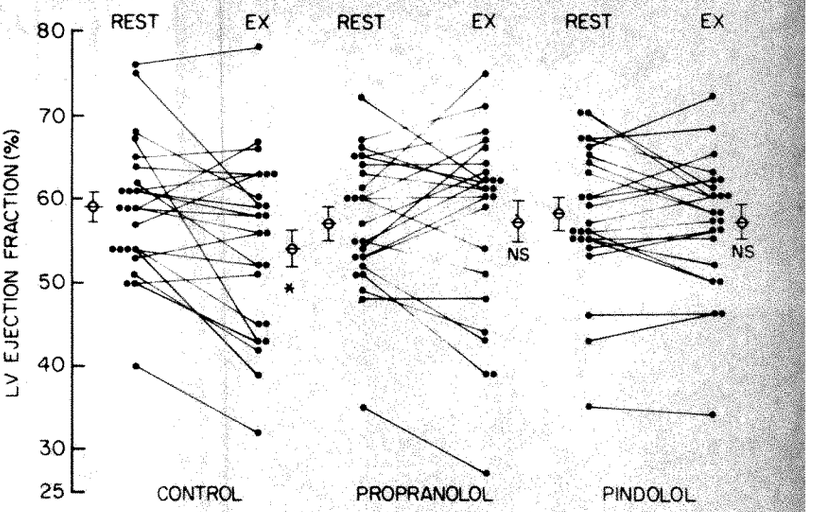



**FIGURE 3.** Effects of propranolol and pindolol on global LV function. Data represent individual and group (mean ± standard error of the mean) values, at rest and during peak exercise (EX). Exercise ejection fraction after both beta-adrenoreceptor antagonist drugs were similar. * $p < 0.05$; NS = $p > 0.05$ versus rest values.

## Discussion

This study shows that pindolol and propranolol, adrenergic beta-receptor antagonist agents with and without intrinsic sympathomimetic activity, respectively, have similar effects on global and regional LV function in patients with angina pectoris. At the doses used, both drugs exerted an equal suppression of the exercise heart rate and had significant and similar antianginal effects.

Differences in the pharmacodynamic and pharmacokinetic properties[8] of the many beta-adrenoreceptor antagonists available have led investigators to postulate the theoretical advantages of some over others when treating patients with angina pectoris.[9–11] One such ancillary property is the intrinsic sympathomimetic activity or partial agonist activity. Drugs with this characteristic cause a measurable agonistic response when they interact with beta-adrenergic receptors in the absence of a primary agonist such as adrenaline or isoprenaline; this can be demonstrated in the adrenalectomized animal treated beforehand with reserpine.[9] Although drugs with and without partial agonist activity have been available for patient treatment for several years, the clinical significance of this property remains uncertain.[10,12] It has been suggested that drugs with partial agonist activity induce less subjective and objective respiratory impairment in patients with bronchospastic disease and lessen exercise cardiac output to a reduced degree in patients with hypertension[13,14] than drugs without partial agonist activity.

Thadani et al[1,2,15] and others[16–18] found that beta-adrenoreceptor antagonist drugs with and without partial agonist activity are equally effective in the treatment of angina pectoris. However, no information is available regarding the role of the partial agonist activity on global and regional LV function. We therefore elected first to compare pindolol and propranolol because pindolol is the drug with the most pronounced partial agonist activity.[19] Second, because myocardial oxygen supply and demand in patients with chronic, stable angina pectoris are at equilibrium at rest and myocardial ischemia develops only during stress, we studied the effects of both drugs on ventricular function at rest as well as during exercise. Third, we used the

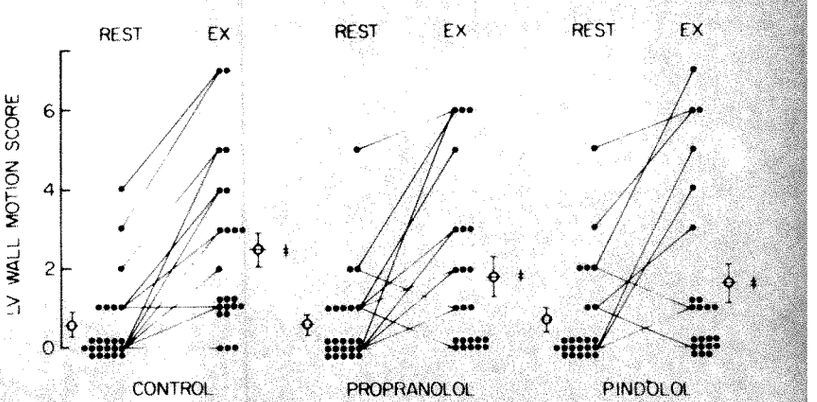



**FIGURE 4.** Effects of propranolol and pindolol on regional LV function. Data represent individual and group (mean ± standard error of the mean) values, at rest and during peak exercise (EX). LV exercise wall motion score improved significantly ($p < 0.01$) after both beta-adrenoreceptor antagonists. There was no significant difference ($p > 0.05$) in exercise LV wall motion score between the 2 drugs. ‡ $p < 0.001$ versus rest values.

electrocardiographic-multigated blood pool cardiac scintigraphy, a reliable, noninvasive technique well-suited for repeated measurements at rest and during exercise.[3-5]

On the basis of previous experience with the drugs tested,[10,16,20] we used 2 dose levels. With use of only 2 dose levels, it is possible that the optimal dosage may not have been reached in a few patients; however, a significant beta-adrenoreceptor blocking effect was obtained at the doses used. Our results are in agreement with more comprehensive dose-response studies in which pindolol, 10 to 20 mg/day, and propranolol, 160 to 320 mg/day, were found to be well within the therapeutic range.[15,21,22]

Several aspects of our study need further comment. Open trials do not constitute worthwhile evidence of treatment efficacy. However, our principal aim was to assess the effects of pindolol and propranolol on objective measurements of LV function. The antianginal efficacy of the drugs used was not in question and a double-blind study was not vital. All radionuclide studies were analyzed blindly at the end of the trial. Although we did not have formal run-in and trial-proper periods, and we were not concerned about possible carry-over effects, we believe that the random distribution of the order of treatment and control sequences (Table I) and the existence of 2 dose levels reconciled these deficiencies in design. In those subjects who received 320 mg/day of propranolol or 20 mg of pindolol/day, an actual run-in period was present. Moreover, rest-exercise studies were carried out after a minimum of 4 weeks of treatment and the carry-over effect by then should have been nonexistent. Lastly, patients were carefully selected and all had uncomplicated, stable angina pectoris and an ischemic electrocardiographic response to exercise. This may impose limitations in applying the results to a broader clinical population, but is necessary for meaningful comparison of the drug effects.

At the doses used, pindolol and propranolol were efficacious antianginal agents. Both drugs reduced clinical and electrocardiographic signs of myocardial ischemia, and improved exercise tolerance to a similar degree. No further comments are needed regarding these effects because many previous well-designed studies[16,23] have shown similar results.

**LV function changes at rest:** In patients with normal or near normal LV function, previous studies have shown that oral administration of propranolol did not significantly influence resting global or segmental systolic LV function as assessed by radionuclide methods.[23-26] In patients with moderate to marked LV dysfunction,[26] or when studies were performed in the upright position,[27] a decreased LV ejection fraction was observed after propranolol administration. The results of the present study, which largely involved patients with normal or near normal LV function studied in the supine position, are in keeping with these observations.

LV ejection fraction and wall motion patterns at rest were also minimal and were not significantly affected by oral pindolol at clinically effective doses. Moreover, with a few exceptions, individual responses to propranolol were closely correlated with those to pindolol.

The comparative angiographic response to propranolol and pindolol, or between beta-adrenergic receptor antagonists with and without partial agonist activity, has not previously been reported. Frishman et al[10] found that the LV ejection fraction improved significantly after pindolol but was significantly reduced compared with control values after propranolol. The differences between the results in that study[10] and ours are unlikely to reflect differences in study design because the clinical, electrocardiographic, and circulatory changes were similar to those in the present study. Two factors may account for the divergent results: (1) The ejection fraction in Frishman's study was derived from the M-mode echocardiogram. This method has recognized limitations, especially in subjects with coronary heart disease in whom localized areas of LV dysfunction may go undetected. The left ventricle was assumed to have the shape of a cube.[10] With the radionuclide method, counts in the entire ventricle are included to calculate ejection fraction, and no assumptions are made to the LV shape. Several investigations using radionuclide methods[23-26] have shown that resting ejection fraction is not significantly altered by oral administration propranolol at the doses used in Frishman's study. (2) We administered pindolol at approximately one third of the dose given by Frishman et al.[10] Future studies should investigate whether larger doses of pindolol may increase resting ejection fraction.

**LV function changes during exercise:** The beneficial effects of oral propranolol on LV function during exercise in patients with stable angina pectoris has previously been documented.[24-26] In our study, both propranolol and pindolol prevented the ejection fraction from decreasing significantly with exercise, and both drugs improved exercise wall motion score to the same extent.

The mechanisms whereby beta-adrenoreceptor antagonists improve global and segmental systolic function during exercise in patients with coronary artery disease are not known. Possible mechanisms include a decrease in myocardial oxygen requirements, an improved total myocardial blood flow, or a favorable redistribution of myocardial blood flow. We conclude that this mechanism is independent of the presence or absence of intrinsic sympathomimetic activity.

A major shortcoming of the present study was failure to measure LV volumes. Possible differences in the effects of propranolol and pindolol on ventricular volumes were not assessed.[28,29]

**Effects of treatment in relation to the basal status of LV function:** If partial agonist activity has any beneficial effect on LV function, this effect would be more important in patients with impaired or borderline LV performance.[9,10,12] The patient group in this investigation included, with 1 exception, subjects with normal or near normal LV function. Thus, we cannot make any valid conclusions regarding the comparative effects of propranolol and pindolol on LV function in patients with poor LV performance.

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## References


1. **Thadani U, Davidson C, Singleton W, Taylor S.** Comparison of the immediate effects of five beta-adrenoreceptor-blocking drugs with different ancillary properties in angina pectoris. N Engl J Med 1979;300:750–755.
2. **Thadani U, Davidson C, Singleton W, Taylor S.** Comparison of five beta-adrenoreceptor antagonists with different ancillary properties during sustained twice daily therapy in angina pectoris. Am J Med 1980;68:243–250.
3. **Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS.** Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary artery disease. N Engl J Med 1977;296:839–844.
4. **Manyari DE, Nolewajka A, Purves P, Donner A, Kostuk WJ.** Comparative value of the cold-pressor test and supine bicycle exercise to detect subjects with coronary artery disease using radionuclide ventriculography. Circulation 1982;65:571–579.
5. **Kostuk WJ, Chamberlain M, Sang H.** Radionuclide angiocardiography, a noninvasive method for evaluating left ventricular ejection fraction and regional wall motion: comparison with contrast left ventricular angiography. Can Med Assoc J 1978;119:877–883.
6. **Aellig WH.** Beta-adrenoceptor blocking activity and duration of action of pindolol and propranolol in healthy volunteers. Br J Clin Pharmacol 1976; 3:251–257.
7. **Robertson D, Kostuk WJ, Ahuja S.** The localization of coronary artery stenosis by 12 lead ECG response to graded exercise test: support for intercoronary steal. Am Heart J 1976;91:437–444.
8. **Gibson DG.** Pharmacodynamic properties of beta-adrenergic receptor blocking drugs in man. Drugs 1974;7:8–38.
9. **Barrett AM, Nunn B.** Intrinsic sympathomimetic activity in relation to the precipitation of heart failure by beta adrenoceptive blockade. Arch Int Pharmacodyn Ther 1971;189:168–179.
10. **Frishman W, Kostis J, Strom J, Hossler M, Elkayam U, Goldner S, Silverman R, Davis R, Weinstein J, Sonnenblick E.** Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 6. A comparison of pindolol and propranolol in treatment of patients with angina pectoris. The role of intrinsic sympathomimetic activity. Am Heart J 1979;98:526–535.
11. **Parratt JR, Marshall RJ.** Beta adrenoreceptor blocking drugs in acute experimental myocardial ischemia (abstr). Presented to the Eighth World Congress of Cardiology, Tokyo, September 1978.
12. **Frishman W, Silverman R, Strom J, Elkayam U, Sonnenblick E.** Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 4. Adverse effects. Choosing a beta-adrenoreceptor blocker. Am Heart J 1979;98: 256–262.
13. **Beumer HM, Hardunk HJ.** Effects of beta-adrenergic blocking drugs on ventilatory function in asthmatics. Eur J Clin Pharmacol 1972;5:77–85.
14. **Franciosa JA, Johnson SM, Tobian LJ.** Exercise performance in mildly hypertensive patients. Impairment by propranolol but not oxprenolol. Chest 1980;78:291–299.
15. **Thadani U, Sharma B, Meeran MK, Majid PA, Whitaker W, Taylor SH.** Comparison of adrenergic beta-receptor antagonists in angina pectoris. Br Med J 1973;1:138–142.
16. **Boakes AJ, Prichard BNC.** The effect of AH5158, pindolol, propranolol, and D-propranolol on acute exercise tolerance in angina pectoris. Br J Pharmacol 1973;47:673P–674P.
17. **Sowton E, DasGupta DS, Baker I.** Comparative effects of beta adrenergic blocking drugs. Thorax 1975;30:9–18.
18. **Jackson G, Atkinson L, Oram S.** Double-blind comparison of timolol, propranolol, practolol, and placebo in the treatment of angina pectoris. Br Med J 1975;1:708–712.
19. **Barrett AM, Carter J.** Comparative chronotropic activity of beta-adrenoceptive antagonists. Br J Pharmacol 1970;40:373–480.
20. **Nair DV.** A double blind trial of visken (LB-46), in the treatment of angina pectoris. Indian Heart J 1972;2(Suppl I):183–191.
21. **Aravanis C, Michaelides G.** Results of the use of a new beta-adrenergic blocker (LB-46) in angina pectoris. Acta Cardiol 1970;25:501–509.
22. **Alderman EL, Davies RO, Crowley JJ, Lopez MG, Brooker J, Friedman J, Graham A, Matlof H, Harrison DC.** Dose response effectiveness of propranolol for the treatment of angina pectoris. Circulation 1975;51: 964–975.
23. **Marshall RC, Berger HJ, Reduto LA, Cohen LS, Gottschalk A, Zaret BL.** Assessment of cardiac performance with quantitative radionuclide angiocardiography. Effects of oral propranolol on global and regional left ventricular function in coronary artery disease. Circulation 1978;58:808–814.
24. **Battler A, Ross J Jr, Slutsky R, Pfisterer M, Ashburn W, Froelicher V.** Improvement of exercise-induced left ventricular dysfunction with oral propranolol in patients with coronary heart disease. Am J Cardiol 1979; 44:318–324.
25. **Marshall RC, Wisenberg G, Schelbert HR, Henze E.** Effect of oral propranolol on rest, exercise and postexercise left ventricular performance in normal subjects and patients with coronary artery disease. Circulation 1981;63:572–583.
26. **Rainwater J, Steele P, Kirch D, LeFree M, Jensen D, Vogel R.** Effect of propranolol on myocardial perfusion images and exercise ejection fraction in men with coronary artery disease. Circulation 1982;65:77–81.
27. **Port S, Cobb F, Jones RJ.** Effects of propranolol on left ventricular function in normal men. Circulation 1980;61:358–366.
28. **Slutsky R, Karliner J, Ricci D, Kaiser R, Pfisterer M, Gordon D, Peterson K, Ashburn W.** Left ventricular volume by gated equilibrium radionuclide angiography: a new method. Circulation 1979;60:556–564.
29. **Moniz de Bettencourt J, Gomes-Pinto B.** Les modifications de la dynamique cardiaque dans l'angine de poitrine et l'action du propranolol et du pindolol chez le sujet normal et ches le malade angineux. Ann Cardiol Angeiol 1975;24:453–460.

# Determination of the Angiographic Appearance of Coronary Collateral Vessels: The Importance of Supplying and Recipient Arteries

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**The appearance of coronary collateral vessels at coronary angiography generally is believed to provide additional information regarding coronary flow and myocardial oxygen supply beyond that obtained from angiographic assessment of the large coronary arteries. To evaluate the adequacy of this assumption, to determine the relation between the angiographic appearance of coronary arteries and of coronary collateral vessels, and to gain additional insight into the mechanisms governing collateral flow in man, the coronary arteriograms of 121 patients in whom at least 1 coronary artery manifested ≥75% stenosis (193 arteries demonstrated ≥90% stenosis, and 94 of these were totally occluded) were examined. Collateral vessels were graded absent, "poor," or "good" based on the size and intensity of filling. Stenosis of the recipient artery significantly affected the angiographic appearance of collaterals vessels. No artery with <90% stenosis received angiographically detectable collateral vessels; 118 of the 193 vessels with ≥90% stenosis received collateral vessels: 79 of 94 (84%) totally occluded arteries versus 39 of 99 (39%) with ≥90% but <100% stenosis ($p < 0.001$). Good collateral vessels went to 70 of the 79 (89%) totally occluded arteries, but only 17 of 39 (49%) subtotally occluded arteries ($p < 0.001$). Of the 87 good collateral vessels, only 16 (18%) were supplied by single arteries manifesting ≥75% stenosis; of 31 poor collateral vessels, 20 (65%) were supplied by arteries with ≥75% stenosis ($p < 0.001$). When the patency of all the arteries that could supply collateral vessels to the 94 totally occluded was semiquantitated, the extent of obstruction of the potential suppliers was significantly greater in those arteries with none or poor collateral vessels ($p < 0.001$ for both groups of arteries with good collateral vessels).**

**It is concluded that the angiographic appearance of the recipient and supplying coronary arteries is a major predictive factor in the angiographic appearance of coronary collateral vessels.**

Coronary collateral vessels, described anatomically in 1907,[1] were first observed angiographically by Molnar[2] in 1960. However, the factors which determine coronary collateral flow in man, and therefore the determinants of the angiographic appearance of collateral vessels, are poorly understood. In addition, the precise relation between the angiographic appearance of the large coronary arteries and the appearance of collateral vessels has not been well defined. While it is generally accepted that collateral vessels can be visualized only when they supply a stenotic artery, the degree of stenosis required for visualization has varied widely among reported investigations.[2–11] Moreover, the relation between the extent of recipient artery stenosis and the angiographically demonstrable characteristics of the collateral vessel is uncertain.[5,10–13] Finally, little direct attention has been focused on the effect of stenosis in the artery supplying the collateral vessel on the angiographic appearance of the collateral vessel, although the preponderance of data suggest, surprisingly, that stenosis of the supplying arteries is not an important factor in the appearance of the collateral vessel.[13–17]

Clarification of the relation between the angiographic appearance of large coronary arteries and of collateral vessels is of potential value. To the extent that the appearance of collateral vessels can be predicted from the severity of stenosis of large arteries, current concepts regarding the functional, clinical, and surgical importance of angiographically demonstrable collateral vessels may require revision.

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Therefore, to clarify the relation between the angiographic appearance of coronary arteries and coronary collateral vessels, we assessed the coronary angiograms obtained in 121 patients with ischemic heart disease.

## Methods

**Patients:** Coronary angiography was performed in 121 patients (85 men and 36 women) ranging in age from 33 to 75 years (average 54). All patients had clinically apparent ischemic heart disease. Angiograms were selected for inclusion in this study on a random basis from among patients who underwent coronary arteriography at the New York Hospital in 1979 to 1980. Angiograms then were excluded from assessment unless at least 1 coronary artery manifested ≥75% reduction in luminal diameter in at least 1 angiographic view. Twenty-six patients manifested such stenoses in 1 major artery; in 42 patients, 2 major arteries were affected; and in 53 patients, all 3 major arteries were affected. Angiograms demonstrating ≥50% stenosis of the left main coronary artery were excluded. Patients with valvular, congenital, or primary myocardial heart disease detectable at catheterization or echocardiography were excluded from study. Patients were included irrespective of the presence or absence of clinical evidence of previous myocardial infarction.

**Angiography:** Catheterization was carried out with the patients under mild sedation (sodium pentobarbital), with local anesthesia, and in the fasting stage. No nitrate vasodilators were administered within 4 hours of catheterization, and no other vasodilator agents were employed in the treatment of these patients.

Selective coronary arteriography was performed by the Judkins technique, using Renografin®-76 contrast medium. All angiograms were recorded at 60 frames/s on 35 mm Kodak CFS film using a General Electric Fluoricon 300 system. Radiographic parameters were automatically adjusted to attain consistent and optimal film quality. A standard injection routine was utilized in an attempt to deliver contrast at a uniform rate during each injection. Film was processed in a Jameson 54 processor and densitometric quality control measures were employed regularly to ensure optimal and consistent film quality. The left coronary artery was routinely visualized in at least 4 views. Each segment of all arteries was visualized in at least 2 orthogonal (or nearly orthogonal) views. Caudad and cephalad angulation was used routinely in at least 2 views in each patient. Thus, every attempt was made to minimize variation in coronary artery and collateral appearance due to technical factors.

**Assessment of anatomy:** To assess stenosis of coronary arteries receiving or supplying collateral vessels, the severity of obstruction of each atherosclerotic lesion was defined as the greatest percent reduction in luminal diameter that was seen in any view compared to the nearest proximal section that was judged free of disease. Lesions were stratified into 4 levels of obstruction (<75%, ≥75 to 89%, ≥90 to 99%, 100%),[18] with caliper measurements employed to quantify luminal diameter reduction. The most severe of serial stenoses was used in stratifying those arteries with multiple lesions.

In this study, extent of collateral flow to a distal segment of an obstructed artery was assessed only if obstruction was present in the proximal or mid-portions of 1 of the 3 major coronary arteries (left anterior descending, circumflex, and right) or in the proximal or mid-portion of 1 of the major branches of a major artery. (If the only ≥90% stenosis, or the most severe stenosis, was in the distal portion of an artery, that vessel was not included in the analysis of collateral flow. There were 5 such arteries among the diseased arteries.) Collateral vessels were considered present (1) if a totally obstructed artery was visualized on homolateral injection; (2) if a subtotally obstructed artery was seen to fill in a retrograde fashion on homolateral injection; or (3) if an artery filled on contralateral injection. Collateral vessels were graded as good, poor, or absent based on a modification of the criteria of Levin[5]: good collateral vessels caused complete opacification of the portion of the recipient coronary artery distal to the obstruction lesion. Poor collateral vessels caused faint or incomplete visualization of the recipient artery distal to its obstructing lesion (with concomitant clear visualization of the region proximal to any obstruction in the injected artery, indicating technically adequate contrast administration). If there were multiple collateral vessels, only the vessel with the best grade was used in analysis. Multiple poor collateral vessels were treated as a single poor vessel.

Assessment of both coronary stenosis and collateral grade was performed independently by 2 observers; in cases of disagreement, a final decision was reached by consensus after joint review of the angiogram. To establish the reliability of our observations, a subgroup of 27 angiograms was reassessed by 1 observer several months after initial reading. There was complete agreement (24 of 24) between initial and follow-up readings of those stenoses graded as 100%; 91% (29 of 32) concordance of those lesions initially read as ≥90% to 99%; and 76% (16 of 21) concordance of those lesions initially read as ≥75 and <90%, with 2 of the 5 disagreements resulting in downgrading the severity of stenosis. There was 93% (27 of 29) concordance of those collaterals initially graded good, and 90% (9 of 10) concordance of those collaterals initially graded poor. Therefore, we believe our method of analysis is sufficiently reproducible to permit firm conclusions from data based on the large number of observations involved in this study.

To evaluate arteries with clearly supplied collateral vessels, the extent of stenoses was defined by the most severe reduction in luminal diameter proximal to the origin of the collateral vessel. If the stenosis was ≥75% of luminal diameter, the supplying artery was termed *obstructed*, and if stenosis was <75%, the artery was termed *nonobstructed*.

Finally, to determine the importance of obstructive disease in all arteries with potential for supplying collateral vessels, each totally occluded artery was considered to be potentially supplied by branches of either of the 2 other major arteries, and by the proximal portion of the occluded artery itself. Stenosis of each potential supplier was assessed by caliper measurement, as above; a stenosis causing a ≥75% reduction in luminal diameter was considered to indicate that a potential supplier was obstructed. As Levin has demonstrated, potential suppliers differ in probability of supplying collateral vessels to specific totally occluded arteries. Therefore, to each potential supplying artery, we assigned a relative weight (Table I) according to the probability that the artery would supply a collateral vessel (after Levin[5]). The system was designed such that when the relative weights assigned to branches of any major artery were summed, the result was equal to the relative weight assigned to the major trunk artery. The number of obstructed suppliers, each multiplied by its weight, was summed. The resulting quantity was termed the *supplier obstructive index*. The supplier obstructive index ranged from 0 (all potential suppliers having <75% stenosis) to 11 (all potential suppliers manifesting ≥75% stenosis).

**Statistics:** The chi-square test was used to compare frequency of observation between groups. The Kruskal-Wallis one-way analysis for K groups[19] was used to establish the existence of a difference in supplier obstructive index among our patient subgroups; the Kruskal-Wallis test as modified by Dunn[19] was used to compare supplier obstructive indexes among specific subgroups.

## Results

The 121 patients had a total of 269 arteries with ≥75% reduction in luminal diameter: 76 of the 269 arteries manifested ≥75% but <90% stenosis; 99 of 269 arteries manifested ≥90% but less than total occlusion; and 94 of 269 arteries were totally occluded. Thus, 193 arteries manifested ≥90% stenosis.

**TABLE 1 Potential Supplier Scoring System***

| Totally Occluded Artery | Potential Supplier | Relative Weight |
|---|---|---|
| LAD | LAD (Proximal) | 4 |
| | Septal | 3 |
| | Diagonal | 1 |
| | Cx (Proximal to All OMs) | 2 |
| | (Distal to an OM) | 1 |
| | ≥1 OMs | 1 |
| | RCA (Proximal) | 5 |
| | (Distal to AM) | 3 |
| | Distal to PDA | 2 |
| | PDA | 2 |
| Cx | LAD and/or DIAG | 2 |
| | Cx (PROX to all OMs) | 7 |
| | (Distal to an OM) | 3 |
| | 1 or more OMs | 3 |
| | RCA | 2 |
| RCA | LAD (Proximal) | 4 |
| | (Distal) | 1 |
| | Septal | 3 |
| | Cx (Proximal) | 5 |
| | (Distal to 1 OM) | 3 |
| | 1 or more OMs | 2 |
| | RCA (Proximal) | 2 |
| | (Distal) | 1 |

* Based on relative quantitative importance (weight) of potential collateral supply (see text).
The maximal possible supplier obstructive index is 11.
Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; OM = obtuse marginal branch of the left circumflex artery; Prox = proximal (in LAD, proximal to first septal perforating artery; in Cx, proximal to first obtuse marginal; in RCA, proximal to acute marginal; RCA = right coronary artery. Parentheses indicate portions of a major artery.

**Effect of recipient stenosis on collateral frequency and grade:** The presence or absence of angiographically apparent collateral vessels was significantly affected by the severity of stenosis of the potential recipient artery. Of the 193 vessels with ≥90% stenosis, 118 (61%) received collateral vessels. In contrast, none of the 76 arteries with ≥75% but <90% stenosis received collateral vessels ($p < 0.001$). Of the 99 vessels with ≥90% stenosis that were not totally occluded, 39 (39%) received collateral vessels, while 79 of the 94 (84%) totally occluded vessels received collateral vessels ($p < 0.0001$) (Fig. 1).

Similarly, the grade of angiographically apparent collateral vessels was significantly affected by the severity of recipient artery stenosis. Of the 118 arteries receiving collateral vessels of either grade, collaterals supplying 87 arteries were graded good. Good collateral vessels supplied 70 of 94 (74%) of totally occluded arteries, but only 17 of 99 (17%) of subtotally occluded arteries ($p < 0.001$) (Fig. 2). Conversely, of the 79 collateral vessels to totally occluded arteries, 70 (86%) were good. In contrast, of the 39 collateral vessels to subtotally occluded arteries, 17 (44%) were good ($p < 0.001$).

**Effect of supplier stenosis:** Stenosis of the single artery most clearly supplying angiographically apparent collateral vessels significantly affected the grade of the collateral vessel. Thus, only 16 (18%) of the 87 good collateral vessels were supplied by obstructed (that is, with ≥75% stenosis proximal to the origin of the collateral) arteries; in contrast, 20 (65%) of the 31 poor collateral vessels had obstructed sources of supply ($p < 0.001$) (Fig. 3).

If a collateral vessel arose from an obstructed supplier, it invariably went to an artery whose stenosis was greater than that of the supplier. Sixteen collateral vessels clearly arose from single obstructed suppliers. Five collateral vessels arose from an artery with ≥75%

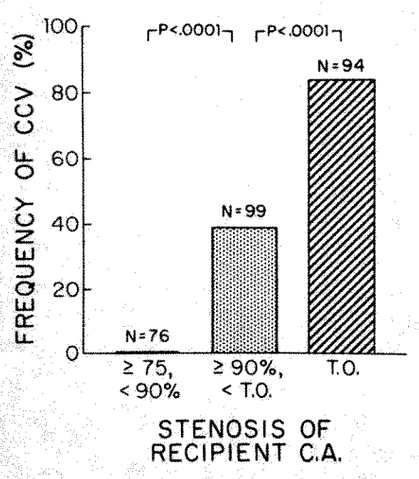



**FIGURE 1.** The frequency of angiographically demonstrable coronary collateral vessels (CCV) in arteries with ≥75% but <90% stenosis, with ≥90% stenosis but less than total occlusion (T.O.), and with total occlusion.

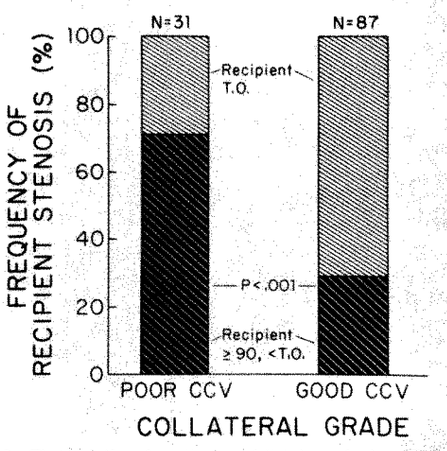



**FIGURE 2.** The relative frequency of total occlusion (T.O.), and of ≥90% stenosis but less than total occlusion, in arteries receiving poor and good coronary collateral vessels. Most arteries receiving good coronary collateral vessels (CCV) manifested total occlusion, while most arteries receiving poor coronary collateral vessels had less severe stenosis.

stenosis and each supplied a totally occluded artery; the 11 collateral vessels from ≥90% stenotic arteries also invariably supplied totally occluded arteries.

The importance of patency of supplying arteries in collateral appearance was confirmed by assessment of all *potential* sources of collateral supply. To eliminate the effect of variations in recipient artery obstructions, the analysis was limited to assessment of collateral vessels to the 94 totally occluded arteries. As shown in Figure 4, the extent of obstruction of potential suppliers (supplier obstructive index) was significantly higher in those arteries with no or poor collateral vessels ($p < 0.001$ for both groups of arteries versus arteries with good collateral vessels).

## Discussion

Our data indicate that the angiographic appearance of collateral vessels in patients with coronary artery occlusive disease is determined in large part by the presence and severity of stenosis of the large coronary arteries *supplying* and *receiving* the collateral flow.

We found that collateral vessels arose more frequently from nonobstructed than from obstructed arteries. The intensity of collateral filling at angiography was also influenced by supplier obstruction. Finally, the integrity of *potential* suppliers, as determined by our supplier obstructive index, affected the frequency and quality of collateral vessels to totally occluded arteries. While most totally occluded arteries received good collateral vessels, the absence of collateral vessels, or the presence of only poor ones, generally was seen only if most or all of the potential suppliers were obstructed.

The preferential origin of collaterals from nonobstructed arteries has not been previously appreciated. Similarly, the influence of supplier stenosis on collateral grade has not been reported. Analyses of the influence of potential suppliers on the likelihood of collateral development have yielded conflicting results. Most have suggested that stenotic lesions in potential suppliers have no effect on collateral appearance.[15–17] Although the issue of "potential suppliers" was not directly considered, evidence suggesting the lack of importance of potential suppliers can be inferred from the findings of Hamby et al,[17] who assessed the frequency of collateral supply to totally occluded left anterior descending or right coronary arteries. These investigators found that the presence or absence of collateral supply to either artery was unaffected by the presence of hemodynamically important obstructions of other arteries.[17] However, Hamby et al excluded from assessment those patients with total occlusion of potential suppliers, and defined other potential suppliers as obstructed if these manifested stenoses of ≥50%, a more lenient definition than that employed in the present study. Thus, the study design of Hamby et al differed significantly from ours, precluding direct comparison.

The relative unimportance of potential supplier stenosis also is implied by reports suggesting that the extent of visualization of collateral vessels is proportional to the overall severity of obstructive disease of the large coronary arteries.[15,16] If this were true, increasing collateralization might be expected to occur as potential suppliers develop increased disease, a conclusion which is directly contradicted by our findings. However, analyses leading to such conclusions generally have not considered the severity or location of the obstructive lesions in recipient arteries and potential suppliers, perhaps explaining in part the discrepancy between previous findings and those of the present study.

In contrast, in a study of the effects of collateral vessels on left ventricular function at rest and during exercise, Schwarz et al[14] concluded that collaterals are seen more frequently in patients with a single occlusion

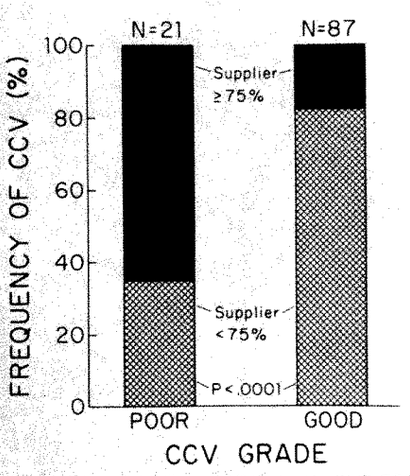



**FIGURE 3.** The relative frequency of "obstructed" (≥75% stenosis, **solid bar**) nonobstructed (<75% stenosis, **hatched bar**) suppliers to poor and good coronary collateral vessels (CCV). Good coronary collateral vessels usually have nonobstructed suppliers; poor coronary collateral vessels usually have obstructed suppliers.

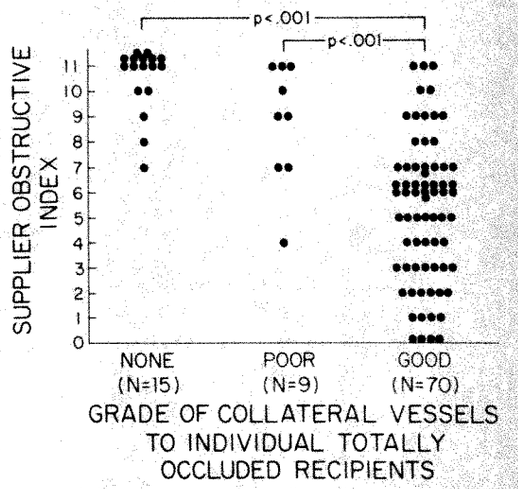



**FIGURE 4.** The supplier obstructive index, a measure of the patency of all arteries potentially supplying collateral vessels to totally occluded recipients, is higher when collateral vessels are absent or poor than when collateral vessels are graded good at angiography. The Supplier Obstructive Index was significantly ($p < 0.001$, by Dunn modification of Kruskal-Wallis test[19]) higher for the groups with no or poor collateral vessels than for the group with good collateral vessels.

than in patients with multiple occlusions.[14] However, their published data actually indicate that the proportion of well-collateralized totally occluded arteries was similar in patients with 1 or 2 totally occluded arteries. Accurate interpretation of the data of Schwarz et al is difficult, however, because the characteristics of the stenotic but not totally occluded arteries were not described.

Although our findings regarding the importance of the characteristics of supplying arteries are at variance with previous reports, our data are consistent with those of other investigators in demonstrating the importance of the severity of obstruction of recipient arteries in determining collateral vessel appearance. Nonetheless, differences exist between our findings and those of some previous studies. We were unable to demonstrate collateral vessels to arteries with <90% reduction in luminal diameter. Other investigators have noted angiographically apparent collateral vessels supplying arteries variously reported to manifest ≥50%,[11] ≥75%,[8,10] and ≥90%[2-4,6] stenoses. The source of this discrepancy is not entirely clear. However, several of the earlier studies did not separate patients with ≥90% stenosis from those with ≥50% and ≥75% obstructive lesions, thus potentially masking a relation between frequency of collateral vessels and severity of recipient artery obstruction. In addition, criteria employed in defining the severity of stenosis often have not been described, providing a potential source of inter-study variation. Finally, it is possible that interobserver variation in angiographic interpretation of coronary artery stenosis may be in part responsible for differences in results, though interobserver variability has been shown to be of relatively little importance when stenosis is ≥90%,[20] the lesion of greatest interest in our assessment.

Among patients with ≥90% stenosis, we found that the frequency and semiquantitative grade of collateral appearance was directly related to the presence of total occlusion. Thus, 84% of totally occluded arteries received collateral supply, while 39% of subtotally occluded arteries were so supplied. Though exceptions exist,[10] most investigators have found a similar relation between collateral frequency and total coronary artery occlusion.[11-13]

It is clear from our data that the relation we have observed, while highly statistically significant, do not describe the characteristics of all supplier-collateral recipient systems, that is, some good collateral vessels arise from obstructed suppliers and not all totally occluded arteries receive good collateral vessels. There are several potential explanations for the limitations of our observations. Of course, it is not possible to exclude the effects of factors unrelated to the extent of large coronary artery stenosis in modifying our results. Such additional influences, described previously by others,[5,11,15,21,22] include genetic predisposition of collateral formation, extent of regional ischemia, extent of physical activity, rate of progression of stenosis in the recipient artery, and concomitant hypoxia and/or anemia. In addition, the transcollateral pressure gradient, probably the major determinant of collateral vessel appearance at angiography, is dependent on the precise degree of luminal obstruction in supplying and recipient vessels. Clearly, although our grading system is highly reproducible and permitted stratification of patients into groups according to angiographic descriptors, no visually based angiographic grading system can precisely quantify anatomic obstruction,[23] or account for tubular stenoses, multiple stenoses, or concentric versus eccentric stenoses. Therefore, we would expect that although our angiographic assessment should generally reflect anatomic findings, an exact correlation would be unlikely, and precise estimate of pressure gradients across obstructive lesions should not be possible in every case.

Our data support the concept, well-substantiated in experimental animals,[24,28] that the specific transcollateral pressure gradient is of primary importance in determining the angiographic appearance of collateral vessels in man, and hence in determining the appearance of the distal portion of obstructed recipient arteries. Further, these results suggest that in the absence of an increase in systemic arterial (perfusion) pressure, collateral flow might be expected to increase only if (1) an increase occurs in the severity of obstruction of the recipient artery, or (2) if a decrease occurs in the severity of obstruction of supplying or potentially supplying arteries. Thus, our data may explain the inability of interventions such as diet and exercise to increase collateral development,[26,27] since neither of these interventions has been shown to decrease the severity of stenotic lesions in man. Similarly, our results are consistent with the finding of a longitudinal angiographic study which indicated that collateral vessels appear only with progression of the severity of a stenotic lesion in a recipient artery.[28]

Our findings have potential practical importance. Appropriate criteria for selection of patients for coronary bypass grafting, based both on myocardium at risk of ischemic damage and on subsequent risk to life, now are the subject of intense concern. As Levin[5] noted, autorevascularization by collateral flow may be sufficient in some cases to obviate the need for surgical intervention. Therefore, proper interpretation of the potential clinical importance of angiographically demonstrable collateral vessels may be essential. Our data suggest the possibility that, even if the angiographic appearance of a collateral vessel is good, decisions regarding the adequacy of collateral flow should perhaps take into account the characteristics of the supplying and recipient arteries. Moreover, of interest in patients in whom bypass grafting is to be undertaken, our data suggest the possibility that the absence of angiographic evidence of widely patent (and, hence, clearly graftable) distal segments of occluded vessels may result from extensive occlusion of potential suppliers, rather than from the intrinsic condition of the distal recipient vessel. If this is so, then planning of bypass grafting procedures must involve some means, perhaps intraoperative, to assure identification of potentially operable, although angiographically inadequate, distal vessels. Thus, our findings indicate that more complete understanding of the functional and clinical implications of angiographically demonstrable collateral vessels is of primary importance if therapeutic decisions are to be properly based on angiographic data.

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## References


1. **Spalteholz W.** Die coronararterien des herzens. Verh Anat Ges 1907;21: 141–153.
2. **Molnar W, Meckstroth CV, Nelson SW, Booth RW.** Trans-carotid coronary arteriography in man with emphasis on inter-coronary arterial anastomosis. Radiology 1960;75:185–195.
3. **Sheldon WC.** On the significance of coronary collaterals. Am J Cardiol 1969;24:303–304.
4. **Tabau JE, Chaitman BR, Bourassa, Lesperance J, Dupras G.** Importance of coronary collateral circulation in interpreting exercise test results. Am J Cardiol 1981;47:27–32.
5. **Levin DC.** Pathways and functional significance of the coronary collateral circulation. Circulation 1974;50:831–837.
6. **Sesto M, Schwarz F.** Regional myocardial function at rest and after rapid ventricular pacing in patients after myocardial revascularization by coronary bypass graft or by collateral vessels. Am J Cardiol 1978;43:920–928.
7. **Gensini GC, Esente P, Delmonico JE.** Coronary collaterals and coronary backflow recordings in patients with coronary artery disease (abstr). Am J Cardiol 1960;31:134.
8. **Frick MH, Valle M, Korhola O, Riihimaki E, Wiljasalo M.** Analysis of coronary collaterals in ischemic heart disease by angiography during pacing induced ischemia. Br Heart J 1976;38:186–196.
9. **Bodenheimer MM, Banka VS, Hermann GA, Trout RG, Pasdar H, Helfant RH.** The effect of severity of coronary artery obstructive disease and the coronary collateral circulation on local histopathologic and electrocardiographic observations in man. Am J Med 1977;63:143–149.
10. **Cohn PF, Madder DE, Holman BS, See JR.** Effect of coronary collateral vessels on regional myocardial blood flow in patients with coronary artery disease. Am J Cardiol 1980;46:359–364.
11. **Valle M, Miljasalo M, Frick MH, Korhola O, Suoranta H, Tallroth K.** Collateral circulation before and after coronary artery reconstruction. Ann Clin Res 1975;7:251–257.
12. **Berger BC, Matson DD, Taylor GJ, Burwell LR, Martin RP, Beller GA.** Effect of coronary collateral circulation on regional myocardial perfusion assessed with quantitative thallium-201 scintigraphy. Am J Cardiol 1980;46:365–370.
13. **Hecht HS, Aroesty JM, Morkin E, LaRaia PJ, Paulin SV.** Role of the coronary collateral circulation in the preservation of left ventricular function. Radiology 1975;114:305–313.
14. **Schwarz F, Flameng W, Enssien R, Sesto M, Thormann J.** Effect of coronary collaterals on left ventricular function at rest and during stress. Am Heart J 1978;95:560–577.
15. **Helfant RH, Kemp HG, Gorlin R.** Atherosclerosis, coronary collaterals and their relation to cardiac function. Ann Intern Med 1970;73:189–193.
16. **Nieminen MS, Valle M, Lassela E, Heikkila J, Hekali P, Frick MH.** Global and regional left ventricular contractility and collaterals in stable ischemic heart disease. Clin Cardiol 1980;3:163–168.
17. **Hamby RI, Eintabliam AGOP, Schwartz A.** Reappraisal of the functional significance of the coronary collateral circulation. Am J Cardiol 1980;38: 305–309.
18. **Gensini GG.** Coronary Arteriography. Mt. Kisco, NY: Futura, 1975:260–271.
19. **Hollander M, Wolfe DA.** Non-Parametric Statistical Methods. New York: John Wiley & Sons, 1973:115–116, 125.
20. **Pepine CJ, Feldman RL, Conti CR.** An unrecognized potentially serious limitation of coronary angiography (abstr). Circulation 1976;53:Suppl II: II-162.
21. **Goldberg S, Grossman W, Markis JE, Cohen MV, Baltaxe HA, Levin DC.** Total occlusion of the left main coronary artery. Am J Med 1978; 64:3–10.
22. **Pepler W, Meyer B.** Interarterial coronary anastomoses and coronary arterial pattern: a comparative study of South African Bantu and European hearts. Circulation 1960;24:14–22.
23. **Vlodaver A, Edwards JE.** Pathology of coronary atherosclerosis. Prog Cardiovasc Dis 1971;14:256–273.
24. **Berne RM, Rubio R.** Acute coronary occlusion: early changes that induce dilatation and the development of collateral circulation. Am J Cardiol 1969;24:276–281.
25. **Gregg DE.** The natural history of coronary collateral circulation. Circ Res 1974;35:335–344.
26. **Barmeyer J.** Physical activity and coronary collateral development. Adv Cardiol 1976;18:104–112.
27. **Nolewajka AJ, Kostuk WJ, Rechnitzer PA, Cunningham A.** Exercise and human collateralization: an angiographic and scintigraphic assessment. Circulation 1979;60:114–121.
28. **Bemis CE, Gorlin R, Kemp HG, Herman MV.** Progression of coronary artery disease: a clinical arteriographic study. Circulation 1973;47:455–464.

# Identification of Septal Ischemia During Exercise By Q-Wave Analysis: Correlation With Coronary Angiography

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**Septal Q-wave amplitudes were studied in lead $CM_5$ to evaluate its utility in predicting segmental coronary artery pathoanatomy. Q-wave amplitudes were measured in 41 patients with coronary artery disease (CAD) before and immediately after treadmill exercise. All patients studied had either significant single-vessel CAD (>70% diameter reduction) or normal coronary anatomy; 13 had left anterior descending (LAD) CAD, 8 had right coronary occlusions, 8 had left circumflex (LC) CAD, and 12 had angiographically normal coronary arteries.**

**Septal Q-wave amplitude measurements at rest and during peak exercise were recorded in 0.5 mm increments and classified as increasing in 20 patients, decreasing in 8, and no change in 13 with exercise. All 13 patients with isolated LAD narrowing had either no change (5 patients) or a decrease (8 patients) in the septal Q wave with exercise. Statistical analysis revealed 62% sensitivity and 100% specificity for single LAD narrowing if a decreasing Q wave was noted with exercise. Patients with isolated right or LC CAD or normal coronary anatomy had mixed septal Q-wave responses to exercise. Only patients with LAD narrowing had reductions in Q-wave amplitude with treadmill exercise. This finding suggests that low Q-wave voltage and its failure to increase after exercise imply abnormal septal activation, reflecting loss of contraction associated with ischemia from LAD narrowing.**

Exercise testing is a valuable noninvasive tool for diagnosing and monitoring CAD.[1-3] S-T segment depression is considered the hallmark of exercise-induced myocardial ischemia.[4] Unfortunately, the predictive value of the S-T segment response in exercise is subject to the population tested and fails to distinguish with certainty those with or without CAD.[5] As a result of this incidence of false-positive and false-negative results from exercise tests employing analysis of the S-T segment alone, other electrocardiographic indexes have been developed to enhance the diagnostic and prognostic value of exercise testing.[6-8] Additionally, multivariate analysis has been proposed to enhance the accuracy of the exercise test.[9,10]

We recently reported our experience with the septal Q wave in exercise testing.[11] In 100 patients evaluated with exercise tests and coronary angiography, the septal Q wave in bipolar lead $CM_5$ is smaller in patients with CAD than in normal subjects both at rest and in the immediate postexercise recovery period ($p < 0.001$) (Fig. 1 and 2). The average septal Q wave in patients with CAD was 0.5 mm at rest and 0.5 mm in immediate postexercise recovery period. The average septal Q wave in normal patients was 1.0 mm at rest and 2.0 mm in the immediate postexercise recovery period. An increase in the septal Q-wave amplitude with exercise identified a false-positive S-T segment response to stress in 75%

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of the cases. Absence of the septal Q wave in bipolar lead $CM_5$ with S-T segment depression identified a true-positive response in 100% of the cases studied. Thus, measurement of the septal Q wave appears to be a useful adjunctive measurement in exercise testing, with its major application in confirming a true-positive response with concomitant S-T segment depression. These data suggest that low septal Q-wave voltage and its failure to increase with exercise imply abnormal septal activation, reflecting loss of contraction associated with ischemia. Unfortunately, specific localization of this electrocardiographic event with coronary artery pathoanatomy was difficult, since 77% of the patients with CAD studied had 2- or 3-vessel disease. This report focuses on the septal Q wave in exercise and corresponding coronary artery segment pathoanatomy (Fig. 1 and 2).

## Methods

**Patients:** The patient were sequentially selected from a computer search of our files to obtain subjects who had both exercise testing and coronary angiograms that fulfilled the criteria necessary for the study; normal coronary anatomy or single-vessel CAD (luminal diameter reduction >70%). No patient was previously studied. Treadmill exercise test records and coronary angiograms of patients referred for evaluation of chest pain were reviewed retrospectively. Patients with an abnormal electrocardiogram at rest were excluded, including left ventricular hypertrophy, right ventricular hypertrophy, left bundle branch block, right bundle branch block, or preexcitation syndromes. Patients with the clinical diagnosis of valvular heart disease or myocardial infarction, and patients taking digitalis or beta-adrenergic blocking drugs were excluded. Of 41 patients studied, 12 had normal coronary anatomy (9 men and 3 women aged 45 to 68 years [mean 62]); 13 had LAD CAD, 8 had right CAD, and 8 had LC CAD. Patients with CAD were aged 36 to 67 years (mean 61); 15 were men and 14 women.

**Treadmill stress test:** The interval between the exercise test and the coronary angiogram ranged from 1 to 60 days. Patients were subjected to a progressive maximal exercise test according to the Ellestad protocol using a 3-lead system consisting of a bipolar lead $CM_5$, a bipolar lead III, and unipolar lead $V_1$. Significant S-T segment depression was upsloping in the immediate postexercise period. The 3 electrocardiographic leads were monitored simultaneously and continuously during and after exercise. All subjects with normal coronary angiogram results were exercised to ≥90% of their normal age-predicted heart rate response to exercise. The septal Q wave was measured only in the bipolar lead $CM_5$ in the period immediately after exercise with the patient standing. This Q wave was compared with that in the standing control period. A 10 mm/mV calibration was used. The septal Q-wave amplitude was measured from the isoelectric line for 5 to 10 beats. The average amplitude was approximated to the nearest 0.5 mm increment. The septal Q waves were measured by either the first or second author and reviewed by the fourth. The treadmill exercise test was examined independently without prior knowledge of the coronary angiogram.

**Cardiac catheterization:** This procedure was performed using either the Sones or Judkins technique. No patient had clinical heart failure at the time of catheterization. Coronary angiography was performed using 35 mm film with multiple views. Single plane left ventricular angiography was performed in the right anterior oblique projection. The criteria for diagnosis of CAD was >70% diameter reduction of the lumen of the artery.

The coronary anatomy and left ventricular angiogram were graded without prior knowledge of the exercise test results by

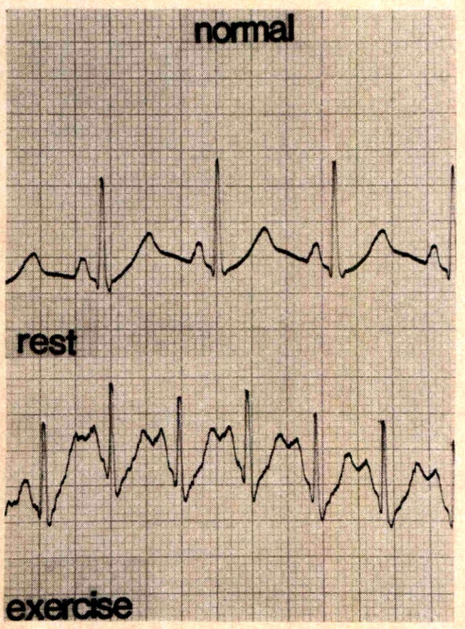



**FIGURE 1.** Q-wave response to exercise in a patient with normal coronary anatomy. The surface electrocardiogram (lead $CM_5$) demonstrates increased Q-wave amplitude with exercise.

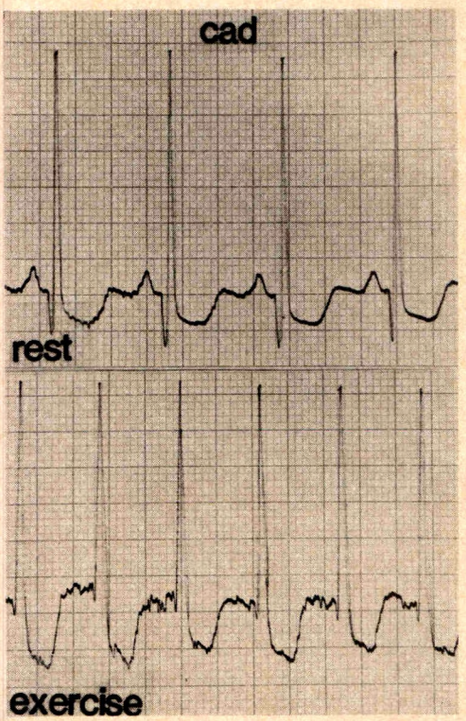



**FIGURE 2.** Q-wave response to exercise in a patient with single-vessel left anterior descending coronary artery disease (cad).

2 independent observers; any discrepancies were resolved by a third observer.

**Statistical evaluation:** Sensitivity was defined as true-positive responses/true-positive + false-negative responses. Specificity was defined as true-negative responses/true-negative + false-positive responses. The sensitivity, specificity, and predictive value for the septal Q-wave change was determined and compared within the multiple patient cohorts.

## Results

**Normal coronary anatomy:** Of the 12 patients with normal coronary angiograms, 9 had an increase in septal Q-wave amplitude with exercise. The increase in septal Q-wave amplitude with exercise was 0.5 mm in 6 patients and 1.0 mm in 3 patients. Three patients had no change in septal Q-wave amplitude with exercise. No patient had a loss of septal Q-wave amplitude with exercise (Fig. 3).

**Single vessel coronary artery disease:** *Left anterior descending:* Of the 13 patients with significant stenosis (>70% cross-sectional area luminal narrowing) isolated to the LAD coronary artery, 8 (62%) had diminution of their septal Q-wave amplitude with exercise. This loss in septal Q-wave amplitude with exercise was 0.5 mm in 4 patients and 1.0 mm in 4 patients. Five patients had no change in septal Q-wave amplitude with exercise. No patient exhibited an increase in septal Q-wave amplitude with exercise (Fig. 3).

*Left circumflex:* Of the 8 patients with isolated significant stenosis to the LC coronary artery, none demonstrated a reduction of septal Q-wave amplitude with exercise. An increase in septal Q-wave amplitude with exercise was present in 5 patients: 0.5 mm in 1 patient, 1.0 mm in 3 patients, and 2.5 mm in 1 patient. Three patients had no change in septal Q-wave amplitude with exercise (Fig. 3).

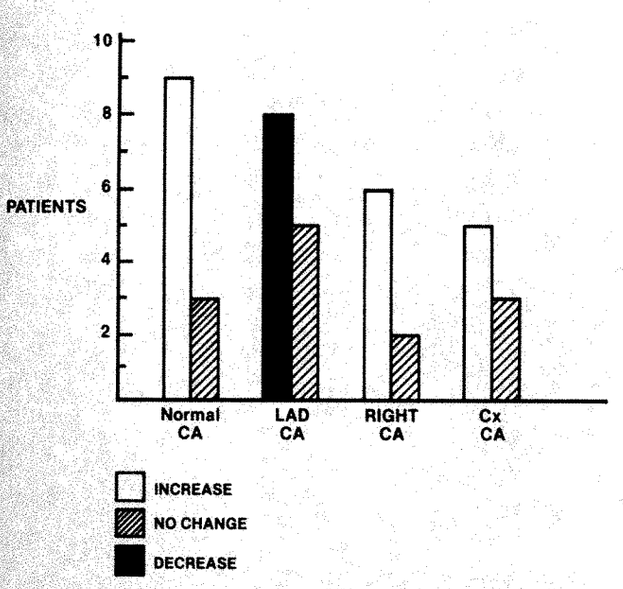



**FIGURE 3.** Septal Q-wave response to exercise in patients with normal or single-vessel coronary artery disease. A decrease in Q-wave amplitude with exercise is seen only in patients with left anterior descending (LAD) coronary artery disease. CA = coronary anatomy; Cx = circumflex.

**TABLE I Statistical Analysis of Septal Q-Wave Response to Exercise and Single Vessel Left Anterior Descending Coronary Artery Disease**

| | Sensitivity | | Specificity | | Predictive Value | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Decreasing Q wave | 62 | 8/13 | 100 | 33/33 | 100 | 8/8 |
| Decreasing or no change in Q wave | 100 | 13/13 | 71 | 20/28 | 62 | 13/21 |

*Right:* Of the 8 patients with significant stenosis isolated to the right coronary artery, none demonstrated a reduction of the septal Q wave with exercise. An increase in septal Q-wave amplitude with exercise was recorded in 6 patients: 0.5 mm in 4 patients, 1.0 mm in 1 patient, and 2.0 mm in 1 patient. Two patients had no change in septal Q-wave amplitude with exercise (Table I).

## Discussion

**Q wave and resting electrocardiography:** Initial ventricular activation originates from the ventricular septum, with Q waves being recorded in both the frontal and precordial planes. Normal Q-wave ranges of amplitude and duration have been previously reported.[12,13] In 1955, Burch[14] described an electrocardiographic syndrome characterized by absence of the Q wave in leads 1, aVL, $V_5$, and $V_6$ due to septal fibrosis. In 1960, Burch and De Pasquale[15] reported cardiac pathologic findings in 142 patients with this electrocardiographic syndrome. Occlusive CAD usually involving the LAD coronary artery or scarring in the septum with little or no scarring in other areas of the myocardium was common. They concluded that the mechanism of the septal fibrosis in patients with prolonged periods of angina pectoris is obscure, but may be due to spasm of the penetrating septal arteries with progressive myocardial injury and eventually septal fibrosis. The changes were confirmed vectorcardiographically by Cabrero.[16]

**Q wave and exercise electrocardiography:** Bruce et al[17] studied 73 volunteers undergoing maximal treadmill exercise testing. Increase in Q-wave amplitude was seen as a normal response to exercise ($p < 0.01$). Recently, Wolthuis et al[18] reported that lead $CM_5$ had the most prominent Q wave and attained the most negative amplitude with exercise.

The current literature is scant with reports of exercise Q-wave responses in patients with abnormal coronary anatomy. Greenspan et al[19] prospectively evaluated and correlated exercise-induced Q waves during treadmill testing with findings at cardiac catheterization. Of 560 patients undergoing treadmill exercise testing, 13 had new Q waves in leads $V_1$ through $V_3$ and 1 had exercise-induced Q waves in leads II, III, and aVF. Of 10 patients who underwent cardiac catheterization, 6 had normal coronary anatomy and 2 had documented previous anterior myocardial infarction. The authors

concluded that exercise-induced Q waves were not diagnostic of underlying coronary disease.

In a recent report, we studied exercise Q-wave responses in bipolar lead $CM_5$. Q-wave amplitude was measured in 50 patients with CAD and 50 normal subjects in the control (pretest) and immediate postexercise period. In 100 patients evaluated by coronary angiography, the septal Q-wave lead $CM_5$ was smaller in patients with CAD than in normal subjects at rest and during the immediate postexercise period. Absence of or embryonic (0.5 mm) Q wave in lead $CM_5$ was significantly more common in patients with CAD at rest and after exercise than in normal subjects. An increase in Q-wave amplitude with exercise identified a false-positive S-T segment response to exercise in 75%, and absence of the Q wave in lead $CM_5$ with S-T segment depression after exercise identified a true-positive response in 100% of the cases. Low Q-wave voltage and failure to increase after exercise suggested a reduction in the septal current of depolarization, reflecting loss of contraction associated with ischemia of the septum. Of our 50 patients with coronary heart disease, 45 had LAD narrowing in addition to narrowings in other coronary arteries.

This report focuses on the correlation of coronary artery pathoanatomy with the exercise septal Q-wave response. All 13 patients with isolated LAD narrowing had either no change (5 patients) or a decrease (8 patients) in the septal Q wave with exercise (Fig. 3). Statistical analysis revealed 62% sensitivity and 100% specificity for single-vessel LAD coronary narrowing if a decreasing Q wave was noted with exercise (Table I). Patients with isolated right or LC narrowing or normal coronary arteries had mixed septal Q-wave responses to exercise; 20 patients had an increase while 13 patients had no change in septal Q wave with exercise. Only patients with LAD narrowing had reduction in Q-wave amplitude with exercise. The 100% sensitivity seen with a decreasing or no change in Q-wave amplitude for LAD narrowing (13 of 13 patients) most likely will decrease as the population studied increases. In a previous longer study,[11] 45 patients with LAD narrowing had a sensitivity of 87% when analyzing a decrease or no change in the exercise Q wave.

This study implies that a decreasing septal Q wave with exercise denotes LAD coronary narrowing and is of benefit in analysis of the S-T segment depression. The exclusions in this study diminish the number of problems related to misinterpretation of the exercise test and the predictive value might be reduced in an expanded population.

## References


1. **Ellestad MH, Wan KMC.** Predictive implications of stress testing. Circulation 1975;51:363–369.
2. **Ellestad MH, Cooke BM, Greenberg PS.** Stress testing: clinical application and predictive capacity. Prog Cardiovasc Dis 1979;21:431–460.
3. **Bruce RA, De Raven TA, Hossack KF.** Value of maximal exercise tests in risk assessment of primary coronary heart disease events in healthy men. Five years experience of the Seattle Heart Watch Study. Am J Cardiol 1980;46:371–378.
4. **Goldschlager N, Selzer A, Cohn K.** Treadmill stress tests as indicators of presence and severity of coronary artery disease. Ann Intern Med 1976; 85:277–286.
5. **Borer JS, Brensike JF, Redwood DR, Itcoitz SB, et al.** Limitations of the electrocardiographic response to exercise in predicting coronary artery disease. N Engl J Med 1975;293:367–371.
6. **Bonoris PE, Greenberg RS, Castellanet MJ, et al.** Predictive value of R wave amplitude changes in treadmill stress test (abstr). Circulation 1977;56:Suppl III:III-197.
7. **Bonoris PE, Greenberg PS, Christison GW, et al.** Evaluation of R wave amplitude vs ST segment depression in stress testing. Circulation 1978; 57:904–910.
8. **Bonoris PE, Greenberg PS, Christison GW, et al.** Ability of R wave amplitude changes to reduce false negative and false positive response by ST depression in treadmill stress testing (abstr). Am J Cardiol 1978;41:378.
9. **Berman JL, Wynne J, Cohn PB.** A multivariate approach for interpreting treadmill exercise tests in coronary artery disease. Circulation 1978;58: Suppl III:III-505–III-512.
10. **Greenberg PS, Ellestad MH.** Prospective application of the multivariate approach to enhance the accuracy of the treadmill stress test. J Electrocardiol 1982;15:143–148.
11. **Morales-Ballejos M, Greenberg P, Ellestad MH, Bible M.** The septal Q wave in exercise testing: angiographic correlation. Am J Cardiol 1981;48: 247–251.
12. **Goldberger, AL.** Recognition of ECG Pseudo-Infarct Patterns. Mod Concepts Cardiovasc Dis 1980;49:13–18.
13. **Lepeschkin E.** In: Altnan PL, Sittmer DS eds. Respiration and Circulation. Bethesda, MD: Federation of American Societies for Experimental Biology, 1971:277.
14. **Burch GE.** An electrocardiographic syndrome characterized by absence of the Q wave in leads 1, AVL, $V_5$ and $V_6$. Am Heart J 1956;51:487–488.
15. **Burch GE, De Pasquale N.** A study at autopsy of the relation of absence of the Q wave in leads 1, AVL, $V_5$ and $V_6$ to septal fibrosis. Am Heart J 1960;60:336–340.
16. **Cabrero E, Garcia-Font R, Gaxiola A, Plieggi F.** The vector cardiogram of ventricular activation in chronic coronary heart disease. Am Heart J 1957;55:557–571.
17. **Bruce R, Mazzarella J, Jorden J, Green E.** Quantitation of QRS and ST segment responses to exercise. Am Heart J 1966;71:455–466.
18. **Wolthuis R, Froelicher V, Hopkirk A, Fisher J, Keiser N.** Normal electrocardiographic waveform characteristics during treadmill exercise testing. Circulation 1979;60:1028–1035.
19. **Greenspan M, Anderson G.** The significance of exercise induced Q waves. Am J Med 1979;67:454–459.

# Surgery for Coronary Heart Disease Due to Mucocutaneous Lymph Node Syndrome (Kawasaki Disease)

## Report of 6 Patients

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**Early and late surgical results in 6 patients with coronary heart disease secondary to mucocutaneous lymph node syndrome (MLNS) (Kawasaki disease) are presented. There were 5 male patients and 1 female patient, ranging in age from 2.5 to 26 years at the time of operation. They had severe coronary artery narrowings, obstructions, and aneurysms with or without mitral regurgitation. Previous myocardial infarction was documented in 5 patients. Aortocoronary bypass grafting utilizing the autologous saphenous vein was performed in 5 patients; in the remaining patient, mitral valve replacement was carried out.**

**No operative or late deaths have been encountered. A long-term bypass graft patency was demonstrated in patients aged 26, 17, and 10 years with resulting clinical, angiographic, or scintigraphic improvements, or a combination of these. However, the graft that had been patent in a 4-year-old boy was found completely obstructed 3 years after surgery without any symptomatic changes. The formation of rich collateral channels was found. The risk of saphenous vein graft closure may be high in young growing children. In older children or adolescents, however, coronary vein bypass grafting for this specific inflammatory coronary artery lesion has been effective with long-term graft patency. Severe mitral regurgitation is also an indication for surgery, but poor left ventricular function associated with mitral regurgitation, probably secondary to myocarditis, persists after surgery and may give rise to future problems.**

It is now well known that mucocutaneous lymph node syndrome (MLNS) or Kawasaki disease causes inflammatory coronary arterial and myocardial lesions that may result in coronary artery aneurysms, obstructions, embolism, myocardial infarction, or papillary muscle dysfunction, or a combination of these. Surgery has been attempted for these inflammatory coronary artery lesions and sequelae of myocardial injury such as papillary muscle dysfunction resulting in mitral insufficiency.[1–7] However, the significance and late results of surgical treatment for MLNS have not yet been reported. This report reviews our surgical experiences with 6 patients, and describes late results and problems after surgery.

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### Methods

**Patients:** Clinical and angiographic features of 6 patients treated surgically are presented in Table I. There were 5 male patients and 1 female patient; their ages at operation ranged from 2.5 to 26 years. Five patients underwent aortocoronary bypass grafting using autologous saphenous veins; 1 patient aged 2.5 years had mitral valve replacement with use of a porcine xenograft for severe mitral regurgitation secondary to papillary muscle infarction. The patients underwent surgery at least 1 year after the subsidence of acute illness of MLNS. Left main trunk lesions were present in 3 patients; 3-vessel lesions including coronary aneurysms, narrowings, and obstructions were noted in 4 patients. Electrocardiography documented myocardial infarction in 5 patients, inferior wall infarcts in 3, and anteroseptal infarcts in 2. Mitral regurgitation was demonstrated in 2: 1 patient (Case 1) with a 38% regurgitant ratio and the other (Case 4) with 71% severe regurgitation. The left ventricular ejection fraction calculated from cineangiograms ranged from 0.35 to 0.56. Except for Case 4, the ejection fractions were maintained well over 0.4.

Among the 6 patients, no operative or late deaths have been encountered. The postoperative follow-up periods extended

**TABLE I Surgery for Heart Disease Due to Mucocutaneous Lymph Node Syndrome**

| Case | Age (yr) & Sex at Op | MI | MR | Coronary Arteries (N or A) | Preop LVEF | CABG | Grafts Patent | Postop NYHA |
|---|---|---|---|---|---|---|---|---|
| 1 | 26M | + | + | LM, LAD, R | 0.41 | + (LAD, R) | + (3 yr) | II |
| 2 | 4M | + | − | LAD, LC, R | 0.45 | + (LAD, R) | + (1 mo), − (3 yr) | I |
| 3 | 4M | + | − | R | 0.56 | + (R) | No study | I |
| 4 | 2.5M | + | + | LM, R | 0.35 | −, MVR | . . . | I |
| 5 | 17M | + | − | LAD, LC, R | 0.46 | + (LAD, LC) | + (2.5 yr) | I |
| 6 | 10F | − | − | LM, LAD, R | 0.54 | + (LAD, R) | + (LAD, 1 yr), − (R) | I |

A = aneurysm; CABG = coronary artery bypass graft; LAD = left anterior descending artery; LC = left circumflex artery; LM = left main; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = mitral regurgitation; MVR = mitral valve replacement; N = narrowing or obstruction; NYHA = New York Heart Association functional class; Op = operation; Postop = postoperative; Preop = preoperative; R = right coronary artery; + = yes; − = no.

from 1 to 8 years. At present, Patient 1 is in the NYHA[8] functional class II and the remaining 5 patients are in class I. Patient 4 has been receiving digitalis and Patient 5 has been taking a small dose of procainamide for arrhythmia. The other patients are medication-free at present.

The operative techniques used for these patients were essentially the same as those used for adult patients with atherosclerotic coronary artery disease. Under cardiopulmonary bypass with moderate hypothermia, aorta-graft anastomosis was performed with 6-0 monofilament sutures and graft-coronary artery anastomosis was carried out with 7-0 monofilament sutures. Both continuous and interrupted sutures were used. The graft material used for the 5 patients were all autologous saphenous veins harvested from the patients' thighs. Brief histories of the patients follow.

## Case Reports

**Patient 1** had a large anteroseptal infarction at age 26 years; study revealed the presence of a large left main trunk aneurysm with stenosis of the left anterior descending artery and total occlusion of the right coronary artery. This patient had a history of high fever associated with skin rash at age 14 years which was diagnosed as probable rheumatic fever at that time. We included this patient in our series because of close similarity to the lesions of MLNS (MLNS has also been reported in young adult patients[9,10]). Two aortocoronary bypass grafts were placed to the left anterior descending and right coronary arteries. The grafts was demonstrated angiographically to be widely patent 3 years after surgery with asymptomatic total occlusion of the left main trunk aneurysm.[1] This patient had had total obstruction of the right coronary artery before operation, and therefore at present, all of his original coronary arteries are obstructed. Postoperative angiograms also showed the irregular coil-shaped posterior descending artery. He has been working daily in the office with some easy fatigability for 8 years after operation.

**Patient 2** was a 4-year-old boy who had temporary circulatory arrest (possibly ventricular fibrillation) with spontaneous recovery after anteroseptal infarction. Total obstructions of the right coronary and left anterior descending coronary arteries, and a small aneurysm of the origin of the circumflex artery were demonstrated by selective coronary arteriography[11] at age 3 years. He underwent double aortocoronary bypass grafting to the right coronary and left anterior descending coronary arteries utilizing the autologous saphenous vein. Two grafts were widely patent 1 month after operation.[2] However, both grafts were found to be totally occluded 3 years after surgery with no symptomatic changes. The restudy was performed in this patient for the purpose of an angiographic follow-up. At present, there are no signs of myocardial ischemia detectable either with exercise electrocardiography or exercise thallium-201 myocardial scintigraphy. It was impossible to identify the time of graft occlusion during the 3-year follow-up. The obstructed right coronary and left anterior descending arteries were perfused by the excellent intra- and intercoronary collateral channels. The distal right coronary artery was connected with the well-developed intracoronary collateral vessels and the left anterior descending artery was perfused through the conus branch of the right coronary artery, proximally and through the apical branch of the circumflex artery, distally.

**Patient 3** was also a 4-year-old boy who sustained an small inferior wall myocardial infarction subsequent to total obstruction of the origin of the right coronary artery. He underwent coronary bypass grafting to the large dominant right coronary artery. He has been followed up for 6 years and is doing well at present, but an angiographic restudy has not yet been performed because of postoperative hepatitis.

**Patient 4** had congestive heart failure and cardiac cachexia at age 2.5 years resulting from severe mitral regurgitation that occurred after inferior wall infarction.[4] The right coronary artery was totally occluded near its origin. The cause of mitral regurgitation was papillary muscle dysfunction, and his left ventricular contraction was markedly depressed with an ejection fraction of 0.35. He underwent mitral valve replacement using a 27 mm porcine xenograft and has been followed up for 3 years. Postoperatively, the left atrial volume has decreased significantly from 220 to 84 ml/m$^2$; however, generalized poor contraction of the left ventricle has not been improved with an actual reduction of the ejection fraction from the preoperative value of 0.35 to 0.26 after operation. The contraction impairment of the left ventricle in this patient is much worse than expected from the electrocardiographic inferior wall infarction, and this fact may suggest the associated myocardial involvement subsequent to MLNS myocarditis. Little pathologic change was identified in the excised mitral leaflets, but extensive myocardial injury with fibrosis was demonstrated in the posterior papillary muscle.[4] The porcine xenograft that has been implanted in this patient has recently shown degenerative changes with resultant stenosis. Reoperation may be required in the future.

**Patient 5** was a 17-year-old boy who had a history of MLNS at age 4. He had been doing well until 1 year before operation, when multiple and repetitive premature ventricular contractions appeared and worsened during exercise, accompanied by a fainting sensation. However, angina pectoris was not apparent. Left ventriculography demonstrated reduced contraction of the anterior and inferior walls with a global ejection fraction of 0.46. Coronary arteriography demonstrated total occlusion of the right coronary artery with intracoronary collateral formation and severe proximal stenoses of the left anterior descending and left circumflex arteries associated with aneurysms (Fig. 1, top). Although he had no obvious angina pectoris, the presence of severe coronary narrowing and refractory ventricular ectopic contractions during exercise prompted surgery. Two aortocoronary saphenous vein bypass grafts were placed to the left anterior descending and circumflex arteries. Ventricular ectopic beats have become controlled with a small dose of procainamide after operation. Two grafts have been patent for 2.5 years after surgery (Fig. 1, bottom). At present, the patient is completely asymptomatic with excellent exercise ability.

**Patient 6** was a 10-year-old girl who had MLNS at age 7. She noted an oppressive feeling in the anterior chest while exercising. A study revealed the presence of a large aneurysm in the left main trunk with a total occlusion of the left anterior descending artery at its origin,

filled retrogradely from the circumflex artery. The right coronary had a small aneurysm at its origin (Fig. 2, top). Hypoperfusion in the anterior wall was clearly demonstrated by exercise thallium-201 myocardial scintigraphy with recovery 2 hours after exercise by the redistribution study. The patient underwent double aortocoronary bypass grafting to the left anterior descending and right coronary arteries using the autologous saphenous vein and is now completely free from angina pectoris.

Angiographic and scintigraphic evaluations were repeated 1 year after operation. The thallium-201 uptake defect during exercise observed in the anterior wall of the left ventricle before surgery improved significantly after revascularization. The left anterior descending coronary graft was patent. Although the right coronary artery graft was closed, the original right coronary artery was patent with no scintigraphic perfusion defects (Fig. 2, bottom).

## Discussion

Studies regarding surgical treatment for coronary heart disease subsequent to Kawasaki disease are still very limited,[1–7] and little is known of the indications for and long-term results of surgical treatment for this inflammatory pediatric coronary artery disease. We are most concerned with the long-term significance of surgical treatment for this disease and the fate of the saphenous vein aortocoronary bypass grafts implanted during childhood. Although our surgical experiences are also limited, we discuss here some of the findings obtained from 6 patients who underwent surgery.

From our experience, we have confirmed that aortocoronary bypass surgery is effective in selected patients with coronary lesions resulting from Kawasaki disease. Clinical, functional,[2,12] and scintigraphic evaluations in early and late postoperative periods have shown that aortocoronary bypass grafts are functioning well long after operation in our older children or adolescents. In younger children, however, long-term patency of aortocoronary autologous saphenous vein bypass grafts cannot be confirmed from our results. In a 4-year-old boy, the graft that had been patent 1 month after op-

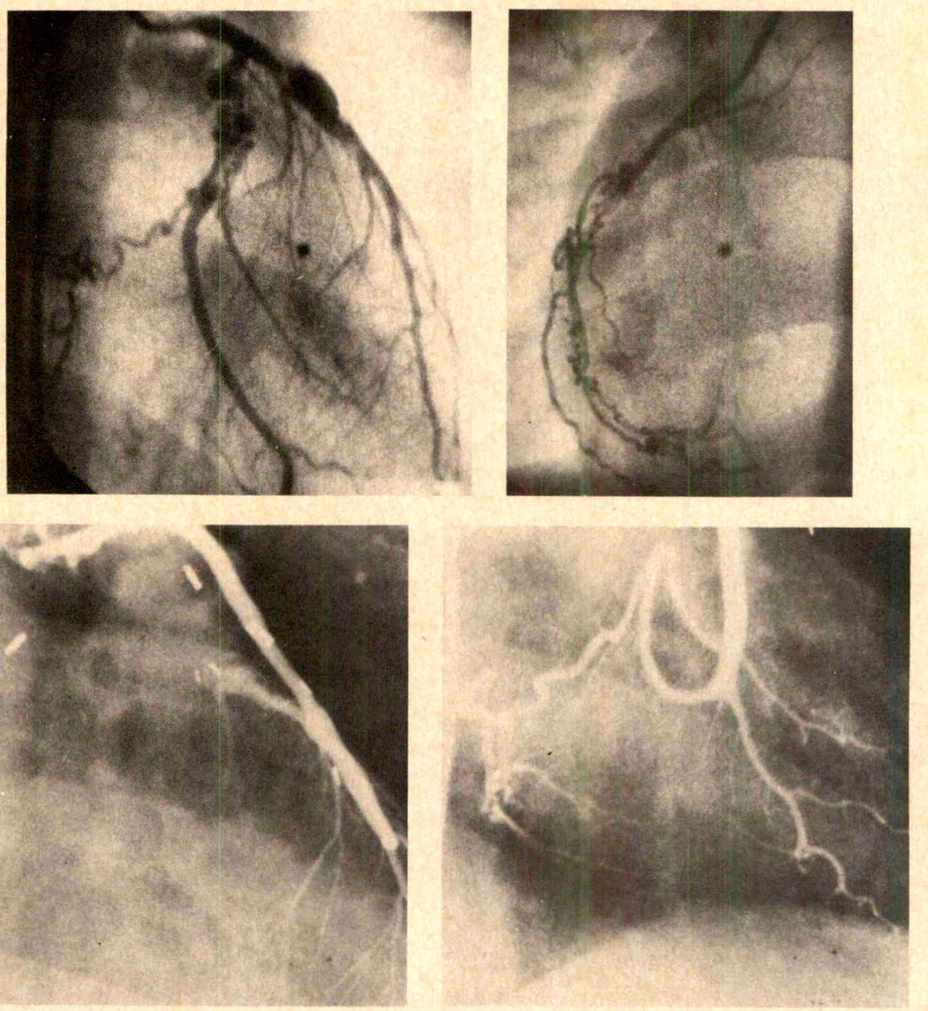


**FIGURE 1.** Patient 5. Pre- and postoperative coronary arteriograms. **Top left,** an aneurysm and a severe stenosis just proximal to the aneurysm were present in the left anterior descending artery. The circumflex arteries had stenosis with coil-shaped collateral connections. **Top right,** the right coronary artery was occluded with intracoronary collateral connections. The autologous saphenous vein bypass grafts to the left anterior descending artery (**bottom left**) and the circumflex artery (**bottom right**) are patent 2.5 years after surgery. The patient is now completely asymptomatic.

eration was found completely occluded 3 years later with no symptomatic changes. Rich collateral channels maintained the adequate myocardial perfusion and, thus, the graft appeared to have occluded slowly. The cause of graft occlusion in this child is not clear. Graft closure might have resulted from simple degenerative mediointimal hyperplasia, but failure of nongrowing conduits in the growing heart of children has been considered[2]; this hypothesis cannot be denied from our present experience. The internal mammary artery graft, although technically more difficult to perform in small children, may be more adequate because it may simultaneously grow, whereas the saphenous vein conduit does not.

**Conclusion:** From our limited experience, in conjunction with that reported by others,[5–7] we believe that aortocoronary bypass grafting utilizing autologous saphenous veins is effective in the treatment of MLNS coronary artery lesions at least in selected older children or adolescents. The adequate age for coronary revascularization in Kawasaki disease has not yet been determined. Judging from our experiences and those of others,[2,6] we consider that an age over rather than under 8 to 10 years would be more appropriate for the use of nongrowing saphenous vein conduits, although more clinical evaluation is required.

Mitral regurgitation due to Kawasaki disease is usually associated with poor left ventricular function

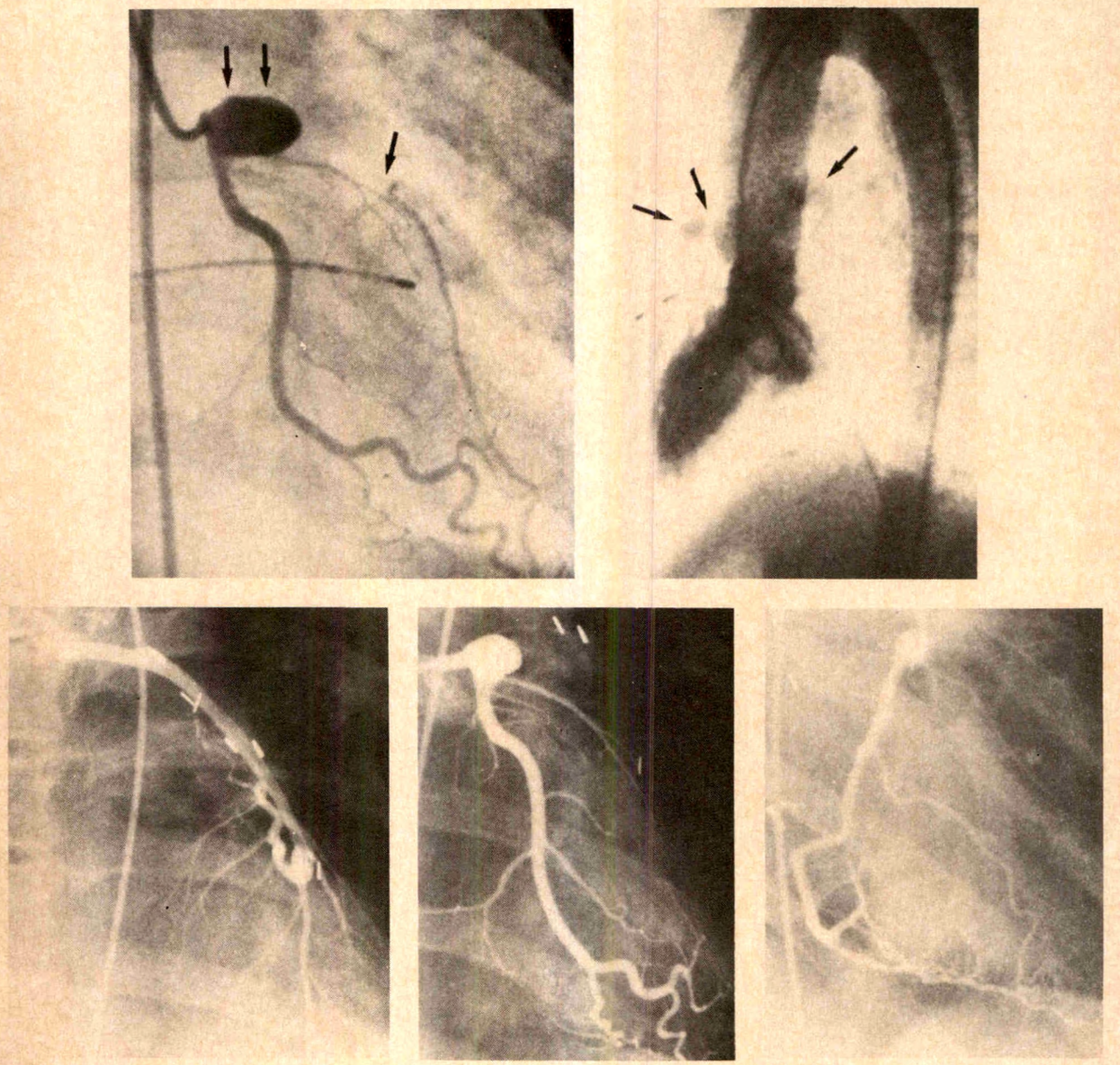


**FIGURE 2.** Patient 6. Pre- and postoperative coronary arteriograms. **Top left,** a large aneurysm was present in the left main artery with the left anterior descending artery totally occluded at its origin and retrogradely filled through the apical connection with the circumflex artery. **Top right,** a small aneurysm was present at the origin of the right coronary artery. **Bottom left,** the graft to the left anterior descending artery is patent 1 year after surgery. **Bottom center,** the circumflex artery is patent, originating from the left main trunk aneurysm which is somewhat reduced in size. **Bottom right,** although the right coronary graft has been occluded, the original right coronary artery is patent with no flow delay.

and complicated coronary artery lesions.[4] Mitral valve replacement[4] or repair[3] has offered good clinical amelioration, but long-term results have not been fully warranted not only because of the unavailability of suitable valve prostheses in children, but also because of associated poor left ventricular function probably secondary to accompanying myocarditis.[4]

## References


1. **Kitamura S, Kawashima Y, Miyamoto K, Kobayashi T, Matsuda H, Ohgitani N, Kodama K, Minamino T, Manabe H.** Multiple coronary artery aneurysms resulting in myocardial infarction in a young man. J Thorac Cardiovasc Surg 1975;70:290–297.
2. **Kitamura S, Kawashima Y, Fujita T, Mori T, Oyama C, Fujino M, Kozuka T, Nishizaki K, Manabe H.** Aortocoronary bypass grafting in a child with coronary artery obstruction due to mucocutaneous lymph node syndrome. Report of a case. Circulation 1976;53:1035–1040.
3. **Konishi Y, Tatsuta N, Miki S, Chiba Y, Kao CT, Hikasa Y, Yokota M, Nishioka K, Ueda T, Kamiya T, Sugiyama T.** Mitral insufficiency secondary to mucocutaneous lymph node syndrome. A case report of successful surgical treatment. Jpn Circ J 1978;42:901–909.
4. **Kitamura S, Kawashima Y, Kawachi K, Harima R, Ihara K, Nakano S, Shimazaki Y, Mori T.** Severe mitral regurgitation due to coronary arteritis of mucocutaneous lymph node syndrome. J Thorac Cardiovasc Surg 1980;80:629–636.
5. **Wada J, Endo M, Takao A, Kawamura T.** Mucocutaneous lymph node syndrome. Successful aortocoronary bypass homograft in a 4-year-old boy. Chest 1980;77:443–446.
6. **Sandiford FM, Vargo TA, Shih J-Y, Pelargonio S, McNamara DG.** Successful triple coronary artery bypass in a child with multiple coronary aneurysms due to Kawasaki's disease. J Thorac Cardiovasc Surg 1980;79:283–287.
7. **Takeuchi Y, Suma K, Shiroma K, Asai T, Kusakawa S.** Surgical experience with coronary arterial sequelae of Kawasaki disease in children. J Cardiovasc Surg 1981;22:231–238.
8. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 8th ed. Boston: Little, Brown, 1979:290.
9. **Takagi S, Oshimi K, Sumiya M, Gonda N, Kano S, Takaku K, Miyata K, Yaginuma T.** Adult onset mucocutaneous lymph node syndrome with coronary aneurysm. Am Heart J 1981;101:852–853.
10. **Lee TJ, Vanghan D.** Mucocutaneous lymph node syndrome in a young adult. Arch Intern Med 1979;139:104–105.
11. **Kitamura S, Fujino M, Kawachi K, Shimazaki Y, Yagihara T, Sakakibara T, Kawashima Y.** Selective coronary arteriography in pediatric patients. Respir Circ 1980;28:1037–1040 (Japanese).
12. **Kitamura S, Kawashima Y, Kawachi K, Fujino M, Kozuka T, Fujita T, Manabe H.** Left ventricular function in patients with coronary arteritis due to acute febrile mucocutaneous lymph node syndrome or related diseases. Am J Cardiol 1977;40:156–164.

# The Changing "Natural History" of Symptomatic Coronary Artery Disease: Basis Versus Bias

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**In contrast to the 20 to 30% reduction in ischemic heart disease mortality that has been demonstrated by national mortality statistics and by several randomized controlled trials, an uncritical reading of recent "natural history" studies suggests far greater improvements in the survival of symptomatic coronary patients. Although the intrinsic accuracy of such natural history studies is not questioned, attempts to compare patients from different studies and different eras may greatly overestimate the true improvement in natural history because of at least 3 biases in the selection of cases from the spectrum of diseased patients. Because of lead-time bias, patients who are diagnosed earlier live longer regardless of whether interventions are efficacious. Because of referral bias, current patients may have symptoms or anatomy that place them at a different stage of severity than patients who were chosen for earlier studies. Because of incidence-prevalence bias, prevalence studies will be over-represented with survivors of previous incidence cohorts who have slower-progressing disease. We suggest that all natural history studies be carefully scrutinized for such biases before they are compared with each other.**

National statistics indicate that the mortality rate from coronary heart disease (CAD) and acute myocardial infarction declined by about 20% in the United States between 1968 and 1978.[1-5] At the same time that these national mortality rates have been declining, several investigators have reported that the prognosis of their own patients with medically[6] or surgically[7] treated CAD is substantially better than what was reported a decade or so ago. Citing data from several randomized controlled trials,[8-12] some authors have attributed their own uncontrolled observations to improvements in the management of symptomatic patients. However, recent reports of annual mortality rates as low as 1.4%/year[6,7] represent a 76% reduction in annual mortality compared to data from the mid-1960s. This percent reduction is far greater than the change in national mortality statistics or the reductions in mortality that have been reported in any randomized controlled trials of comparable patients. We do not dispute the intrinsic accuracies of any of the uncontrolled studies from the past decade, nor do we dispute the contention that most of the reported patients have done well. We are concerned, however, when "doing well" is equated with "doing better" than patients from different eras or patients from different centers in the same era, because such comparisons are extremely hazardous.

The following discussion demonstrates that attempts to match patients based on 1 or 2 variables such as the number of stenotic vessels or the results of exercise tolerance tests are inadequate for a disease with as broad a spectrum of severity as atherosclerotic CAD. Although epidemiologists have often disagreed about nomenclature, ample methodologic evidence indicates that several distinct types of bias can account for much of the apparent improvement in the prognosis of symptomatic patients with medically treated CAD.[13-18]

## Types of Bias in Patient Selection

To understand the principles of selection bias, it is important first to recognize that many diseases include a wide spectrum of patients[18] who are different in terms

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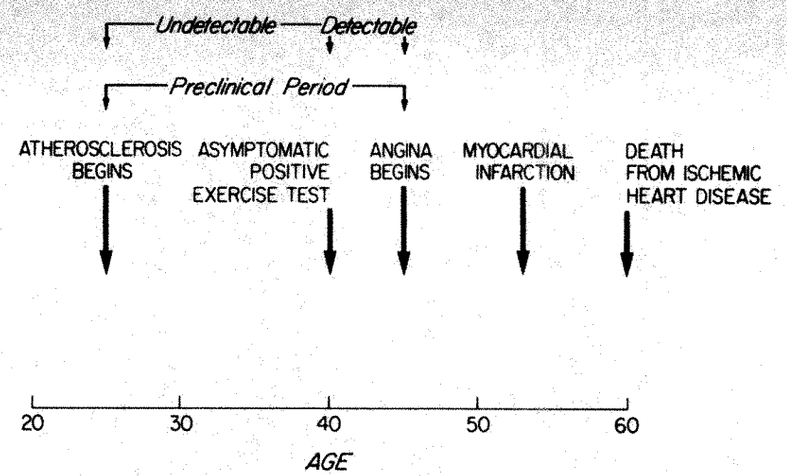



**FIGURE 1.** Natural history of a prototypical patient with CAD. Atherosclerosis begins as an asymptomatic and undetectable pathologic process, proceeds through a detectable preclinical period, and then has a symptomatic period with a duration and expression that vary from patient to patient. If diagnosis is made during the detectable preclinical period, life expectancy is longer than if the disease is diagnosed later, even if there is no difference in the efficacy of the management of the 2 patients (lead-time bias). The reported natural history of a group of symptomatic patients would also depend on their original distribution within the symptomatic phase (referral bias). Even if all patients are at the same phase of the disease when they are originally entered into a study, some will have rapidly progressive and some will have slowly progressive disease. Because the patients with rapidly progressive disease spend less time at any given stage, selecting patients at a particular stage will tend to over-represent the slowly progressive patients and thus to make natural history seem better in a prevalence study than it would in an incidence study (incidence-prevalence bias).

of the severity or the rate of progression of their disease and who thus have different prognoses. The natural history of a particular group of patients with the disease will depend upon the spectrum of patients who are selected for observation.

**Lead-time (starting-time) bias:** Patients whose disease is diagnosed earlier, such as patients whose asymptomatic breast carcinomas are discovered by mammography, may live longer from the time of diagnosis simply because the diagnosis was made earlier and not because any subsequent therapy was efficacious.[13–17] Much like many cancers, atherosclerotic CAD has a long natural history, and it includes several phases (Fig. 1). Autopsy studies from the Korean and Vietnam wars have demonstrated that atherosclerotic lesions in the coronary and systemic arterial circulations may be present in the third decade of life.[19,20] However, most of the affected persons will not become symptomatic or have any signs of CAD detectable by available diagnostic tests for many years. In a prototypical patient (Fig. 1), we speculate that the first diagnosable evidence of CAD may not be present until a person is approximately 40 years old, and an exercise tolerance test, or some other diagnostic test such as an exercise thallium or left ventricular function test, would show abnormalities that are suggestive of CAD. It is assumed that at this time coronary angiography would also document atherosclerosis, even though the anatomical lesions might not be so severe as to warrant surgical or perhaps even medical intervention. At some time after the coronary lesions have been present, the patient will develop symptoms of CAD; the first symptom will usually be angina, but a myocardial infarction will sometimes precede angina.[21] In general, as the patient's anatomic disease progesses, the symptoms will progress as well. A patient who begins with angina that is mild and present only with marked exertion will commonly have the angina gradually worsen, and the course may be punctuated by episodes of unstable angina or myocardial infarction. A patient who presents anew with a first myocardial infarction is likely to have recurrences or to have persistent angina after the infarction. Eventually, the majority of patients with symptomatic CAD will die from their disease and not from some other condition.

The exact time frames displayed in Figure 1 may be prototypical, but they are by no means representative of the course of every patient with CAD. However, issues regarding lead-time bias should be relevant regardless of whether the time spans were contracted or widened. The basic principle is that most patients have an undetectable preclinical phase during which the pathologic process of atherosclerosis is not diagnosable by any available technology.[15] This phase is followed by a detectable preclinical phase during which an exercise test or some other diagnostic test could reveal evidence of atherosclerosis before the patient has any symptoms. It should be obvious that if patients are entered into a study during this preclinical phase, their natural history should be longer than the natural history of patients who are entered in the symptomatic phase, regardless of whether any interventions were actually efficacious for preclinical patients. Similarly, if patients are entered during the early clinical phase, such as when angina is minor or an uncomplicated myocardial infarction has not resulted in serious residual arrhythmias or left ventricular dysfunction, their natural history will be better than the natural history of patients who have had complicated myocardial infarctions or who have unstable angina pectoris. Thus, one would not be surprised

to find that patients who were catheterized for severe angina during the era of internal mammary artery implantation had worse prognoses than current patients who have minimal symptoms and positive exercise tests. This difference in prognosis, based purely on the stage of the disease and not on the efficacy of any intervening therapies, has been called lead-time bias[14,15] or starting-time bias.[16,18]

**Referral (transition) bias:** Another form of bias, which has been termed referral[18] or transition[16] bias, concerns the way in which diseased members of the general population become patients in a particular study at a particular hospital. For example, when a new diagnostic test or a new therapeutic maneuver first becomes available, only the sickest patients are usually studied. If the new technology appears beneficial for these patients, its application will commonly be expanded to include patients who are not as sick. Thus, at first, cardiac catheterizations were performed only on very symptomatic patients who might proceed to internal mammary artery implantations.[22–24] The natural history of such patients would tend to be worse than the natural history of the broader range of patients who had angina. Once a particular therapy or diagnostic procedure is believed to be efficacious, the kinds of patients who are referred for it will tend to be less sick than the original type of patients with whom the therapy or procedure was first tried. These patients will have an inherently better prognosis than the original group of patients, and their better outcome may be due to this inherently better prognosis rather than to improvements in management. Referral bias would also explain how physicians who believe in the efficacy of more conservative therapies may have a large preponderance of patients with better prognoses, simply because primary physicians do not send them their most symptomatic cases.

**Prevalence-incidence (length) bias:** A less obvious type of bias results when one tries to compare natural history based on a study of incident cases to natural history based on a study of prevalent cases[15,17] (Table I). In the former situation, the study population consists entirely of new (incident) cases of the disease that were enrolled into the study at the time of diagnosis. Because of the inherent variability of most diseases, the incident cases will include cases with both short and long survival times. Thus, for example, the Framingham study enrolled healthy people who had no evidence of coronary disease on an entry examination and then reported the natural history of patients who had evidence of the new onset of coronary disease on subsequent yearly examinations.[21]

Conversely, a study based on prevalent cases consists of patients with previously diagnosed disease. Because the prevalence of the disease depends on both the incidence rate of the disease and on the distribution of the survival times, a study based on prevalent cases will likely show a greater proportion of cases with longer survival times (that is, slower progressing disease) than would be seen in a study based on incident cases. This principle is based on the fact that cases with longer survival times, by definition, remain in the pool of prevalent cases for a longer period of time than do their counterparts with shorter survival times. Because of this greater proportion of cases with slower progressing disease, the natural history for prevalent cases may appear to be better than that for incident cases.

**TABLE I Relation Between Incidence and Prevalence**

1. Incidence = newly diagnosed patients in a population previously free of disease/person-years of follow-up
2. Prevalence = proportion of population that has the disease at a given time
3. Therefore, assuming a constant incidence rate and no change in the distribution of life expectancies over time, (prevalence/1 − prevalence) = incidence × average life expectancy of a diseased patient
4. If prevalence is low, prevalence is about equal to incidence × average life expectancy of a diseased patient

This prevalence-incidence bias is closely related to the length bias that has been described in studies of the natural history of cancer.[15] In the cancer screening literature, length bias exists because slow-growing lesions, which are associated with a favorable prognosis, have a longer duration in the detectable preclinical period than do rapidly growing lesions, which are associated with a less favorable prognosis. Therefore, any screening during the detectable preclinical period will yield an over-representation of persons with slow-growing lesions. This length bias described in the cancer literature and the bias we described in the previous paragraphs both result from the selection of prevalent cases either in the detectable preclinical period or in the clinical period.

It should be emphasized that prevalence-incidence (length) bias is distinct from lead-time bias. If the natural history of CAD cases was determined by using the first symptoms of angina as the entry point and if the disease could not be detected earlier, then there would be no possibility of entering patients at an earlier stage, and lead-time bias could not exist. However, prevalence-incidence bias could still occur from the comparison of prevalent cases with incident cases.

These 3 biases (lead-time bias, referral bias, and prevalence-incidence bias), each of which can seemingly improve or worsen the natural history of a disease (Table II), constitute what might be called selection or spectrum bias.[18] If the disease in question has a rather long premorten natural history, different physicians may see patients at different stages. If a new efficacious therapy seems to be available, physicians may respond more vigorously to suggestive signs or symptoms and will use tests to make the diagnosis sooner. This may result in substantial lead-time bias and referral bias when a current series of patients undergoing *any* therapy is compared with a series of patients seen in a previous era.

## Natural History of Medically Treated Coronary Artery Disease: 3 Representative Studies

Although it is not possible for us to present all of the literature regarding the natural history of medically treated patients with symptomatic CAD, 3 prototypical studies that have reported relatively long follow-up periods are adequate to demonstrate the relevance of

**TABLE II Summary of Biases in the Selection of Patients From the Spectrum of Persons With a Disease**

| Types of Bias | Effect on Natural History |
|---|---|
| Lead-time bias | Patients who are diagnosed at an earlier stage of the disease live longer; patients who are diagnosed at a later stage die sooner. |
| Referral bias | Only some diseased persons in a population become part of a particular investigator's natural history study, and these selected persons may have a better or worse prognosis than other people with the same disease. |
| Incidence-prevalence bias | Patients who are at any given stage of disease include some who are progressing rapidly and some who are progressing slowly—the latter will be over-represented in a prevalence study and will make natural history seem better than it would be in an incidence study. |

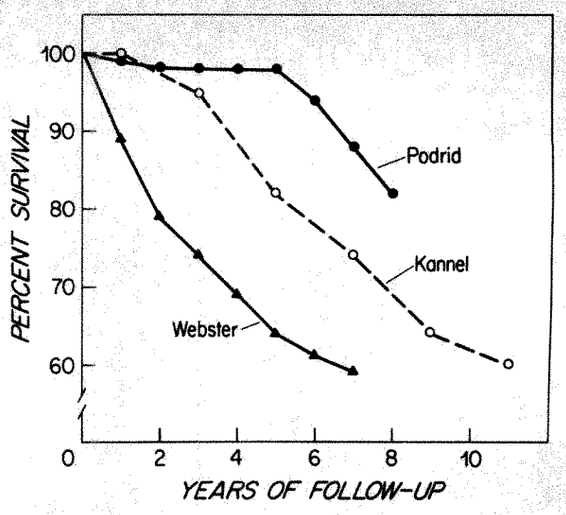



**FIGURE 2.** Survival curves from 3 natural history studies of symptomatic coronary disease. In the Webster study,[21] mortality was very high for the first 3 years, became about 5%/year for years 2 through 5, and then decreased to about 2.5%/year for years 5 through 7. In the true incidence study reported by Kannel,[20] mortality was only about 1.5%/year for the first 3 years but then paralleled the mortality curve of the Webster series. In the more recent study by Podrid et al,[6] mortality was minimal for the first 5 years, but then the mortality curve paralleled the other 2 curves. Although the natural history of symptomatic CAD may in fact be better in 1981 than it was in 1965, much of the difference in these 3 curves can be explained by the biases described in the text.

the biases discussed above. In 1974, Webster et al[22] reported the natural history of 469 patients who had severe proximal lesions in 1, 2, or 3 major coronary vessels at catheterization at the Cleveland Clinic during the years 1960 to 1965.[22] As the investigators indicated, the surgical treatment of CAD was in its infancy during that period, and these patients were treated medically, although they would be considered candidates for coronary bypass surgery in 1981. At 6 year follow-up, the authors reported a total mortality rate of 20% in 1-vessel disease, 40% in 2-vessel disease, and 63% in 3-vessel disease. If all patients were pooled, the overall mortality rate at 6 years was 39%. The survival data from this series (Fig. 2) were similar to the annual mortalities that were reported by 3 other contemporary studies of patients catheterized for symptomatic CAD at other hospitals[23–25] and that were reported by different authors from the same institution in 1978.[26] However, patients from all these series tended to have substantial symptoms, at least partly because surgical therapy for CAD was not well developed in the 1960s. Thus, these studies represented the natural history of a group of patients who were sicker than the average patients with angina of the same era.

In 1971, Kannel and Feinleib[21] reported follow-up data regarding the new cases of angina that were detected by yearly screenings of the Framingham population between about 1949 and 1966.[21] Their men aged >50 years with angina pectoris had about a 4% annual mortality rate after diagnosis (Fig. 2), a mortality rate that was noted to be roughly similar to that associated with survivors of acute myocardial infarction. Although women aged >60 and men aged <50 years had more benign prognoses,[21] the precise data for all such patients were not presented. Thus, the survival curves depicting the natural history of Framingham men aged >50 years provide the best published data regarding the prognosis of an unselected spectrum of incident cases of angina in a defined population.

Most recently, Podrid et al[6] reported on the prognosis of medically treated patients who had ≥2 mm S-T segment depression during exercise testing. Because many patients with such exercise test results will have multivessel disease, their 1.4% annual mortality rate might seem to represent a substantially better natural history than what was reported by Webster[22] or Kannel.[21] Independent of any debates regarding the actual coronary anatomy of Podrid's patients, these patients were substantially less symptomatic than were Webster's patients (Table III). The difference in symptomatic status can be explained by the different criteria by which patients in the 2 studies were referred from the larger population of patients with coronary symptoms. Webster's patients underwent coronary angiography during the early era of the procedure because they were sick enough to be considered for internal mammary

**TABLE III Symptomatic Status of Patients at Entry in 2 Natural History Studies**

| Functional Class* | Webster et al[22] (n = 445†) | Podrid et al[6] (n = 142) |
|---|---|---|
| I | 41 (9%) | 96 (68%) |
| II | 187 (42%) | 46 (32%) |
| III | 139 (31%) | |
| IV | 78 (18%) | 0 |

* In Webster's study,[22] the symptomatic class is as reported by the authors using the New York Heart Association criteria (pooled results for patients with 1-, 2-, and 3-vessel disease). For Podrid's study,[6] the symptomatic class data are estimates made by us based on the investigator's reported duration of exercise using a standard Bruce protocol and on the criteria of the American Heart Association.[27]

† Twenty-four additional patients with atypical angina were not classified by the authors.

artery implantation. Podrid's patients, despite their positive exercise tests, were considered to be tolerating their symptoms to the extent that the investigators did not recommend angiography during an era when the procedure was well established and the surgery that might follow was widely agreed to be efficacious for the amelioration of symptoms.

Our contentions regarding the relevance of lead-time bias and referral bias depend in part on the assumption that patients who have symptoms of angina or congestive heart failure do in fact have poorer prognoses. This assumption has been substantiated by the reports of both Webster[22] and Proudfit[26] from the Cleveland Clinic and by data from Burggraf and Parker,[25] from the Veterans' Administration Cooperative study,[28] and from Duke University Medical Center.[29] Furthermore, a number of studies indicate that the poorer prognosis associated with advanced symptoms is independent of the number of diseased coronary vessels.[22,28,30,31]

The selection of sicker-than-average patients by Webster[22] and less symptomatic-than-average by Podrid[6] would be expected to result in detrimental and favorable lead-time biases, respectively, in comparison with the true incidence study reported by Kannel.[21] In fact, a comparison of the survival rate curves from the 3 studies (Fig. 2) suggests exactly that: after a lag time of about 3 and 5 years, respectively, the annual mortality rate in both the Kannel and Podrid studies becomes about 5 to 6%/year. In the Webster study, the annual mortality rate was very high for the first 2 years, but then became 5%/year for years 3 through 5. By years 6 and 7, the survivors in the Webster series had only a 2.5%/year mortality rate, which may be a reflection of incidence-prevalence bias. Figure 2 also demonstrates the potential confusion inherent in quotations of yearly mortality rate statistics: the yearly mortality rate for a group of patients may vary markedly during different segments of the follow-up period.

Because each of these 3 studies had fewer patients in the later years of follow-up than in the earlier years, the standard deviation of their later mortality rate figures is less certain. Nevertheless, the parallel portion of the mortality rate curves in the various studies suggests that the early favorable natural history statistics of some series of patients with CAD may be misleading because lead-time bias and referral bias may have resulted in the selection of a patient population that has a very favorable short-term (up to perhaps 6 years) prognosis, simply on the basis of their inherent characteristics and not on the basis of any therapeutic intervention.

The pertinence of lead-time bias and incidence-prevalence bias can be further demonstrated by the long-term follow-up data regarding coronary patients from Johns Hopkins.[32] Using a anatomic CAD severity score, Humphries et al showed that the 53% 5-year survival rate of patients with severe disease was significantly worse than the 91% 5-year survival rate of patients with moderate disease. However, during follow-up years 6 through 10, the mortality rate in the group with severe CAD was very low, whereas the mortality rate among patients in the group with moderate disease was substantial; by 10 years after arteriography, the survival rates in the 2 groups were virtually identical. These findings suggest that the differences in early survival rates were related to lead-time bias and that lead-time bias can be overcome if the follow-up is long enough. The flat portion of the curve from years 6 through 10 in the patients with severe CAD was also probably a function of survivor effect: independent of the biases that we have discussed, the survivors of a high death rate period may often have a much lower subsequent mortality rate than the entire cohort had during the high death rate period.

These considerations emphasize that series that have reported a favorable prognosis for selected patients followed for only 5 to 6 years may not have a sufficient duration of follow-up for the lead-time bias to disappear. We do not dispute the contention that some therapies may actually act by delaying rather than preventing mortality, but any such contentions must be shown to be free of lead-time bias.

## Suggested Approach to Interpretation of Studies

There is no doubt that national mortality statistics show about a 20% decrease in CAD mortality rates over the past 10 years. Similarly, randomized controlled trials have shown that some medical[8–10] and surgical[11,12] interventions can reduce mortality rates in selected types of patients by about 30%. Although readers should look carefully for lead-time bias, referral bias, and incidence-prevalence bias in all natural history studies, these data suggest that they must look especially carefully at any study whose patients with medically treated CAD seem to have >30% reduction in mortality rates compared with concurrent or historical control series.

It is important to recognize that the biases that we have discussed cannot be negated by demonstrating that patients are matched with regard to 1 or 2 particular factors. Even sophisticated multivariate matching techniques[33] may not be sufficient if the patients in 2 studies have such inherently different prognoses that the relevant variables in 1 study are not pertinent to the other. Also, most published reports do not provide data in a format that allows subsequent investigators to perform such sophisticated matching techniques. If, however, patients can be suitably matched based on the spectrum of disease and on their prognostic factors,[34,35] concurrent nonrandomized control subjects may sometimes provide enough data for interstudy comparisons. Nevertheless, except when they are contraindicated by logistics or by expense, randomized controlled trials remain the least biased method for comparing the efficacy of various management strategies, and series based on incident cases in a nonreferral population remain the best way to determine natural history.

## References

1. Vital Statistics of the United States. Vol II. Mortality, Part A. Hyattsville, MD: National Center for Health Statistics, 1968–1975.
2. Monthly Vital Statistics Report, Advance Report, Final Mortality Statistics. Hyattsville, MD: National Center for Health Statistics, 1976, 1977.
3. Monthly Vital Statistics Report, Provisional Statistics, Annual Summary for the United States. Hyattsville, MD: National Center for Health Statistics, 1978.
4. **Cooper R, Stamler J, Dyer A, Garside D.** The decline in mortality from

coronary heart disease, U.S.A., 1968–1975. J Chronic Dis 1978;31: 709–720.
5. **Goldman L, Cook F, Hashimoto B, Stone P, Muller J, Loscalzo A.** Evidence that hospital care for acute myocardial infarction has not contributed to the decline in coronary mortality between 1973–74 and 1978–79. Circulation 1982;65:936–942.
6. **Podrid PJ, Graboys TB, Lown B.** Prognosis of medically treated patients with coronary-artery disease with profound ST-segment depression during exercise testing. N Engl J Med 1981;305:1111–1116.
7. **Lawrie GM, Morris GC, Howell JF, Tredici TD, Chapman DW.** Improved survival after 6 years in 1,144 patients after coronary bypass surgery. Am J Cardiol 1978;42:709–715.
8. **The Norwegian Multicenter Study Group.** Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801–807.
9. **Multicentre International Study.** Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol: a multicentre international study. Br Med J 1975;3:735–740.
10. **β-Blocker Heart Attack Study Group.** The β-blocker heart attack trial. JAMA 1981;246:2073–2074.
11. **European Coronary Surgery Study Group.** Coronary-artery bypass surgery in stable angina pectoris: survival at two years. Lancet 1979;I:889–893.
12. **Takaro T, Hultgren HN, Lipton MJ, Detre KM,** and participants in the study group. The VA cooperative randomized study of surgery for coronary arterial occlusive disease. II. Subgroup with significant left main lesions. Circulation 1976;54:Suppl III:III-107–III-117.
13. **Hutchison GB, Shapiro S.** Lead time gained by diagnostic screening for breast cancer. J Natl Cancer Inst 1968;41:665–681.
14. **Zelen M.** Theory of early detection of breast cancer in the general population. In: Henson JC, Mattheiem WH, Rozencweig M, eds. Breast Cancer: Trends in Research and Treatment. New York: Raven Press, 1976:287–300.
15. **Cole P, Morrison AS.** Basic issues in population screening for cancer. J Natl Cancer Inst 1980;64:1263–1272.
16. **Feinstein AR.** Clinical Biostatistics. St. Louis: CV Mosby, 1977:71–88.
17. **Sackett DL.** Bias in analytic research. J Chronic Dis 1979;32:51–63.
18. **Ransohoff DF, Feinstein AR.** Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. N Engl J Med 1975;293:211–215.
19. **Enos WF, Holmes, RH, Beyer J.** Coronary disease among United States soldiers killed in action in Korea. JAMA 1953:152:190–193.
20. **McNamara J, Molot MA, Stremple JF, Cutting RT.** Coronary artery disease in combat casualties in Vietnam. JAMA 1971;216:1185–1187.
21. **Kannel WB, Feinleib M.** Natural history of angina pectoris in the Framingham study. Prognosis and survival. Am J Cardiol 1972;29:154–163.
22. **Webster JS, Moberg C, Rincon G.** Natural history of severe proximal coronary artery disease as documented by coronary cineangiography. Am J Cardiol 1974;33:195–200.
23. **Reeves TJ, Oberman A, Jones WB, Sheffield LT.** Natural history of angina pectoris. Am J Cardiol 1974;33:423–430.
24. **Friesinger GC, Page EE, Ross RS.** Prognostic significance of coronary arteriography. Trans Assoc Am Physicians 1970;83:78–92.
25. **Burggraf GW, Parker JO.** Prognosis in coronary artery disease. Circulation 1975;51:146–156.
26. **Proudfit WL, Bruschke AVG, Sones FM.** Natural history of obstructive coronary artery disease: ten-year study of 601 nonsurgical cases. Prog Cardiovasc Dis 1978;21:53–78.
27. The Committee on Exercise, American Heart Association. Exercise testing and training of apparently healthy individuals: a handbook for physicians. Dallas: American Heart Association, 1972:13.
28. **Detre K, Peduzzi P, Murphy M, Hultgren H, Thomson J, Oberman A, Takaro T.** Effect of bypass surgery on survival in patients in low- and high-risk subgroups delineated by the use of simple clinical variables. Circulation 1981;63:1329–1338.
29. **Harris PJ, Harrell FE, Lee KL, Behar VS, Rosati RA.** Survival in medically treated coronary artery disease. Circulation 1979;60:1259–1269.
30. **Epstein SE, Kent KM, Goldstein RE, Borer JS, Rosing DR.** Strategy for evaluation and surgical treatment of the asymptomatic or mildly symptomatic patient with coronary artery disease. Am J Cardiol 1979;43:1015–1025.
31. **Cohn PF, Harris P, Barry WH, Rosati RA, Rosenbaum P, Waternaux C.** Prognostic importance of anginal symptoms in angiographically defined coronary artery disease. Am J Cardiol 1981;47:233–237.
32. **Humphries JO, Kuller L, Ross RS, Friesinger GC, Page EE.** Natural history of ischemic heart disease in relation to arteriographic findings. Circulation 1974;44:489–497.
33. **Miettinen OS.** Stratification by a multivariate confounder score. Am J Epidemiol 1976;104:609–620.
34. **Feinstein AR, Wells CK.** Randomized trials vs historical controls: the scientific plagues of both houses. Trans Assoc Am Physicians 1977;90: 239–244.
35. **Goldman L, Feinstein AR.** Anticoagulants and myocardial infarction: the problems of pooling, drowning, and floating. Ann Intern Med 1979;90: 92–94.

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*Once-daily application of Transderm-Nitro* was shown to provide effective 24-hour baseline therapy in the step-care approach to angina in a survey* of over 1,000 physicians with more than 10,000 patients under treatment.

Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

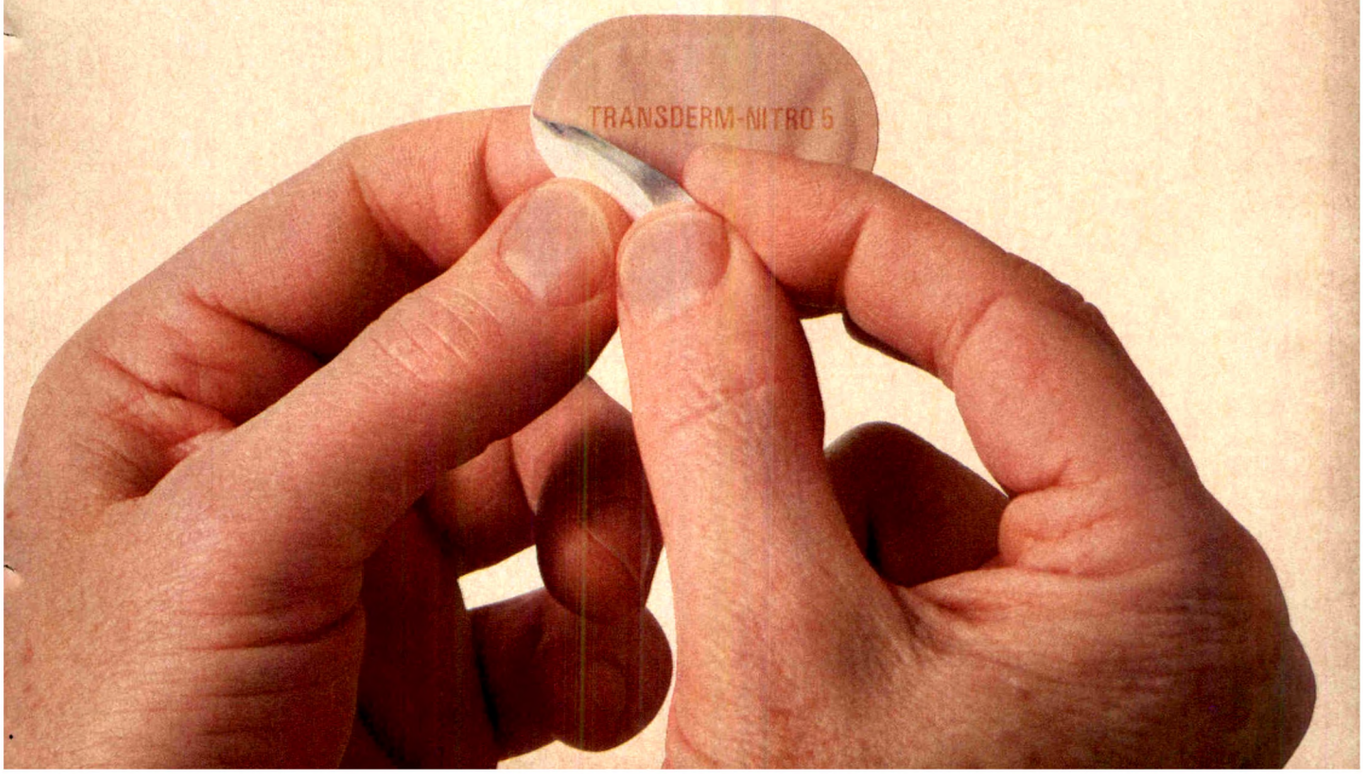
*For full details, please see the Prescribing Information on the next page.*

*Data on file, CIBA Pharmaceutical Company.

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he pioneer in
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# Transderm®-Nitro
## nitroglycerin

one 10-second application
provides 24-hour anginal protection.



# Transderm®-Nitro
nitroglycerin

Simplifies baseline nitrate therapy

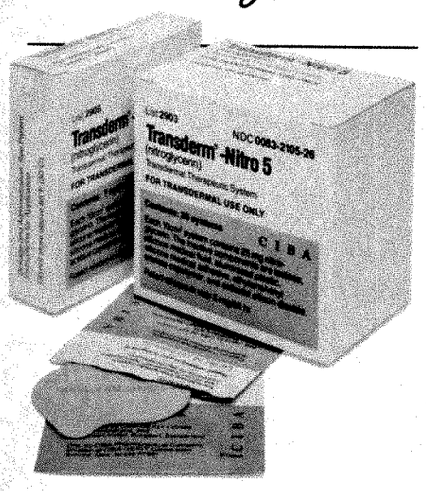
One application provides 24-hour anginal protection

Incorporates the unique, rate-controlling membrane from CIBA, for precise, predictable drug delivery

Simple to use, easy to live with

℞

*Transderm-Nitro 5*
*#30*
*apply one system*
*daily*




629-3688-A

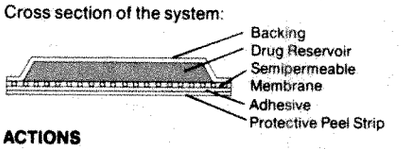
## Transderm®-Nitro (nitroglycerin)
**Transdermal Therapeutic System**

### DESCRIPTION
Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semipermeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 10 and 20 $cm^2$ respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system; 0.5 mg nitroglycerin is delivered *in vivo* for every $cm^2$ of system size.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface towards the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene/vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:




### ACTIONS
When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

### INDICATIONS AND USAGE
Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

### CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

### WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring. In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

### PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

### ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, the dose should be reduced or use of the product discontinued.

### DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

### PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

### HOW SUPPLIED

| Transderm-Nitro System Rated Release *in vivo* | Total Nitroglycerin in System | System Size | Carton Size |
|---|---|---|---|
| 5 mg/24 hr | 25 mg | 10 $cm^2$ | 30 Systems (NDC 0083-2105-26) |
| 5 mg/24 hr | 25 mg | 10 $cm^2$ | 7 Systems (NDC 0083-2105-07) |
| 10 mg/24 hr | 50 mg | 20 $cm^2$ | 30 Systems (NDC 0083-2110-26) |

C82-16 (3/82)

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# CARDIOLOGY 1982

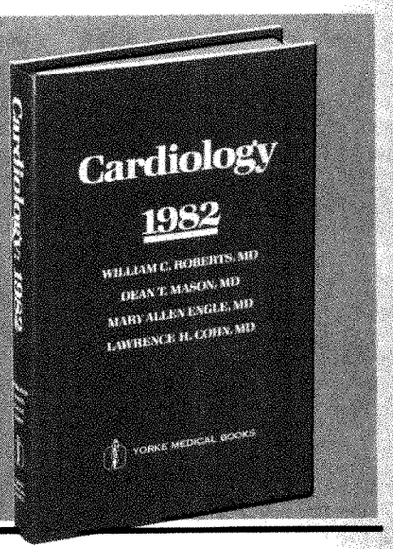
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*written by:*

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- A multidisciplinary approach to clinical and applied research based on an exhaustive search of the year's literature
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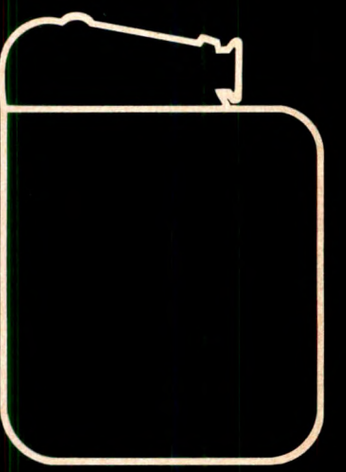
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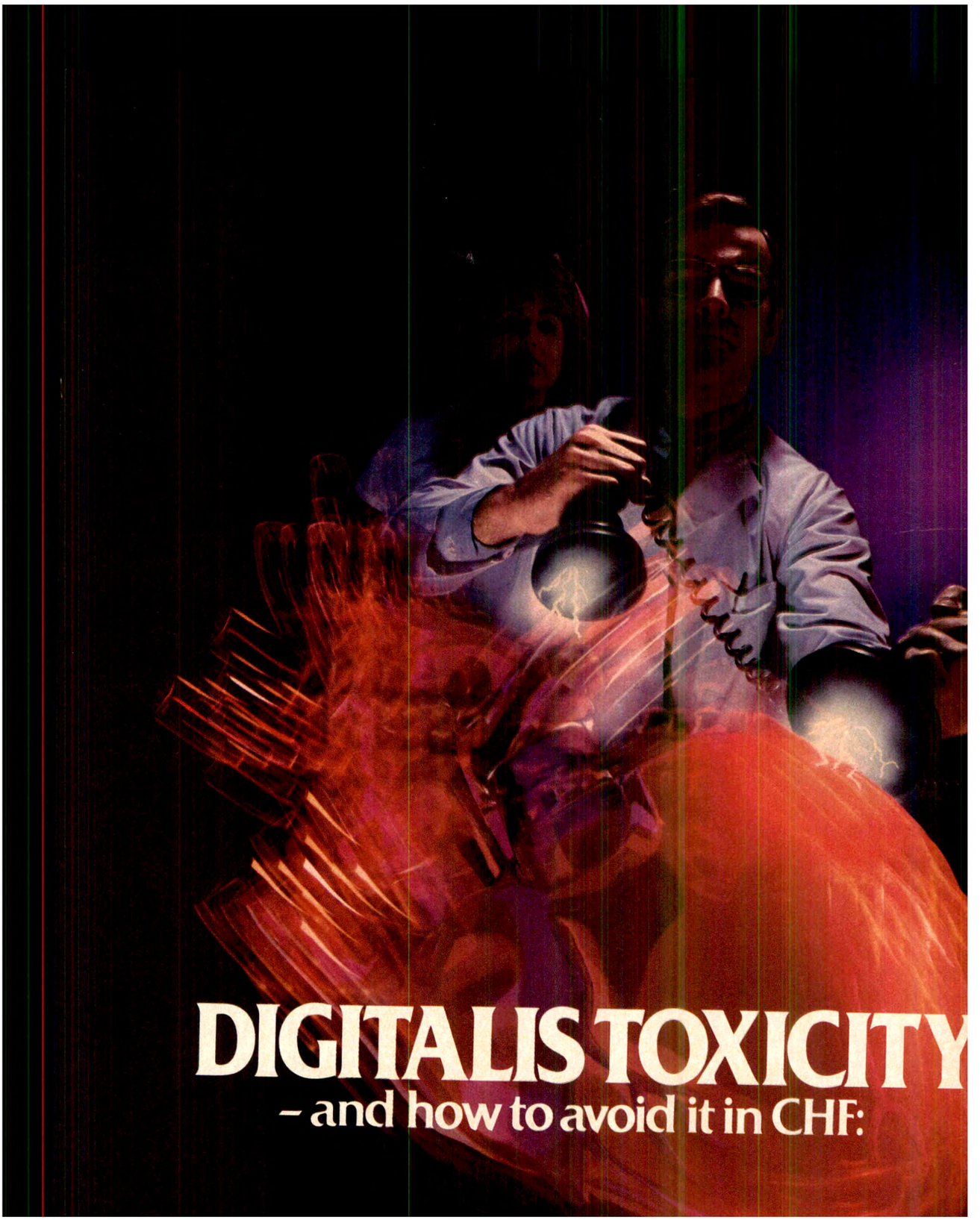


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– and how to avoid it in CHF:

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BRAND OF furosemide

Every CHF patient on a digitalis-diuretic regimen runs the risk of digitalis toxicity.

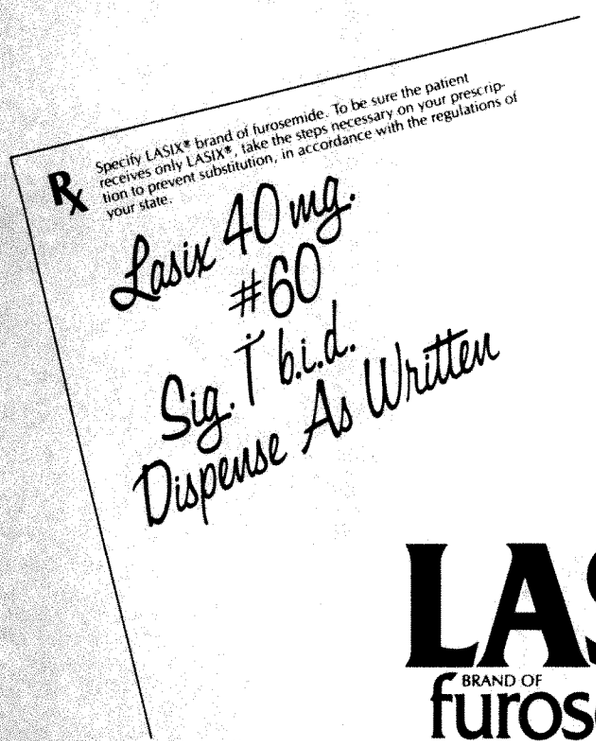
But many patients with impaired renal function are particularly vulnerable because their condition may predispose them to a toxic accumulation of digoxin.

These include the diabetic. The geriatric patient. The patient with renal disease. And the patient with advanced CHF who suffers from hepatic as well as renal complications.

Add to this group the patient on multiple medications with possible drug interactions.

Conditions like these that increase the risk of digitalis toxicity are generally outside the physician's control. But two of the most important *preventive* measures which are not outside the physician's control are precise titration of digitalis, *and the consistent use of one diuretic*.

As to the first, the narrow therapeutic-to-toxic range of digitalis is well known and requires no elaboration.




Naturally, increased renal problems necessitate increased vigilance to any signs of toxicity.

### Why the patient should be maintained on LASIX®

The second precaution is the unvarying use of a single diuretic for a given patient (consistent with proper potassium balance). Thus, if the choice is LASIX®—as it is in most successfully managed CHF cases—the logic behind it is beyond debate. LASIX® is the only diuretic for CHF whose effectiveness has been confirmed in no fewer than 6,000 published papers...which offers the most complete range of dosage forms and strengths for precise titration... and is the most widely available brand of furosemide for filling or refilling your prescription anywhere in the United States. In fact, according to a 1980 nationwide survey,[1] office-based physicians affirmed their confidence in LASIX® by naming it as the medication they prescribe most frequently in office practice.

### Protect your LASIX® prescription: prevent substitution

When you prescribe LASIX®, write the phrase "Do not substitute," or whatever your state requires on the prescription.

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If you are in doubt about a particular generic furosemide, call the offices of the Food and Drug Administration's Bureau of Drugs, Consumer and Professional Relations staff at 301-443-1016.

---

**Reference:** 1. Koch H: Drugs most frequently used in office-based practice: National Ambulatory Medical Care Survey, 1980, Vital and Health Statistics of the Nat Ctr for Health Statistics, No. 78 (May 12) 1982.

**Before prescribing, please consult complete product information, a summary of which appears on the following page.**

# LASIX®

TABLETS: 20, 40 & 80 mg

BRAND OF furosemide

## The diuretic of choice for the digitalized patient.

**Lasix®** (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide) Tablets 20, 40 and 80 mg

**WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.**

**INDICATIONS:** Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

**CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.**

**WARNINGS:** Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, $CO_2$, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

**PRECAUTIONS:** As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

**PREGNANCY:** Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**ADVERSE REACTIONS:** Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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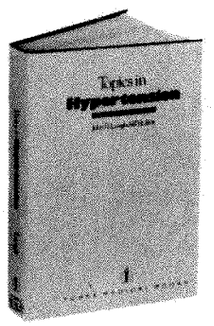
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# Intermittent, Continuous Outpatient Dobutamine Infusion In the Management of Congestive Heart Failure

MARK M. APPLEFELD, MD, KATHRYN A. NEWMAN, RN, MS, WILLIAM R. GROVE, MS, FREDERICK J. SUTTON, MD, DAVID S. ROFFMAN, PHARM D, WILLIAM P. REED, MD, and STEVEN E. LINBERG, PhD

**The use of outpatient dobutamine infusions by a small, portable infusion pump in 3 patients with intractable congestive heart failure (CHF) is described. With this therapy left ventricular function improved and CHF resolved in each. Tolerance to dobutamine was obviated by giving infusions twice weekly. Except for 3 mild infections around the catheter exit site, there have been no complications of this therapy in 58 cumulative patient weeks.**

Therapy of intractable CHF is a frustrating clinical problem. In addition to repeated hospitalizations, patients with CHF have significant early mortality.[1] The past decade has clarified the importance of preload and afterload in the pathophysiology of CHF,[2] and agents to manipulate these variables are now widely used.[3,4] Despite their beneficial effects, significant problems, that is, tolerance or adverse effects, remain with the long-term use of these drugs.[3,4] Newer oral inotropic agents[5,6] are investigational and thus are not viable alternatives in the management of chronic CHF.

Dobutamine is an efficacious inotropic agent in the short-term therapy of CHF. Although tolerance may develop to this drug,[7] its use is primarily limited by the need for intravenous administration. We recently began a clinical trial in which 24-hour infusions of dobutamine are given twice weekly to outpatients with intractable CHF. Dobutamine is given by a portable infusion pump (Cormed, model ML6-6) through a chronic indwelling venous catheter (Hickman) surgically inserted in the external jugular vein and located proximally to the right atrium. The distal end of this catheter exits in the parasternal area (Fig. 1). Patients are taught proper catheter care including techniques for daily irrigation with saline solution and heparin (total 1,500 units) and how to aseptically connect the catheter to the infusion pump (Fig. 2). Dobutamine is prepared in normal saline solution and the admixed drug placed into the pump reservoir (total final volume 55 ml) by a pharmacist. Patients connect the pump to the catheter and begin the infusion. Infusion rates are calibrated to deliver 2 ml/h. After 24 hours patients turn the pump off, disconnect the system, flush the catheter, and return the pump for filling for the second 24-hour infusion. Our initial success with this therapy—as well as issues raised by it—are the subject of our report.

From the Division of Cardiology (Department of Medicine), the University of Maryland Cancer Center, the Departments of Clinical Pharmacy, Surgery, and the Maryland Institute for Emergency Medical Services at the University of Maryland Hospital, Baltimore, Maryland. Manuscript received June 17, 1982; revised manuscript received September 8, 1982, accepted September 17, 1982.

Address for reprints: Mark M. Applefeld, MD, Division of Cardiology, University of Maryland Hospital, 22 South Greene Street, Baltimore, Maryland 21201.

## Case Reports

**Patient 1:** A 47-year-old woman had acute myocardial infarctions in 1973 at age 38 years. In 1980 she was admitted for CHF. Equilibrium-gated blood pool (Medical Data System $A^2$ modification) radionuclide angiocardiography showed a left ventricular ejection fraction (LVEF) of 10% at rest with global dysfunction and 14% on exercise (peak work load 450 kpm). Hydralazine was added and, although efficacious (Table I), was stopped when fever developed. Prazosin (2 mg every 8 hours) was tried but also stopped because of adverse effects.

Nocturnal dyspnea developed and the patient was readmitted in December 1981. Resting LVEF was 13%. Dobutamine therapy (2 μg/kg/min) was begun but the dose was decreased to 1.5 μg/kg/min when angina and premature ventricular contractions developed. On the latter dose, the patient improved hemodynamically, LVEF on radionuclide angiography increased to 27% (Table I), and the angina and premature ventricular contractions abated. After 5 days of dobutamine infusion, symptoms of CHF had resolved and resting LVEF was 27%. A venous access catheter was inserted and the patient was discharged.

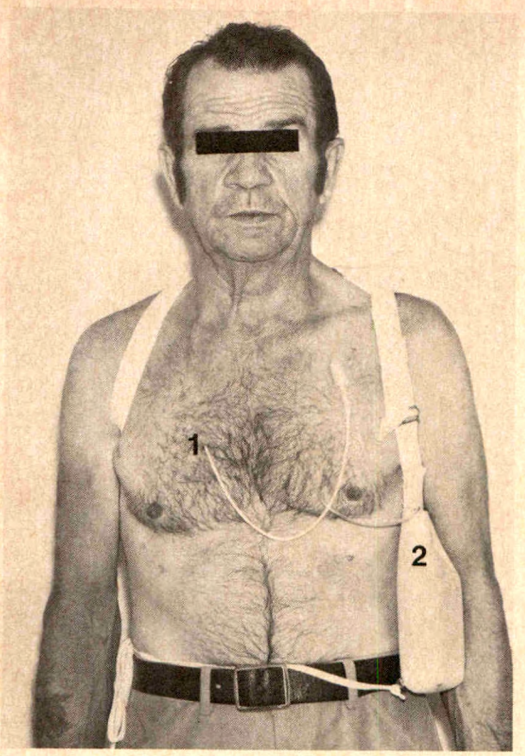



**FIGURE 1.** Patient with Hickman catheter exiting through skin (**1**) and connected to the infusion pump (Cormed) which is worn over the shoulder (**2**) in a soft padded sling.

Continuous dobutamine infusions were given 4 days weekly in addition to her usual daily doses of digoxin (0.25 mg), furosemide (80 mg), and nitroglycerin ointment (3 inches [7.62 cm] every 4 hours). Over the next 14 days she improved from New York Heart Association (NYHA) class 4 to class 2. Three weeks after starting dobutamine therapy the patient had fatigue and an increased jugular venous pressure. LVEF was 13%; dobutamine therapy was stopped. Ten days later she noted mild dyspnea on effort and administration of dobutamine (1.5 $\mu$g/kg/min) was resumed. Five hours later, resting LVEF was 22% and the dyspnea had resolved. To obviate presumed tolerance, we began to treat her with weekly 48-hour continuous dobutamine infusions. During the last 6 months on this therapy, she has not been admitted for CHF and remains in NYHA class 2. Two mild skin infections around the catheter exit site were promptly recognized and treated with oral antibiotic drugs.

**Patient 2:** A 57-year-old man was found to have poorly differentiated lymphocytic lymphoma. He was given chemotherapy (doxorubicin, total dose 550 mg/m$^2$; bleomycin and teniposide) and went into remission. Sixteen months later he noted symptoms of biventricular CHF. Therapy with daily digoxin (0.25 mg) and furosemide (20 mg) resulted in only slight improvement and he was hospitalized. Examination showed blood pressure 90/60 mm Hg, heart rate 80 beats/min and regular, increased venous pressure, a diffuse left ventricular impulse, and an $S_4$ gallop. Resting LVEF by radionuclide angiography was 15%. After drug trials (Table II), dobutamine was started. Resting LVEF was 26% on day 5 of continuous dobutamine (8 $\mu$g/kg/min) infusion and the CHF had resolved. He was discharged to receive continuous dobutamine 4 days each week. After 1 month of therapy tachypnea was noted. Resting LVEF on radionuclide angi-

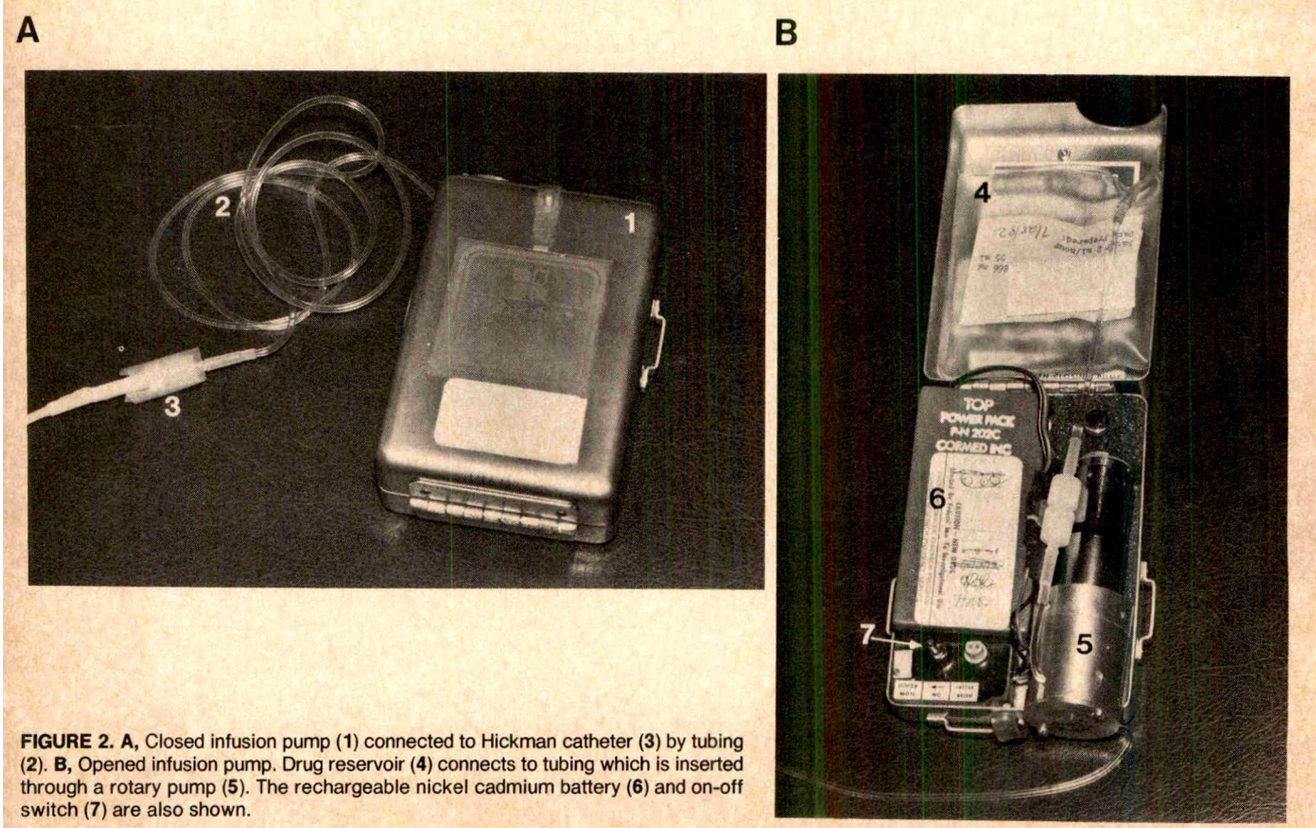



**FIGURE 2. A,** Closed infusion pump (**1**) connected to Hickman catheter (**3**) by tubing (**2**). **B,** Opened infusion pump. Drug reservoir (**4**) connects to tubing which is inserted through a rotary pump (**5**). The rechargeable nickel cadmium battery (**6**) and on-off switch (**7**) are also shown.

**TABLE I Drug Trials in Patient 1**

| | 1980 | | | 1981 | |
|---|---|---|---|---|---|
| | | Hydralazine (mg) | | | |
| | Baseline | 50* | 75* | Baseline | Dobutamine (1.5* μg/kg/min) |
| Blood pressure (mm Hg) | 112/70 | 106/72 | 100/70 | 107/76 | 110/74 |
| Heart rate (beats/min) | 80 | 92 | 94 | 70 | 76 |
| Pulmonary artery, systolic/diastolic (mm Hg) | 55/22 | 36/16 | 50/22 | 35/10 | 34/12 |
| Pulmonary capillary wedge mean (mm Hg) | 20 | . . . | . . . | 8 | 9 |
| Cardiac index (liters/min/m$^2$) | 2.1 | 2.7 | 2.8 | 2.3 | 3.5 |
| Left ventricular ejection fraction (rest) | 10% | . . . | . . . | 13% | 27% |

The resting radionuclide left ventricular ejection fraction was obtained 24 hours after dobutamine infusion was started.
*Measurements made 60 to 90 minutes after dose.

**TABLE II Drug Trials in Patient 2**

| | | Dobutamine (μg/kg/min) | | | Hydralazine (mg) | | | Nitroglycerin Ointment (in) | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 8 | 15 | Baseline | 25† | 75† | Baseline | 1† | 2† |
| Blood pressure (mm Hg) | 96/58 | 114/74* | 108/66 | 92/62 | 92/60 | 100/66 | 92/70 | 100/68 | 100/70 |
| Heart rate (beats/min) | 96 | 108* | 116 | 92 | 96 | 86 | 82 | 104 | 91 |
| Pulmonary artery systolic/diastolic (mm Hg) | 27/13 | 30/15 | 31/14 | 38/13 | 36/13 | 27/10 | 30/8 | 42/17 | 41/3 |
| Pulmonary capillary wedge, mean (mm Hg) | 13 | . . . | . . . | . . . | . . . | . . . | . . . | . . . | . . . |
| Cardiac index (liters/min/m$^2$) | 2.7 | 3.5 | 4.0 | 2.4 | 2.4 | 2.7 | 2.5 | 3.1 | 2.4 |
| Left ventricular ejection fraction (rest) | 15% | 21% | . . . | . . . | . . . | . . . | . . . | . . . | . . . |

Hemodynamic measurements were made 60 minutes after dobutamine was started. The radionuclide left ventricular ejection fraction was obtained 24 hours after dobutamine therapy (8 μg/kg/min) was begun. On day 5 of continuous dobutamine infusion (8 μg/kg/min), this value was 26%.
* Heart rate decreased to 72 beats/min and blood pressure remained unchanged after 24 hours on this dose.
† Measurements made 2 hours after dose.

ography was 15% and dobutamine therapy was stopped. Seven days later he underwent exercise radionuclide angiography (Table III). After this test, 48-hour continuous dobutamine infusions were given weekly. Over the last 22 weeks he has remained in NYHA class 2 and has had no complications from this therapy.

**Patient 3:** A 50-year-old woman had mitral valve replacement and tricuspid anuloplasty. Over the next 18 months she had recurrent biventricular CHF. She was treated with daily digoxin (0.125 mg), hydralazine (50 mg every 6 hours), furosemide (320 mg), and captopril (25 mg every 8 hours). The CHF was refractory to therapy and she was hospitalized. Administration of dobutamine (3 μg/kg/min) and hydrochlorothiazide (50 mg before the morning furosemide dose) was begun. On this therapy she had a diuresis of 45 lb over 3 weeks. There were no significant changes in ventricular function on radionuclide angiography before or during dobutamine therapy. She was discharged to receive continuous 48-hour dobutamine (3 μg/kg/min) infusions weekly as well as daily digoxin (0.125 mg), fuorsemide (240 mg), hydrochlorothiazide (50 mg), hydralazine (50 mg every 6 hours), spironolactone (150 mg), and warfarin. On this regimen her quality of life improved. A mild infection at the catheter exit site was successfully treated with oral antibiotic drugs.

## Discussion

Several aspects of outpatient continuous dobutamine infusions in our patients merit comment. The first is the development of tolerance during the prolonged drug infusions.[7] This occurred in 2 patients during 96- to 120-hour dobutamine infusions, was manifested by dyspnea or tachypnea, and was confirmed by a reduction in LVEF to predobutamine levels. Five to 7 days after dobutamine was stopped, infusions were resumed,

**TABLE III Oxygen Consumption Before, During, and After Treadmill Exercise Test (12 Minutes, Modified Bruce Protocol) in Patient 2**

| | Resting (ml/min) | Peak Exercise (ml/min) | Total Exercise (ml) | Oxygen Debt (ml) |
|---|---|---|---|---|
| Control (no dobutamine) | 216 | 699 | 2,804 | 1,792 |
| Dobutamine (5 hours, 1.5 μg/kg/min) | 250* | 887* | 4,808* | 1,712 |

* Significantly different from control, $p < 0.05$ (paired $t$ test).

LVEF increased, and symptoms were promptly ameliorated. Based on these experiences and previous reports,[7,8] we now give weekly 48-hour continuous dobutamine infusions. During 15 cumulative patient months there have been no hospitalizations for CHF with this therapy. Further, drug tolerance seems to have been circumvented and the quality of life in these patients has improved.

The mechanisms responsible for the sustained clinical improvement in our patients on the days when they do not receive dobutamine are uncertain. However, there is precedence for these observations. Thus, Unverferth et al[9] noted improvement in myocardial function as determined by systolic time intervals and echocardiographic variables in 20 of 30 and 18 of 30 patients, respectively, studied 1 week after 72-hour dobutamine infusions. In that study, improvement was sustained as long as 10 months and has recently been ascribed to a conditioning effect of the drug.[10] Similar effects have been noted in dogs.[11]

It is possible that increased accessibility to medical care or more aggressive treatment of CHF, or both, rather than the chronic use of dobutamine was responsible for the clinical improvement in our patients. It seems unlikely, however, that the former mechanism played a role. Both patients (Cases 1 and 3) hospitalized repeatedly for intractable CHF are well-known to us, are assiduous in following their diets and taking their medications, and have received care by skilled physicians for several years. Also, noninvasive data in 2 patients (Cases 1 and 2) showed improvement in left ventricular function during dobutamine infusion. The role of more vigorous "conventional" therapy is less easy to dismiss. However, in patients (Cases 1 and 2) conventional therapy for CHF was not dramatically changed after dobutamine infusion was started. In Patient 3, such therapy undoubtedly contributed to—but, in our view, does not entirely explain—the clinical improvement observed after dobutamine was begun.

Patient acceptance of the catheter and infusion pump has been excellent. After a training period each patient has willingly assumed responsibility for the care of these appliances. The complication rates for the catheter system are acceptably low. In the initial 106 catheter insertions in our cancer center there have been only 3 instances each of bacteremia and thrombosis in 99 granulocytopenic, immunosuppressed patients. In our patients there have been 3 superficial infections with the use of this catheter. Each was promptly recognized, unassociated with bacteremia, and treated without need for hospitalization. While any infection in patients who may have valvular disease or a prosthetic valve is cause for concern, such risks seem acceptable in the absence of suitable alternatives to treat intractable CHF.

It is obvious that such "unconventional" therapy is not appropriate for every patient who has chronic CHF. However, given a willing patient in whom preload and afterload reducing agents have been unsuccessful, continuous dobutamine infusion should be seriously considered. The availability of a compact, reliable infusion pump[12] now allows such outpatient therapy to be given. Tolerance can apparently be circumvented by administering dobutamine 2 days each week. It is hoped that newer oral inotropic agents will become available to replace the need for this form of therapy. Until such time, however, the continuous intravenous infusion of dobutamine shows promise as an effective form of therapy to improve the quality of life in selected patients with intractable congestive heart failure.

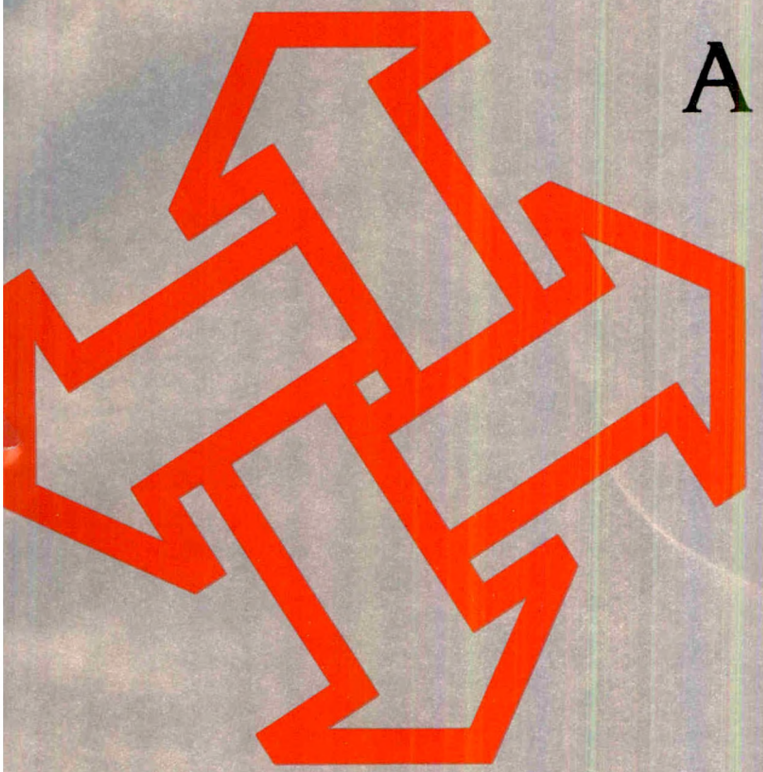
**Acknowledgment:** The authors acknowledge the secretarial assistance of Bonnie J. Dooley. Michael Stewart, MD, and Jeffrey Cole, MD, referred 2 patients for this study. We also thank Cormed (Medina, New York) for partial support of this project.

## References

1. **McKee PA, Castelli WP, McNamara PM, Kannel WB.** The natural history of congestive heart failure: The Framingham Study. N Engl J Med 1971; 285:1441–1446.
2. **Cohn JW, Franciosa JA.** Vasodilator therapy of congestive heart failure. N Engl J Med 1977;297:27–31,254.
3. **Chatterjee K, Massie B, Rubin S, Gelberg H, Brundage BH, Ports TA.** Long-term outpatient vasodilator therapy of congestive heart failure: consideration of agents at rest and during exercise. Am J Med 1978;65: 134–145.
4. **Walsh WF, Greenberg BH.** Results of long-term vasodilator therapy in patients with refractory congestive heart failure. Circulation 1981;64: 499–505.
5. **Le Jemtel TH, Keung E, Sonnenblick EH, Ribner HS, Matsumoto M, Davis R, Schwartz W, Alousi AA, Davolos D.** Amrinone: a new nonglycoside, non-adrenergic cardiotoxic agent effective in the treatment of intractable myocardial failure in man. Circulation 1979;59:1098–1104.
6. **Rude RE, Grossman W, Colucci WS, Benotti JR, Carabello BA, Wynne J, Malacoff R, Braunwald E.** Problems in assessment of new pharmacologic agents for the heart failure patient. Am Heart J 1981;102:584–590.
7. **Unverferth DV, Blanford M, Kates RE, Leier RE, Leier CV.** Tolerance to dobutamine after a 72 hour continuous infusion. Am J Med 1980;69: 262–266.
8. **Colucci WS, Alexander RW, Williams GH, Rude RE, Holman BL, Konstam MA, Wynne J, Mudge GH, Braunwald E.** Decreased lymphocyte beta adrenergic receptor density in patients with heart failure and tolerance to the beta agonist Pirbuterol. N Engl J Med 1981;305:185–190.
9. **Unverferth DV, Magorien RD, Lewis RP, Leier CV.** Long-term benefit of dobutamine in patients with congestive cardiomyopathy. Am Heart J 1980;100:622–630.
10. **Leier CV, Huss P, Lewis RP, Unverferth DV.** Drug-induced conditioning in congestive heart failure. Circulation 1982;65:1382–1387.
11. **Llang CS, Tuttle RR, Hood WB Jr, Garvas H.** Conditioning effects of chronic infusions of dobutamine. J Clin Invest 1979;64:613–619.
12. **Shah AM, MacDonald WC, Goldie JH, Gudauskas GA, Sullivan B.** Ambulatory chemotherapy using a portable Cormed infusion pump ML6-4. St. Louis, MO: American Society of Clinical Oncology Abstracts, 1981:C-796.

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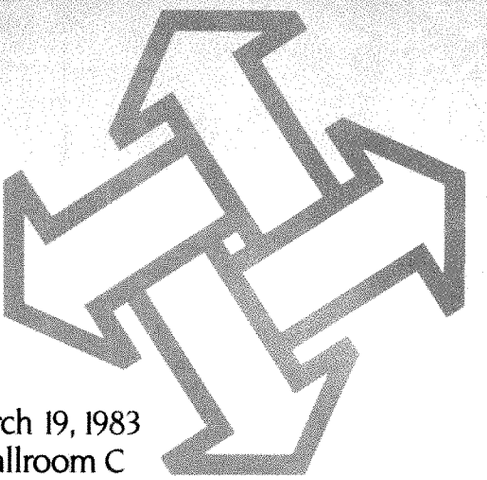
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Ischemic Heart Division
Department of Internal Medicine
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**Calcium in the Pathogenesis and Therapy of Human Hypertension**
David A. McCarron, M.D., F.A.C.P.
Associate Professor of Medicine
Division of Nephrology and Hypertension
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**Calcium Channel Blockers in Congestive Heart Failure**
Wilson S. Colucci, M.D.
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Cardiovascular Division
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**The Hemodynamic and Metabolic Effects of Nifedipine in Normothermic and Hypothermic Cardioplegic Solutions in Animal and Man**
Richard E. Clark, M.D.
Professor of Surgery
Division of Cardiothoracic Surgery
Washington University School of Medicine

**Calcium Channel Blockers in the Therapy of Hypoxic Pulmonary Hypertension: Rationale For Their Use**
Thomas P. Kennedy, M.D.
Assistant Professor of Environmental Health Sciences
Occupational and Pulmonary Medicine Division
The Johns Hopkins School of Hygiene and Public Health

**Calcium Channel Blocking Agents in the Prophylaxis of Asthma**
David G. Tinkelman, M.D., F.A.A.P.
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Medical College of Georgia

**Treatment of Raynaud's Phenomenon With Calcium Channel Blockers**
Craig R. Smith, M.D.
Associate Professor of Medicine
Director of the Division of Internal Medicine
The Johns Hopkins Hospital

**Calcium Channel Blockers: Use in Hypertrophic Cardiomyopathy**
Beverly H. Lorell, M.D., F.A.A.C.
Associate Director
Cardiac Catheterization Laboratory
Brigham and Women's Hospital

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# R-Wave Amplitude Change During Aerobic Exercise In Hypertensive Adolescents After Treatment

BONITA FALKNER, MD, DAVID T. LOWENTHAL, MD, MELTON B. AFFRIME, PharmD, and BARBARA HAMSTRA, RN

**This study attempts to determine whether the blunted reduction in R-wave amplitude during progressive aerobic exercise observed in adolescents with systemic hypertension could be altered by pharmacologic therapy to reduce blood pressure. Twenty-nine hypertensive adolescents were randomly assigned to treatment with either a diuretic, hydrochlorothiazide, or a centrally acting agent, clonidine. After 16 weeks of therapy, casual blood pressure was significantly reduced in both groups. Repeat exercise stress testing on therapy demonstrated a significant change in R-wave response. In both treatment groups the change in R-wave amplitude during exercise corresponded with the R-wave response pattern observed in normotensive control subjects. These observations indicate that the altered R-wave amplitude response to exercise observed in young hypertensive subjects is reversible and suggest that the altered R-wave response before treatment is related to a higher vascular resistance.**

Reports have demonstrated that essential hypertension in adolescence is a recognizable entity.[1,2] Although adolescent hypertension is mild, little is known regarding the hemodynamic components of this phase of hypertension. Studies of borderline hypertension in young adults have demonstrated an increased cardiac index and increased left ventricular ejection rates consistent with high cardiac output. However, some young adults with mild hypertension have increased vascular resistance or a combination of increased resistance and high cardiac output.[3,4] More recent investigations on adolescents with mild hypertension using noninvasive methods report myocardial hypertrophy and altered myocardial function. These observations suggest in some cases the presence of an increase in peripheral vascular resistance.[5,6] In a previous report we investigated the change in R-wave amplitude during aerobic exercise in adolescents. Normotensive adolescents demonstrated a decrease in R-wave amplitude with progressive exercise. Hypertensive adolescents did not demonstrate a similar decrease in R-wave amplitude with progressive exercise despite higher systolic blood pressure and heart rate at each exercise level.[7] This variation in myocardial function in hypertensive adolescents, as evidenced by a difference in R-wave response to exercise, may reflect a level of peripheral vascular resistance greater than that of normotensive subjects. Other possible explanations for the difference in R-wave response in hypertensive subjects were intrinsic myocardial dysfunction or excessive sympathetic stimulation. The objective of this study was to determine whether the R-wave response to exercise in hypertensive adolescents could be altered by pharmacologic intervention directed at lowering the blood pressure.

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## Methods

Twenty-nine hypertensive participants aged 13 to 19 years, who completed the program, constitute the study group. All had blood pressure measurements consistently above the 95th percentile[8] for >3 months before therapy. Basic evaluation excluded secondary causes of hypertension. Additionally, all participants were unresponsive to nonpharmacologic measures for blood pressure reduction. Normotensive control adolescents were healthy adolescent male subjects, all of whom had casual seated blood pressure below the 90th percentile for age. Written informed consent on an institutionally approved protocol was obtained from all participants before exercise testing and therapy were initiated. The first phase of treatment for the hypertensive participants was placebo therapy for 4 weeks. During the placebo phase, dynamic exercise testing was performed; after the placebo period, each subject was randomized into 1 of 2 treatment groups. Group I received

**TABLE I Baseline Values of Hypertensive and Normotensive Subjects**

| | Normotensive Control Subjects (n = 26) | Group 1 (n = 15) Hypertensive HCTZ Rx | Group 2 (n = 14) Hypertensive Clonidine Rx |
|---|---|---|---|
| Mean age (yr) | 16.4 ± 1.4 | 15.4 ± 1.7 | 15.5 ± 1.8 |
| Mean weight (kg) | 72.0 ± 12.8 | 76.0 ± 19.8 | 77.0 ± 19.8 |
| Mean height (cm) | 173.0 ± 10.0 | 168.1 ± 12.9 | 170.5 ± 13.0 |
| Systolic pressure (mm Hg)* | 125 ± 14.0 | Pre 145 ± 6.7 | 145 ± 13.4 |
| | | Rx 138 ± 11.5 < 0.05 | 133 ± 9.7 < 0.01 |
| Diastolic pressure (mm Hg)* | 76 ± 9.7 | Pre 97 ± 7.3 | 99 ± 6.7 |
| | | Rx 91 ± 6.7 < 0.05 | 87 ± 6.9 < 0.001 |
| Heart rate (beats/min)* | 68 ± 9.1 | Pre 85 ± 10.4 | 83 ± 10.4 |
| | | Rx 77 ± 7.0 | 71 ± 7.2 |

* Measurements reflect the average of these determinations for each subject in a seated position.
HCTZ = hydrochlorothiazide; Rx = treatment.

a diuretic, hydrochlorothiazide, at an initial dosage of 25 mg twice daily. Group II received a centrally acting antihypertensive agent, clonidine, with an initial dosage of 0.1 mg twice daily. After 12 weeks of this low dose therapy those patients who had not achieved blood pressure treatment goals of less than the 90th percentile were changed to a larger dose consisting of hydrochlorothiazide 50 mg twice daily or clonidine 0.2 mg twice daily. Those who had achieved blood pressure treatment goals at the low dose continued therapy at the same dosage. Dynamic exercise testing was repeated at 16 to 18 weeks of therapy. Total period of therapy for all participants was 24 weeks.

The method for exercise stress testing is similar to that previously described.[9] After a period of rest and instruction each participant underwent a progressive maximal treadmill test according to the Bruce protocol. A target heart rate of 200 beats/min was used as the predicted end point of exercise. Blood pressure was obtained by standard auscultation using a mercury column sphygmomanometer with an appropriate size cuff. Thus, blood pressure was determined at baseline in the standing position before exercise, at the second minute of each stage of exercise, and through the recovery period of 10 minutes. Heart rate was obtained at baseline and at 1 minute intervals throughout the study by a Quinton oscilloscope electrocardiographic monitor. The electrocardiogram was monitored continuously and a $V_5$ tracing was obtained at 1 minute intervals. In the recovery period measurements of blood pressure and heart rate were obtained with the subject in a seated position. As previously described,[7] the R-wave amplitude was measured from the isoelectric line to the peak of the R wave in millimeters and averaged from 10 consecutive beats. The average amplitude at the second minute of each exercise state was then used as the R-wave amplitude for that stage of the Bruce protocol. The difference in R-wave amplitude from the resting R-wave amplitude in the standing position was computed as the change in R-wave amplitude for each level of progressive exercise.

Pre- and post-treatment data were analyzed for significance by the paired $t$ test. Change in R-wave amplitude during exercise was evaluated by regression analysis. Normotensive and hypertensive exercise response data were compared by a 2-tailed $t$ test.

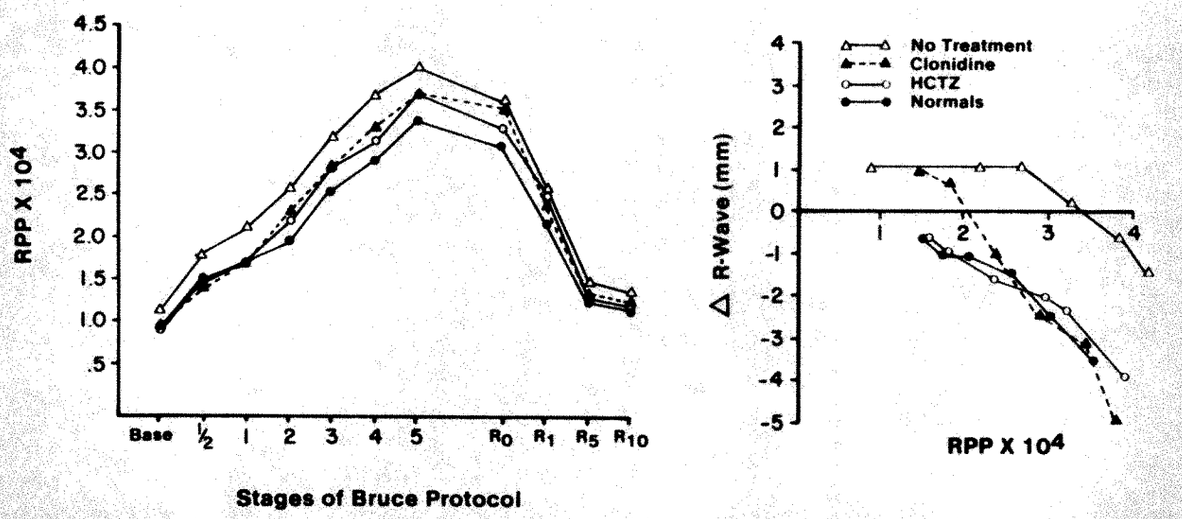



**FIGURE 1. Left panel,** the product of the systolic blood pressure × heart rate (RPP × $10^4$) at each stage of exercise and during the recovery period (R) in minutes. RPP was significantly reduced with clonidine and hydrochlorothiazide (HCTZ) treatment through stage 2 ($p < 0.01$). **Right panel,** the change in R-wave amplitude versus product of the systolic blood pressure × heart rate (RPP × $10^4$). The correlation coefficients are as follows: normotensive subjects RPP = −0.39 (ΔR) + 1.81; $r^2 = 0.88$. Hydrochlorothiazide RPP = −0.37 (ΔR) + 2.04; $r^2 = 0.98$. Clonidine RPP = −0.69 (ΔR) + 1.38; $r^2 = 0.91$.

**TABLE II R-Wave Amplitude During Exercise***

| Group I: Hydrochlorothiazide | | | | | Group II: Clonidine | | | |
|---|---|---|---|---|---|---|---|---|
| Pre Rx | | Post Rx | | | Pre Rx | | Post Rx | |
| Mean | SD | Mean | SD | | Mean | SD | Mean | SD |
| 18.6 | 9.2 | 20.6 | 7.5 | Base | 17.0 | 7.6 | 22.6 | 9.8 |
| 19.4 | 11.4 | 21.4 | 9.4 | 1/2 | 18.2 | 7.6 | 22.1 | 9.2 |
| 19.0 | 11.2 | 21.0 | 8.9 | I | 18.5 | 8.0 | 21.8 | 8.9 |
| 19.0 | 12.2 | 19.7 | 8.8 | II | 18.2 | 7.0 | 21.1 | 9.1 |
| 17.8 | 11.2 | 18.5 | 7.6 | III | 18.2 | 7.8 | 20.6 | 9.7 |
| 17.9 | 10.8 | 17.5 | 9.0 | IV | 16.6 | 7.8 | 20.2 | 7.3 |

* Numbers reflect mean of absolute value for R-wave amplitude in millimeters.

## Results

Thirty adolescents who fulfilled the criteria for sustained hypertension participated in the treatment program. All subjects demonstrated a satisfactory level of compliance in taking medication as checked by pill counts. Fifteen adolescents, 9 male and 6 female, were treated with hydrochlorothiazide (Group I). During the second exercise test all were taking hydrochlorothiazide 50 mg twice daily. Group II, consisting of 15 adolescents, received clonidine. Exercise testing was complete in 14, including 12 males and 2 females. One male adolescent was unable to complete the exercise protocol because of exercise-induced asthma. On repeat testing during therapy, 5 subjects were receiving clonidine 0.1 mg twice daily and 9 were receiving clonidine 0.2 mg twice daily. After 14 weeks of therapy significant blood pressure and heart rate reduction had been achieved.

Table I provides the mean age, weight, and height as well as the casual seated blood pressure and heart rate before and during treatment at the time of repeat exercise study. There is no difference in age, height, and weight in the 2 treatment groups. Also, the age and body size of the hypertensive subjects are similar to those of the normotensive control group.

During graded treadmill exercise there was a progressive increase in systolic pressure and heart rate in all subjects. The left panel of Figure 1 depicts the product of systolic blood pressure and heart rate (SBP × HR) during exercise in normotensive, untreated hypertensive, and hypertensive subjects in the two treatment groups. SBP × HR is greater in untreated hypertensive subjects throughout the exercise. During treatment SBP × HR is significantly reduced ($p < 0.01$) and similar to normotensive control values in the early phase of exercise in both treatment groups. After exercise stage II of the Bruce protocol, SBP × HR of the treated hypertensive subjects is less than pretreatment values, but the reduction is not in a range of statistical significance. The right panel of Figure 1 depicts the correlation of change in R-wave amplitude with SBP × HR in the same groups.

Normotensive control subjects demonstrate a progressive decrease in R-wave amplitude which correlates with increasing product ($r^2 = 0.88$, $p < 0.01$). In hypertensive subjects, only at peak exercise does the R-wave amplitude decrease ($r^2 = 0.33$, is not significant). During therapy the correlation of change in R-wave amplitude with SBP × HR is similar to that in normotensive control subjects in both treatment groups (group I: $r^2 = 0.98$, $p < 0.001$; group II: $r^2 = 0.91$, $p < 0.005$). Correlations of R-wave amplitude change with both systolic pressure and heart rate resulted in a similar pattern.

Table II presents the absolute values of R-wave amplitude during exercise for the 2 treatment groups. Due to variation in R-wave amplitude within groups and variations in electrode placement between exercise tests the change in R-wave amplitude during exercise was used for analysis of the R-wave response to exercise. Figure 2 provides data demonstrating the change in R-wave amplitude at each exercise level. On therapy, hypertensive subjects as a group demonstrate a decrease in R-wave amplitude with graded exercise similar to the response observed in normotensive subjects. The change in R-wave response during treatment in both groups is similar and significantly different by 2-way analysis of variance from the pretreatment R-wave response to exercise ($p < 0.01$).

## Discussion

These results demonstrate a blunted decrease in R-wave amplitude in response to aerobic exercise in untreated hypertensive adolescents. The R-wave response to exercise appears to normalize after approximately 16 weeks of antihypertensive therapy with either hydrochlorothiazide or clonidine. Previous reports indicate that changes in the amplitude of the R wave during exercise may be a more sensitive indication of myocardial dysfunction in adults.[10] Failure of the ischemic ventricle to eject its volume during strenuous aerobic exercise may be responsible for absence of the usual reduction in R-wave amplitude.[11,12] R-wave amplitude change was studied previously in a group of hypertensive adolescents. Compared with age- and weight-matched normotensive subjects, hypertensive subjects did not manifest the decrease in R-wave amplitude with progressive exercise.[7] Because of the young age and the absence of any clinical signs of significant cardiovascular disease in these hypertensive juvenile subjects, mechanisms other than ischemic myocardial dysfunction must be present to account for the difference in R-wave amplitude response to exercise.

This difference in R-wave response was again observed in a group of hypertensive adolescents before

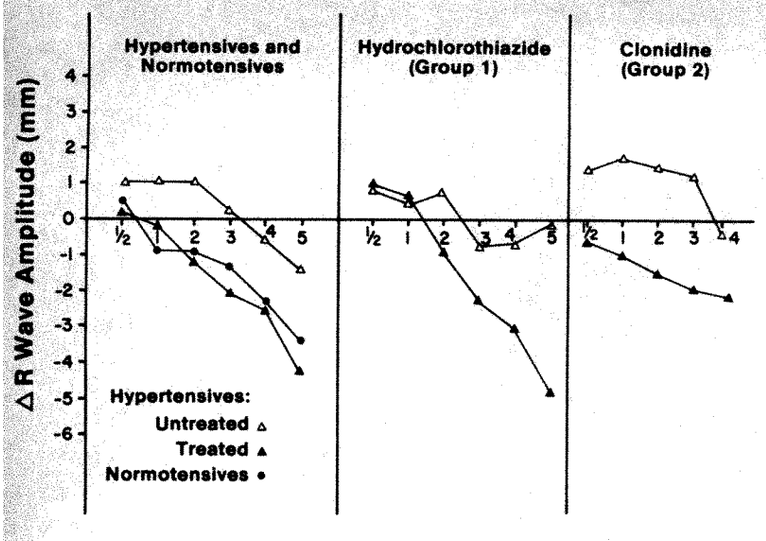



**FIGURE 2.** The mean R-wave amplitude change at each stage of progressive exercise. **Left panel,** normotensive control subjects, all untreated hypertensive subjects as a group, and all hypertensive subjects before and after treatment. **Middle panel,** the R-wave response before and during hydrochlorothiazide therapy. **Right panel,** the R-wave response before and during clonidine therapy.

initiation of pharmacologic therapy to decrease blood pressure. Chronic pharmacologic therapy resulted in significant blood pressure reduction in both treatment groups. Diastolic pressure reduction on clonidine therapy was highly significant. The effect of hydrochlorothiazide on diastolic pressure was less, but at the time of repeat exercise testing the diastolic pressure reduction in the seated position was significant. Therefore, there was a generalized reduction in blood pressure in both treatment groups during the 16 weeks of therapy before the second exercise test. With therapy the systolic pressure and heart rate response during progressive exercise was lower in both treatment groups. Similarly, the product (SBP × HR) was also lower during therapy, but these values were still greater than those of the normotensive control subjects particularly as exercise became more strenuous. Exercise capacity was unchanged after therapy. Each subject was able to exercise to the same level on therapy as they had before treatment.

Hemodynamic studies in hypertensive young adults demonstrated an increased cardiac index and increased left ventricular ejection rate.[13,14] The higher systolic pressure and heart rate in hypertensive adolescents during exercise before therapy relative to those of normotensive subjects matched for age and body size would be consistent with a hyperkinetic cardiovascular state. The hyperkinetic state of borderline hypertension is characterized by an increased cardiac output, increased blood pressure, and normal peripheral vascular resistance.[15] This phase is unlike later hypertension in which cardiac output is normal, blood pressure is increased, and vascular resistance is increased. It has been suggested that vascular resistance is inappropriately normal in early hypertension, when vascular resistance should be lower to offset the increased cardiac output.[16]

Changes in left ventricular mass have been reported in the early phases of hypertension which may be relative to hemodynamic function.[17,18] Echocardiographic studies in some mildly hypertensive adolescents demonstrated decreased left ventricular diastolic volumes,[19] increased posterior wall thickness,[20] increased ventricular septal thickness, and increased cross-sectional muscle area and mass.[5,6] These observations suggest a relative state of left ventricular hypertrophy. Echocardiographic studies in the young have demonstrated alterations in indexes of left ventricular mass. No functional abnormalities of the myocardium have been demonstrated by echocardiography. However, these echocardiographic reports in the young do suggest myocardial involvement in the very early stages of hypertension. The change in R-wave amplitude during progressive aerobic exercise is a measure that can be directly related to myocardial function.

Hypertensive adolescents manifest an R-wave response pattern quite different from that of normotensive control subjects.[7] Furthermore, pharmacologic therapy, which imposed an extended period of blood pressure reduction, resulted in normalization of the R-wave response to exercise despite levels of blood pressure which, although significantly reduced, are still not in the normotensive range.

In this study the normalization of the R-wave response to exercise may be due to a direct drug effect on the myocardium or indirectly to the hemodynamic effects of a lower blood pressure per se. The 2 different pharmacologic treatments had approximately the same effect in altering the R-wave response, although their antihypertensive mechanism differed. The centrally acting agent, clonidine, is a central alpha agonist that diminishes peripheral sympathetic activity. The diuretic hydrochlorothiazide results in salt and volume depletion and alters vascular sensitivity to sympathetic stimuli.[21] The degree of sympathetic nervous system activity involving the myocardium could not provide an explanation for the change in R-wave response. Baseline levels of plasma catecholamines dissociated in the 2 treatment groups after therapy. Resting plasma norepinephrine levels increased in the hydrochlorothiazide-treated group and decreased in the clonidine-treated group.[22] Furthermore, normalization of the

R-wave response was observed in the absence of beta-blocking agents that directly affect the myocardium. Therefore, it is hypothesized that normalization of the R-wave response to exercise observed in both treatment groups is related to the chronic hemodynamic effect of both treatments in lowering peripheral vascular resistance.

These observations need to be supported by further studies in young hypertensive subjects using other pharmacologic and nonpharmacologic measures. However, the findings do suggest the presence of variations of myocardial function in young hypertensive subjects. These variations appear to be reversible, and the results of this study suggest that the blunted R-wave response to exercise before treatment may be related to an increased, or inappropriately normal, vascular resistance.

## References


1. **Kilcoyne MM, Richter RW, Alsup PA.** Adolescent hypertension and prevalence. Circulation 1974;50:758–764.
2. **Kotchen JM, Kotchen TA, Schwertman NC, Kuller LH.** Blood pressure distribution of urban adolescents. J Epidemiol 1974;99:315–324.
3. **Messerli FH, Carvalho JGR, Christie B, Frohlich ED.** Systemic and regional hemodynamics in low, normal and high cardiac output borderline hypertension. Circulation 1978;58:441–448.
4. **Eich RH, Peters RJ, Cuddy RP, Smulyan H, Lyons RH.** The hemodynamics in labile hypertension. Am Heart J 1962;63:188–195.
5. **Zahka KG, Neill CA, Kidd L, Cutilleta MA, Cutilletta AF.** Cardiac involvement in adolescent hypertension. Hypertension 1981;3:664–668.
6. **Schieken RM, Clarke WR, Lauer RM.** Left ventricular hypertrophy in children with blood pressures in the upper percentile of the distribution. Hypertension 1981;3:669–675.
7. **Falkner B, Lowenthal DT, Affrime MB, Hamstra B.** Change in R wave amplitude during aerobic exercise testing in hypertensive adolescents. Am J Cardiol 1982;50:152–156.
8. Report of the Task Force on Blood Pressure Control in Children. Pediatrics 1977;59(Suppl):797–820.
9. **Falkner B, Lowenthal DT.** Dynamic exercise response in hypertensive adolescents. Int J Pediatr Neph 1980;1:161–165.
10. **Bonoris PE, Greenburg PS, Christeson GW, Costellant MJ, Ellestad MH.** Evaluation of R wave amplitude changes versus ST segment depression in stress testing. Circulation 1978;57:904–910.
11. **Brody DA.** A theoretical analysis of intracavity blood loss influence on the heart-lead relationship. Circ Res 1956;4:731–738.
12. **Voukydis PC.** The effect of intracardiac blood on the electrocardiogram. N Engl J Med 1974;291:612–616.
13. **Eich RH, Cuddy RP, Smulyan HI, Lyons RH.** Hemodynamics in labile hypertension: a follow-up study. Circulation 1966;34:299–307.
14. **Frohlich ED, Kozul VJ, Tarazi RC, Dustan HP.** Physiological comparison of labile and essential hypertension. Circ Res 1970;27(Suppl):55–69.
15. **Julius S, Conway J.** Hemodynamic studies in patients with borderline hypertension. Circulation 1968;38:282–288.
16. **Julius S, Pascual A, Sannerstedt R, Mitchell C.** Relationship between cardiac output and peripheral resistance in borderline hypertension. Circulation 1971;43:382–386.
17. **Savage DD, Drayer JIM, Henry WL, Mathews ED, Ware JH, Gardin JM, Cohen ER, Epstein SE, Laragh JH.** Echocardiographic assessment of cardiac anatomy and function in hypertensive subjects. Circulation 1979;59:623–632.
18. **Schlant RC, Felner JM, Heymsfield SB, Gilbert CA, Shulman WB, Tuttle EP, Blumstein BA.** Echocardiographic studies of left ventricular anatomy and function in essential hypertension. Cardiovasc Med 1977;2:477–491.
19. **Goldring D, Hernandez A, Choi S, Lee JY, Londe S.** Blood pressure in a high school population. II. Clinical profile of the juvenile hypertensive. J Pediatr 1979;95:298–304.
20. **Laird WP, Huffines FD, Fixler DE.** Prevalence of left ventricular hypertrophy in hypertensive adolescents. A study correlating x-ray, EKG and echocardiographic findings (abstr). Prev Med 1978;7:101.
21. **Weinburger MH, Ramsdell JW, Rosner DR, Geddes JJL.** Effect of chlorothiazide and sodium on vascular responsiveness to angiotensin II. Am J Physiol 1972;223:1049–1057.
22. **Falkner B, Onesti G, Affrime MB, Lowenthal DT.** The effect of a centrally acting agent versus diuretics on the cardiovascular response to mental stress in adolescent hypertension. Clin Sci 1982;63:455S–458S.

# Increased Plasma Concentrations of Prostacyclin Metabolite 6-Keto-$PGF_{1\alpha}$ in Essential Hypertension

## Influence of Therapy With Labetalol

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**To evaluate the role of the vasoactive prostaglandins prostacyclin and thromboxane $A_2$ in essential hypertension, the stable metabolites 6-keto-$PGF_{1\alpha}$ and thromboxane $B_2$, respectively, were measured in plasma before and after therapy in 7 patients. During the placebo phase, plasma 6-keto-$PGF_{1\alpha}$ levels were significantly greater than normal. Plasma thromboxane $B_2$ levels were not statistically different from those in normal subjects. After intravenous administration of labetalol to the point of blood pressure reduction, neither plasma 6-keto-$PGF_{1\alpha}$ nor thromboxane $B_2$ values changed. With prolonged oral labetalol therapy and concurrent regulation of blood pressure, a significant decrease in plasma 6-keto-$PGF_{1\alpha}$ levels occurred while thromboxane $B_2$ values remained unaltered. Elevation of plasma 6-keto-$PGF_{1\alpha}$ in untreated hypertensive subjects suggests that enhanced vessel wall prostacyclin synthesis may be a protective mechanism to prevent organ damage. As blood pressure is controlled this increase is no longer needed, and prostacyclin generation returns to normal.**

Since the discovery of prostacyclin and thromboxane $A_2$,[1-3] these very labile prostaglandins[3,4] have been implicated in many cardiovascular diseases. The former, synthesized mostly in vessel walls, has potent vasodilatory and platelet aggregation inhibitory properties.[1,5] The latter, synthesized mainly in platelets,[2,6] is a powerful vasoconstrictor[7] and potent platelet aggregant.[2] Recent evidence has demonstrated that prostaglandins may also be involved in the regulation of blood pressure. The drugs interfering with cyclooxygenase activity have been reported to decrease the effectiveness of antihypertensive therapy.[8-11] Some investigators have described a decrease in urinary metabolites of prostacyclin in hypertensive subjects which suggests an imbalance of prostacyclin-thromboxane $A_2$ equilibrium in favor of the latter.[12] Impaired renal production of prostaglandin $E_2$ in essential hypertension has also been reported.[13] Vessels from spontaneously hypertensive rats have been shown to generate unusually large amounts of $PGI_2$.[14,15] Whether a similar phenomenon occurs in human subjects is not known.

This study was designed to evaluate the role of thromboxane $A_2$ and prostacyclin in hypertensive subjects before and after antihypertensive treatment with labetalol, which is an alpha- and beta-adrenoreceptor blocking drug.[16,17]

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### Methods

**Patients and study protocol:** We evaluated 7 hypertensive men, aged 44 to 68 years (mean ± standard error of the mean 54 ± 7). Diastolic blood pressure was 95 mm Hg or higher after the patients had been untreated for at least 2 weeks. All secondary causes of hypertension were excluded. Other exclusion criteria were lung disease, symptomatic coronary heart disease, malignant hypertension, and cerebrovascular or renal impairment. No concomitant antihypertensive, platelet-active, or prostaglandin-active drugs were permitted during the study. All patients gave a written informed consent approved by Institutional Review Committees.

After a 2-week placebo phase, subjects were hospitalized and intravenous labetalol (0.5 to 1.0 mg/kg) was administered to achieve at least 10 mm Hg reduction in diastolic blood pressure. The subjects were then discharged on oral labetalol and readmitted for a second evaluation 6 weeks later. During long-term labetalol treatment, they were followed up on a weekly basis and given increasing doses of labetalol until appropriate blood pressure control (diastolic pressure ≤90 mm Hg) was obtained.

**Blood collection:** Blood samples were collected in the placebo phase, the intravenous labetalol phase, and at the end of oral labetalol phase. Each time, the first 2 ml of blood was

**TABLE I Hemodynamic Effects of Acute Intravenous (IV) and Long-Term Oral Labetalol Therapy in Hypertensive Subjects**

| | Placebo Phase | Acute IV Labetalol | Long-Term Oral Labetalol |
|---|---|---|---|
| Heart rate (beats/min) | 77 ± 3 | 71 ± 4 | 64 ± 4* |
| Systolic blood pressure (mm Hg) | 162 ± 6 | 134 ±6† | 138 ± 6† |
| Diastolic blood pressure (mm Hg) | 98 ± 4 | 80 ± 3† | 82 ± 3‡ |
| Cardiac output (liters/min) | 8.6 ± 1.0 | 8.2 ± 0.9 | 7.2 ± 0.7 |
| Cardiac index (liters/min/$m^2$) | 4.0 ± 0.4 | 3.8 ± 0.3 | 3.3 ± 0.3 |
| Total peripheral resistance (dynes s $cm^{-5}$) | 1,240 ± 184 | 901 ± 184* | 1,227 ± 176 |

* $p < 0.05$ versus placebo phase. † $p < 0.01$ versus placebo phase. ‡ $p < 0.001$ versus placebo phase.

discarded, then 4 ml was gently withdrawn in a polystyrene syringe and immediately transferred into a tube containing aspirin and ethylene diaminetetraacetic acid (EDTA) (1 ml) at 4°C. The tube was centrifuged at 150 *g* for 8 minutes and plasma was transferred for 6-keto-$PGF_{1\alpha}$ and thromboxane $B_2$ determinations.

**Thromboxane $B_2$ and 6-keto-$PGF_{1\alpha}$ determination:** Plasma thromboxane $B_2$ and 6-keto-$PGF_{1\alpha}$ were measured by radioimmunoassay as previously described.[18,19] Lyophilized standards, $^3$H-thromboxane $B_2$ and $^3$H-6-keto-$PGF_{1\alpha}$, and the antibodies raised in rabbits were obtained from New England Nuclear, Boston, Massachusetts. With use of this method, the cross-reactivity of thromboxane $B_2$ antibody with other prostaglandins was as follows: $PGE_2$ 0.2%, $PGA_2$ 0.2%, $PGF_{2\alpha}$ <0.2%, and 6-keto-$PGF_{1\alpha}$ <0.2%. The cross reactivity of 6-keto-$PGF_{1\alpha}$ antibody with other prostaglandins was as follows: $PGF_{2\alpha}$ 2.7%, $PGE_2$ and $TXB_2$ <0.1%, $PGA_2$ 0.1%, and $PGA_1$ <0.3%. The results for both 6-keto-$PGF_{1\alpha}$ and thromboxane $B_2$ were expressed in pg/ml.

**Normal values:** Normal values for plasma 6-keto-$PGF_{1\alpha}$ and thromboxane $B_2$ were determined in venous blood samples withdrawn from 23 healthy subjects (mean age 47 ± 7 years). Blood was withdrawn from the antecubital vein, without tourniquet pressure. The samples were collected and processed in the same manner as described for the patients.

**Statistical analysis:** Results were expressed as mean ± standard error of the mean. Student's *t* test (paired and unpaired data), the Kruskal-Wallis rank sum test, and Wilcoxon signed rank sum tests were used for comparison. Data were examined with regard to relation between changes in prostaglandin values and the blood pressure (systolic, diastolic, and mean) by regression analysis. Data were also analyzed to identify any relation between blood pressure levels and 6-keto-$PGF_{1\alpha}$ concentrations before and after treatment. A p value <0.05 was considered significant.

## Results

**Labetalol and hemodynamic effects:** The hemodynamic effects of labetalol are summarized in Table I. Intravenous labetalol (mean dose 0.6 mg/kg) resulted in a mean plasma level of 105 ± 21 ng/ml of plasma. With this dose, mean blood pressure was lower in each subject, but cardiac output and heart rate were unchanged. The systemic vascular resistance (mean arterial pressure × 80/cardiac output) decreased significantly ($p < 0.025$). With oral labetalol for 6 weeks (1,200 mg/day in 3 subjects and 800 mg/day in 4 subjects), mean plasma levels of 176 ± 59 ng/ml were obtained. Diastolic and systolic blood pressures showed a mean decrease of 16 and 24 mm Hg, respectively. The heart rate decreased significantly. Cardiac output decreased in 6 patients and increased in the remaining patient. Systemic vascular resistance increased in 4 and decreased in 3 patients. Changes in cardiac output and vascular resistance were not significant compared with the placebo phase.

**Thromboxane $B_2$ concentrations (Fig. 1):** Plasma thromboxane $B_2$ concentrations in hypertensive subjects in the placebo phase showed a wide variation

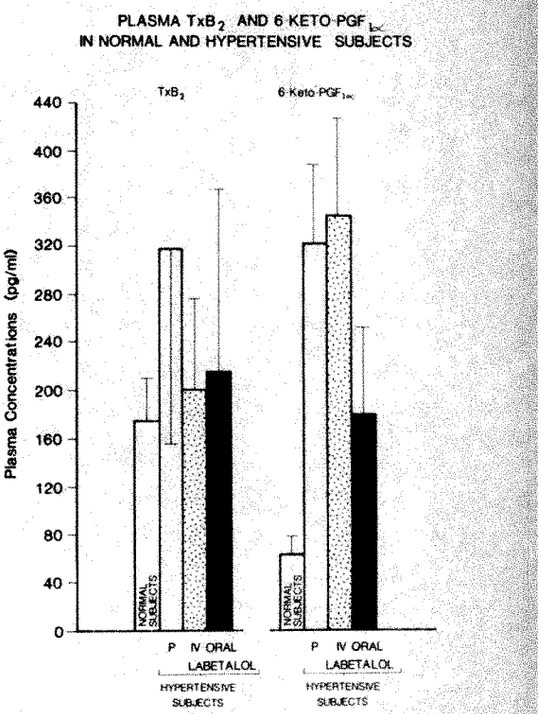



**FIGURE 1.** Plasma $TXB_2$ and 6-keto-$PGF_{1\alpha}$ concentrations in normal and hypertensive subjects. $TXB_2$ levels did not differ in the 2 populations. Plasma 6-keto-$PGF_{1\alpha}$ levels were higher in hypertensive subjects before therapy, and decreased significantly with long-term antihypertensive therapy. Data are expressed as mean ± standard error of the mean. IV = intravenous; P = placebo.

(range 82 to 1,220 pg/ml, mean 318 ± 183 pg/ml). One patient with very high plasma thromboxane $B_2$ concentrations, 1,220 pg/ml, continued to exhibit these high concentrations after short- and long-term labetalol administration (570 and 840 pg/ml, respectively) and on another occasion after discontinuation of labetalol (1,100 pg/ml). The mean plasma thromboxane $B_2$ concentrations in hypertensive subjects in the placebo phase were similar to those in the normal volunteers (175 ± 35 pg/ml). After short-term intravenous and long-term oral labetalol administration, the mean plasma thromboxane $B_2$ concentrations decreased to 200 ± 76 pg/ml and 215 ± 132 g/ml, respectively. None of these values were significantly different from each other or from the normal values.

**Concentrations of 6-keto-$PGF_{1\alpha}$ (Fig. 1):** In the 23 normal subjects, 6-keto-$PGF_{1\alpha}$ concentrations were extremely low: they were undetectable in 7 subjects, and the mean value was 64 ± 14 pg/ml. In contrast, 6 hypertensive subjects in the placebo phase had detectable and markedly elevated plasma 6-keto-$PGF_{1\alpha}$ concentrations (range 190 to 500 pg/ml), and 1 patient had undetectable concentrations throughout the study. The mean value was significantly higher in hypertensive subjects than in the normal volunteers (321 ± 67 versus 64 ± 14 pg/ml, $p < 0.01$). With immediate decrease in blood pressure after intravenous labetalol administration, plasma 6-keto-$PGF_{1\alpha}$ concentrations decreased in only 2 patients compared with the placebo phase, but were still very high (range 0 to 550 pg/ml, mean 344 ± 82 pg/ml; difference not significant compared with the placebo phase). With prolonged oral labetalol therapy and blood pressure reduction, plasma 6-keto-$PGF_{1\alpha}$ concentrations showed a significant decrease from the placebo phase in all 6 patients (range 0 to 500 pg/ml, mean 179 ± 74, $p < 0.05$) or from the short-term intravenous phase (mean 179 ± 74 versus 344 ± 82 pg/ml, $p < 0.05$). These plasma 6-keto-$PGF_{1\alpha}$ concentrations after oral therapy and prolonged blood pressure reduction did not differ significantly from those in the normal subjects.

Analysis of data showed no significant relation between levels of 6-keto-$PGF_{1\alpha}$ and blood pressure before and after treatment. Similarly, there was no correlation between changes in plasma concentrations of 6-keto-$PGF_{1\alpha}$ and reduction in systolic, diastolic, or mean arterial pressure.

## Discussion

**Increase in prostacyclin in hypertension:** This study shows that enhanced prostacyclin but normal thromboxane $A_2$ synthesis is present in patients with essential hypertension. With acute reduction of blood pressure, no significant changes in plasma concentrations occur. However, after prolonged treatment as the blood pressure is controlled for several weeks, prostacyclin metabolite in plasma decreases. Because 6-keto-$PGF_{1\alpha}$ is a major metabolite of prostacyclin, increased levels in the untreated hypertensive subjects could imply either enhanced degradation of prostacyclin with subsequent increased synthesis, or a primary increase in prostacyclin synthesis with concomitant increases in its metabolite concentration in plasma. The latter hypothesis is supported by animal experiments that demonstrate enhanced basal prostacyclin synthesis by vessels from spontaneously hypertensive rats.[14,15] The fact that plasma 6-keto-$PGF_{1\alpha}$ concentrations return to normal after prolonged antihypertensive therapy leads us to believe that enhanced prostacyclin synthesis by vessel walls in hypertensive patients may be a protective mechanism against organ damage. As blood pressure is adequately controlled, this compensatory mechanism is no longer necessary, and the prostacyclin synthesis by vessel walls may gradually return toward the normal state. In agreement with this "protective mechanism" concept is the observation that in stroke-prone, spontaneously hypertensive rats with an increase in vascular prostacyclin synthesis, prostacyclin-synthesizing capability is lost just before the evolution of stroke.[14]

**Mechanism of increased prostacyclin synthesis:** The mechanism of enhanced prostacyclin synthesis is still unclear. It is known that prostacyclin synthesis increases markedly with trauma[20] and increased intravascular stress.[14,15] Stress states such as exercise,[21] smoking,[22] ischemia, and venous stasis[23] also cause an increase in prostacyclin synthesis. Whether labetalol itself affects $PGI_2$ generation is not known. However, we observed no change in plasma 6-keto-$PGF_{1\alpha}$ with intravenous labetalol administration. With prolonged antihypertensive therapy, a marked decrease in blood pressure was accompanied by a decline in 6-keto-$PGF_{1\alpha}$ levels. It is tempting to postulate that a new state of prostacyclin synthesis develops with prolonged antihypertensive therapy. Although plasma concentrations of labetalol with oral therapy were similar to those with short-term intravenous administration, direct effects of labetalol on prostacyclin synthesis and release cannot be excluded. We found no correlation between decline in plasma concentrations of 6-keto-$PGF_{1\alpha}$ and decrease in blood pressure. Further studies are needed in a large number of patients to determine whether the decrease in plasma 6-keto-$PGF_{1\alpha}$ concentration is observed with other antihypertensive drug regimens and if plasma 6-keto-$PGF_{1\alpha}$ concentrations correlate with changes in blood pressure.

**Platelets and thromboxane $A_2$ in hypertension:** In some previous studies, certain platelet function variables have been reported to be abnormal in hypertensive patients.[24,25] These abnormalities may be corrected with control of blood pressure. However, plasma thromboxane $B_2$ concentrations in the normal range in treated or untreated hypertensive subjects as seen in this study do not suggest a primary role for thromboxane $A_2$ in the genesis of essential hypertension. In a recent study, Frishman et al[26] administered labetalol to patients with angina pectoris and hypertension, but failed to observe any significant antiplatelet effects of labetalol. This is in agreement with our observations of unchanged plasma thromboxane $B_2$ concentrations in hypertensive patients.

**Implications:** We therefore conclude that prostacyclin synthesis is increased in hypertensive human subjects; this may be a protective mechanism against

organ damage. Increase in prostacyclin synthesis occurs most probably in response to decreased blood flow and increased intravascular stress. As blood pressure is decreased, prostacyclin synthesis returns to normal levels. However, as in other biologic systems, the adjustment of vascular tone and regulation of prostaglandin synthesis by vessel wall does not occur immediately.

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## References


1. **Gryglewski RJ, Bunting S, Moncada S, Vane JR.** Arterial walls are protected against deposition of platelet thrombi by a substance (PGX) which they make from endoperoxide. Prostaglandins 1976;12:685–713.
2. **Hamberg M, Svenson J, Samuelsson B.** Thromboxanes. A new group of biologically active compounds derived from prostaglandin endoperoxides. Proc Natl Acad Sci 1975;72:2994–2998.
3. **Moncada S, Gryglewski RJ, Bunting S, Vane JR.** An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature 1976;263:663–665.
4. **Pifer DD, Cagen LM, Chesney CM.** Stability of prostaglandin $I_2$ in human blood. Prostaglandins 1971;21:165–175.
5. **Moncada S, Vane JR.** The discovery of prostacyclin: a fresh insight into arachidonic acid metabolism. In: Kharasch N, Fried J, eds. Biochemical aspects of prostaglandins and thromboxanes. New York: Academic Press, 1968:155–177.
6. **Svenson J, Hamberg M, Samuelsson B.** On the formation and effects of thromboxane $A_2$ in platelets. Acta Physiol Scand 1976;98:285–295.
7. **Needleman P, Minkes M, Raz A.** Thromboxanes: selective biosynthesis and distinct biological properties. Science 1976;193:163–165.
8. **Patak RV, Mookerjee BK, Bentzel CJ, Hysert PE, Babej M, Lee JB.** Antagonism of the effects of furosemide by indomethacin in normal and hypertensive man. Prostaglandins 1975;10:649–659.
9. **Durao V, Prata MM, Goncalves LMP.** Modification of anti-hypertensive effect of beta-adrenoreceptor blocking agents by inhibition of endogenous prostaglandin synthesis. Lancet 1977;2:1005–1007.
10. **Slack BL, Warner ME, Keiser HR.** The effect of prostaglandin synthetase inhibition on the action of hydralazine (abstr). Circulation 1978;58:Suppl II:II-21.
11. **Easton PA, Koval A.** Hypertension reaction with sulindac. Can Med Assoc J 1980;122:1273–1274.
12. **Grove JH, Lebel M, Gbeassor FM.** Variations in urinary metabolites of prostacyclin and thromboxane $A_2$ in essential hypertension (abstr). Clin Res 1980;28:685 A.
13. **Tan SY, Sweet P, Mulrow PJ.** Impaired renal production of prostaglandin $E_2$: a newly identified lesion in human essential hypertension. Prostaglandins 1979;15:139–149.
14. **Okuma M, Yamori Y, Ohta K, Ichino H.** Production of prostacyclin like substance in stroke-prone and stroke resistant spontaneously hypertensive rats. Prostaglandins 1979;17:1–7.
15. **Pace-Asciak CR, Carrara MC, Rangaraj G, Nicolaou KC.** Enhanced formation of $PGI_2$, a potent hypotensive substance, by aortic rings and homogenates of spontaneously hypertensive rats. Prostaglandins 1978;15:1005–1012.
16. **Collier JG, Dawnay NAH, Nachev CH, Robinson BF.** Clinical investigation of an antagonist of $\alpha$ and $\beta$-adrenorecepors-AH 5158 A. Br J Pharmacol 1972;44:286–293.
17. **Mehta J, Cohn JN.** Hemodynamic effects of labetalol, an alpha and beta blocking agent, in hypertensive subjects. Circulation 1977;55:370–375.
18. **Mehta J, Mehta P.** Effect of propranolol therapy on platelet release and prostaglandin generation in patients with coronary heart disease. Circulation 1982;66:1294–1299.
19. **Mehta J, Mehta P.** Dipyridamole and aspirin in relation to platelet aggregation and vessel wall prostaglandin generation. J Cardiovasc Pharmacol 1982;4:688–693.
20. **Mehta P, Mehta J.** Prostacyclin and thromboxane release following mechanical trauma to human vessels (abstr). Blood 1981;58 Suppl:236A.
21. **Mehta J, Mehta P, Horalek C.** The significance of platelet-vessel wall prostaglandin equilibrium during exercise-induced stress. Am Heart J 1982, in press.
22. **Mehta P, Mehta J.** Influence of nicotine on platelet and vessel wall prostaglandins (abstr). Clin Res 1981;29:814 A.
23. **Neri Serneri GG, Masotti G, Poggeni L, Galanti G.** Release of prostacyclin into the blood stream and its exhaustion in humans after local blood flow changes (ishcemia and venous stasis). Thromb Res 1980;17:197–208.
24. **Poplawski A, Skorulska M, Niewiarowski S.** Increased platelet adhesiveness in hypertensive cardiovascular disease. Atherosclerosis 1981;1:721–723.
25. **Mehta J, Mehta P.** Platelet function in hypertension and effect of therapy. Am J Cardiol 1981;47:331–334.
26. **Frishman WH, Strom JA, Kirschner M, Poland M, Klein N, Halprin S, Le-Jemtel TH, Kram M, Sonnenblick EH.** Labetalol therapy in patients with systemic hypertension and angina pectoris: effects of combined alpha and beta-adrenoreceptor blockade. Am J Cardiol 1981;48:917–928.

# Analysis of Ventricular Emptying and Filling Indexes During Acute Increases in Arterial Pressure

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**Using equilibrium radionuclide angiography, an evaluation was made of the response of left ventricular ejection and filling rates at rest and during acute increases in afterload in 8 normal volunteer subjects and 10 patients with previous transmural myocardial infarctions. Using the postatropine point for comparison, normal patients increased ejection time and decreased peak ejection rate (−3.90 ± 0.49 vol/s to −3.41 ± 0.95 vol/s) and peak filling rate (3.94 ± 0.88 vol/s to 3.51 ± 0.38 vol/s). Infarct patients had similar responses, although all indexes were lower than the corresponding values in the normal subjects. At rest, the ratio of peak filling to emptying rate was similar in the normal subjects and the infarct patients (1.01 ± 0.24 versus 0.99 ± 0.25, respectively) and maintained that relationship after atropine (0.91 ± 0.11 versus 0.81 ± 0.21) and at the peak increase in arterial pressure (1.07 ± 0.21 versus 1.02 ± 0.32). The ratio of time to peak filling/time to peak emptying behaved in similar fashion regardless of the differences in the absolute values.**

**In this study, left ventricular filling and emptying behaved in a similar fashion in response to the alteration in arterial pressure in normal subjects and in patients with previous myocardial infarctions.**

Numerous investigators have recommended the use of left ventricular velocity and acceleration indexes of left ventricular performance.[1–7] These variables are difficult to measure noninvasively and are influenced by changes in the compliance of the arterial vasculature and by aortic flow dynamics.[8–14] Difficulties with measurement of these variables have led others to investigate the rate of change of ventricular volume during ejection as an alternative.[15,16] Little data exist on the response of peak ejection rate, time to peak ejection rate, or ejection time to afterload stress.[17,18] Recently, we validated the accuracy of the peak rate of ventricular emptying (peak − dV/dt) derived from gated blood images as an accurate noninvasive radionuclide index of left ventricular systolic function.[19] Others have demonstrated the accuracy of the timing of systolic events during the ejection phase of the cardiac cycle from equilibrium radionuclide volume curves.[20]

In previous work, we examined the effects of curve-merging techniques in attempts to characterize diastolic performance derived from radionuclide volume curves[21] and subsequently applied these techniques to patients during supine bicycle exercise.[22] Recent studies have reported that diastolic performance may aid in discriminating subtle abnormalities in left heart performance in patients with coronary artery disease.[23–25]

The purposes of our present study were (1) to examine peak ejection rate (peak −dV/dt) and peak filling rate (peak +dV/dt) in normal subjects and in patients with previous myocardial infarctions; (2) to examine the time during ejection and filling that peak −dV/dt and peak +dV/dt occur in normal subjects and infarct patients; and (3) to assess the utility and response of these variables during acute increases in afterload.

## Methods

**Study:** The study was undertaken in 18 normotensive male volunteers. Ten subjects (mean age 50 years, range 41 to 69) had had a previous transmural myocardial infarction at least 6 months earlier, as evidenced by a typical history of chest pain, elevated serum creatinine kinase levels, and characteristic electrocardiographic changes. No patient had clinical evidence of valvular heart disease or peripheral vascular disease and none had ingested any medications except diuretics within 48 hours of the study. Six had anterior and 4 had inferior infarctions.

The other 8 subjects were normal control volunteers (mean age 36 years, range 19 to 58) with no clinical evidence of cardiovascular disease. They were taking no medications and had no abnormalities on resting or exercise electrocardiograms. Written informed consent was obtained from all subjects and the protocol was approved by the Committee on Investigations Involving Human Subjects of the University of California, San Diego. Smoking and the consumption of caffeine-containing beverages were not permitted for 4 hours before the study.

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On arrival at the laboratory, subjects were instructed to lie in the supine position and remain still throughout the study. A 19 gauge "butterfly" needle was inserted into a vein in the right arm for administration of pharmaceuticals. An 18 gauge intravenous cannula (Jelco) was introduced into a forearm vein for blood sampling.

A single crystal gamma camera (Picker Dyna-Mo) fitted with a parallel hole, general purpose collimator was then positioned over the subject's chest wall in a 45° left anterior oblique position, with 5 to 10° caudal tilt. The camera position was then further adjusted if necessary so that the image of the left ventricle was clearly separated from that of the right ventricle and the left atrium. Thereafter, the camera position remained unchanged.

**Measurements:** One lead from a surface electrocardiogram was continuously displayed on a cardiac monitor (Hewlett-Packard). A precise heart rate was obtained at each phase in the study from the number of cardiac cycles recorded by the gamma camera during a 5 minute electrocardiogram gated left ventricular scintigram.

Blood pressure was measured in duplicate from the right arm every 60 seconds during left ventricular scintigraphy, using a standard mercury sphygmomanometer (Baumanometer). Systolic blood pressure was derived from the mean of 10 readings taken over a 5-minute period (blood pressure was also measured in the left arm at the beginning of the study and disparities between the 2 arms of >10 mm Hg were not found).

The patient's own red cells were labelled ex vivo with technetium-99m using the method of Smith and Richards.[26] Briefly, 4 ml of venous blood was drawn into a heparinized syringe and incubated for 5 minutes with freeze-dried stannous citrate in a sterile evacuated glass tube. The tube was then centrifuged upside-down for 5 minutes at 1,300 *g* and the red cells carefully removed by needle aspiration through the rubber stopper. Finally, the red cells were incubated in a sterile tube containing technetium-99m (Nuclear Pharmacy) for a further 5 minutes before the red cell suspension, containing 15 to 20 mCi of technetium-99m was reinjected by way of the butterfly needle to effect the blood pool label. Care was taken to ensure a sterile technique and also to minimize damage to the red cells during the labelling procedure.

**Protocol:** The protocol has been previously described.[27–29] After the subjects were in a basal hemodynamic state, a 5-minute equilibrium left ventricular scintigram, gated from a modified $V_5$ electrocardiographic lead, was obtained. Blood pressure was measured in duplicate each minute. At the midpoint of the scintigraphic acquisition, a 10 ml venous sample was withdrawn, from which 4 ml was pipetted for later gamma counting. Then, 1 mg of atropine sulphate (Abbott) was injected intravenously over 1 to 2 minutes. This was done to minimize the baroreflex mediated bradycardia that accompanies the infusion of pressor agents such as phenylephrine. After a further 10 minutes, left ventricular scintigraphy, blood sampling, and blood pressure measurements were repeated.

Next, an 80 μg/ml solution of phenylephrine hydrochloride in normal saline solution was infused by means of a variable delivery rate pump (Ivac). The infusion was commenced at 80 μg/min and titrated to produce target increments in systolic pressures of 15, 30, and 45 mm Hg. When each target level of systolic pressure had been reached, it was held stable for 5 minutes while left ventricular scintigraphy was repeated. The heart rate was maintained within 6 beats/min of the value achieved after the administration of atropine, by supplementary intravenous injections of atropine (0.1 to 0.3 mg) when necessary. In 4 patients with coronary artery disease, only 2 increments of phenylephrine were used because of the initial low blood pressure.

**Cardiac data analysis:** Equilibrium radionuclide studies were processed using a general purpose nuclear medicine computer ($A^2$ Medical Data Systems). Data recorded from each cardiac cycle during the 5 minutes of acquisition were divided into 54 equal time frames and integrated to construct a composite cardiac cycle. The raw data underwent frequency filtering (7 point temporal, and 5 point spatial) before region assignments and curve analyses. Once the filtered composite cycle was available, a rectangular region of interest was placed around the end-diastolic left ventricular image, and an edge detection program was used to define the boundary of the left ventricle throughout the cardiac cycle. (The edge detection algorithm uses both absolute count rate and the second derivative of the count rate change in each picture element for boundary location.) Background counts were automatically assigned in the end-systolic frame and subtracted from the left ventricular regions-of-interest to correct for noncardiac activity. The 5-minute (background subtracted) count rate exceeded 5,000 in the left ventricular region-of-interest at end-diastole in all studies. Thus, a background corrected time-activity curve from the left ventricle was obtained, from which ejection fraction was calculated using the following equation: Ejection Fraction = [(end-diastolic counts) − (end-systolic counts)]/(end-diastolic counts).

From the background-corrected time activity curve, a first-derivative curve (frame-by-frame dV/dt) could then be constructed (Fig. 1 and 2). Left ventricular ejection time (LVET) was determined directly from the radionuclide volume curve,[20] and defined as the time from the early apex to the lowest nadir of the curve. This was automatically determined by the computer. The time to peak −dV/dt and + dV/dt was defined from the onset of the QRS on the original count volume-time curve. During radionuclide data acquisition cardiac cycles that fell outside a ±10% range of the R-R interval were excluded to prevent distortion of the time-activity curve.

The "weighted forward backward break-up volume curve" was utilized in this study, and has become a standard commercial algorithm used by many laboratories for the evaluation of cardiac function. Methods for merging the forward and backward derived curves and the importance of a number of weighting techniques have been investigated in our laboratory. Ejection fraction as well as peak ejection and filling rates have been derived from either QRS-gated forward, reverse, or composite curves generated by both linear and exponential weighting of the forward and reverse break-up curves. These values were compared with results obtained from the mean heart rate volume curves. Linear weighting interpolation for deriving the composite curve provided a reasonable approximation of the mean heart rate volume curve. However, the correlation of filling rates and later portions of the diastolic volume curve could be more accurately characterized by the forward reverse break-up technique than by using the forward curve alone.[21] In the present study, for analysis of forward break-up, the radionuclide volume curves were gated with respect to the onset of QRS (end-diastole) and averaged with a symmetric weight distribution forward in time after the +10% R-R interval exclusion. Beats were weighted proportionately with respect to the mean heart rate beat with the mean heart rate beats receiving the greatest weight. The reverse break-up curve was obtained by aligning the tail end of the curves (backward in time) with the same weights. The forward and reverse generated curves were then combined to generate the composite volume curve. The composite curves were produced by assuming that the initial 25% portion of the forward curve and the terminal 25% portion of the reverse curve were accurate and that the remaining intermediate portions of the curves could be obtained by linear weighting of the forward and reverse curves. The ejection fraction, filling

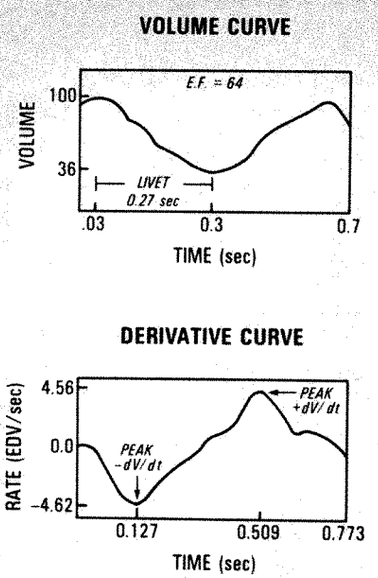



**FIGURE 1.** A volume and derivative curve are shown. +dV/dt = filling rate; −dV/dt = emptying rate; EDV = end-diastolic volume; LVET = left ventricular ejection time.

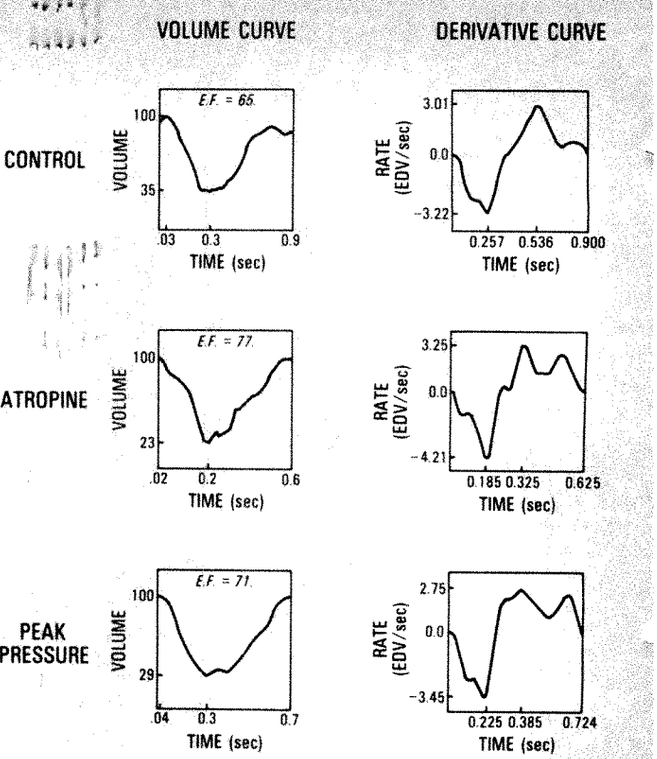



**FIGURE 2.** Response to pressure overload. First-derivative and volume curves are shown from a normal subject in the control state, after atropine administration, and at peak pressure.

fraction, peak filling rate, and the time from end-systole to peak filling rate were determined from the merged, composite (that is, interpolated) volume-time curves.

Left ventricular end-diastolic volume was calculated by a technique previously validated in our laboratory[27–29] and in others[30–35] as follows. Left ventricular counts at end-diastole (corrected for frame time and the number of cardiac cycles processed) were divided by counts from whole blood drawn at the midpoint of each study, corrected for background activity, elapsed time, and radioactive decay. In previous studies we have used a regression equation derived from previous radionuclide and contrast ventriculographic comparisons.[29] Because this equation was not available for the particular camera and collimator used in this study, relative volume units were used, rather than absolute volumes.

All volumes are given as units/$m^2$ body surface area. In our laboratories, the reproducibility over time of end-diastolic volume and ejection fraction using this method was ±6.1% and ±3%, respectively.[29] Inter- and intraobserver variability have both been found to be approximately 4%.[27–29]

**Statistics:** Data are given as the group mean ± 1 standard deviation. Comparisons within and among groups were performed by the appropriate paired or unpaired Student's *t* test. Correlations were tested by linear regression analysis. Differences within groups were tested with a repeated measures analysis of variance.[36]

## Results

**Resting hemodynamics (Tables I to III, Fig. 3 to 6):** Heart rate was similar in the control subjects and infarct patients (62 ± 4 beats/min versus 65 ± 11 beats/min, p = not significant [NS]), as was the arterial blood pressure (120/74 ± 7/6 mm Hg versus 119/77 ± 11/8 mm Hg, p = NS). Ejection fraction was greater in the normal control subjects (0.66 ± 0.07) than the infarct patients (0.52 ± 0.18, p <0.01), as was peak − dV/dt (−3.53 ± 0.32 vol/s versus −2.60 ± 1.01 vol/s, p <0.01). Left ventricular ejection time was similar in both groups (0.25 ± 0.03 second versus 0.29 ± 0.08 second in the infarct patients). The time to peak − dV/dt was similar in both groups (0.164 ± 0.04 second versus 0.19 ± 0.06 second in the infarct patients, p = 0.08), as was the time to peak +dV/dt (0.50 ± 0.03 second versus 0.51 ± 0.07 second in the infarct patients). Peak +dV/dt was greater in the normal subjects than in the patients (3.56 ± 0.83 vol/s versus 2.60 ±1.01 vol/s, p<0.01). However, the ratio of filling rate to emptying rate was similar in both groups (1.01 ± 0.24 in normal subjects and 0.99 ± 0.25 in the infarct patients), as was the ratio of time to peak filling/time to peak emptying (3.20 ± 0.85 versus 3.07 ± 1.38 in the infarct patients).

End-diastolic volume was greater (4.33 ± 1.29 versus 3.90 ± 0.83 units/$m^2$, p <0.05), stroke volume lower (2.25 ± 1.0 versus 2.59 ± 0.98 units/$m^2$, p <0.05), and cardiac index lower (146.3 ± 20.2 versus 160.6 ± 24.3 units/min/$m^2$, p <0.05) in the infarct patients when compared with the normal subjects.

**Atropine response (Tables I to III, Fig. 3 to 6):** Heart rate increased similarly in both groups (88.9 ± 4.6 beats/min in the normal subjects and 83.3 ± 8.5 beats/min in the infarct patients, p = NS), as did arterial blood pressure (123/77 ± 16/13 mm Hg in the normal subjects and 125/76 ± 17/9 mm Hg in the infarct patients).

Ejection fraction remained unchanged in the normal subjects (0.66 ± 0.07 to 0.65 ± 0.06) and in the infarct patients (0.52 ± 0.18 to 0.49 ± 0.17). Ejection time declined in the normal subject (0.25 ± 0.03 second to 0.19

**TABLE I Radionuclide Indexes**

| | Ejection Fraction | Ejection Rate (Vol/s) | Filling Rate (Vol/s) |
|---|---|---|---|
| Control | | | |
| NLS | 0.66 ± 0.07 | 3.5 ± 0.32 | 3.6 ± 0.83 |
| PTS | 0.52 ± 0.18* | 2.6 ± 1.0* | 2.5 ± 0.72* |
| Atropine | | | |
| NLS | 0.65 ± 0.06 | 3.9 ± 0.49 | 3.9 ± 0.88 |
| PTS | 0.49 ± 0.17* | 3.3 ± 1.3* | 2.5 ± 0.89* |
| Peak phenyl | | | |
| NLS | 0.56 ± 0.08† | 3.4 ± 0.95† | 3.5 ± 0.38† |
| PTS | 0.45 ± 0.17* | 2.4 ± 0.74* | 2.3 ± 0.44* |

* $p < 0.05$ versus normal subjects.
† $p < 0.05$ versus atropine data point.
NLS = normal control volunteers; Peak phenyl = data from peak phenylephrine infusion rate; PTS = patients with previous infarction.

**TABLE II Radionuclide Timing Variables**

| | $TTP_E$ | $TTP_F$ | FR/ER | $TTP_F/TTP_E$ |
|---|---|---|---|---|
| Control | | | | |
| NLS | 0.16 ± 0.04 | 0.50 ± 0.03 | 1.01 ± 0.24 | 3.2 ± 0.85 |
| PTS | 0.19 ± 0.06* | 0.51 ± 0.07 | 0.99 ± 0.25 | 3.1 ± 1.4 |
| Atropine | | | | |
| NLS | 0.19 ± 0.04 | 0.48 ± 0.04 | 0.91 ± 0.11 | 2.6 ± 0.47† |
| PTS | 0.19 ± 0.07 | 0.47 ± 0.07 | 0.81 ± 0.21 | 2.6 ± 0.67† |
| Peak phenyl | | | | |
| NLS | 0.19 ± 0.02 | 0.49 ± 0.06 | 1.07 ± 0.21 | 2.6 ± 0.3† |
| PTS | 0.20 ± 0.05 | 0.52 ± 0.07 | 1.02 ± 0.32 | 2.8 ± 0.9 |

* $p = 0.08$ versus normal subjects.
† $p < 0.05$ versus control values.
FR/ER = peak +dV/dt/peak −dV/dt; NLS = normal control volunteers; Peak phenyl = data from peak phenylephrine infusion rate; PTS = patients with previous infarction; $TTP_E$ = time from peak of QRS to peak −dV/dt; $TTP_F$ = time from peak of QRS to peak +dV/dt.

**TABLE III Derived Radionuclide Timing Variables**

| Time | ED − ER | ES − FR | $\frac{ED - ER}{ET}$ | $\frac{ES - FR}{DT}$ |
|---|---|---|---|---|
| Control | | | | |
| NLS | 0.104 ± 0.009 | 0.19 ± 0.011 | 0.42 ± 0.07 | 0.29 ± 0.04 |
| PTS | 0.152 ± 0.007* | 0.190 ± 0.012 | 0.52 ± 0.05* | 0.32 ± 0.04 |
| Atropine | | | | |
| NLS | 0.104 ± 0.008 | 0.200 ± 0.011 | 0.54 ± 0.05 | 0.55 ± 0.17 |
| PTS | 0.146 ± 0.009* | 0.182 ± 0.010 | 0.61 ± 0.04* | 0.42 ± 0.06 |
| Peak phenyl | | | | |
| NLS | 0.118 ± 0.010 | 0.196 ± 0.017 | 0.54 ± 0.05 | 0.54 ± 0.6 |
| PTS | 0.168 ± 0.010* | 0.197 ± 0.014 | 0.58 ± 0.04 | 0.54 ± 0.7 |

* $p < 0.05$ versus normal subjects.
See Table II for explanation of abbreviations. ED − ER = time from end-diastole (peak of volume curve) to peak − dV/dt; ES − FR = time from end-systole (nadir of volume curve) to peak + dV/dt. DT = diastolic time (R-R interval—time from peak of QRS to nadir of volume curve); ET = ejection time.

± 0.03 second), as well as in the infarct patients (0.29 ± 0.08 second to 0.24 ± 0.07 second, both $p < 0.05$). Once again, peak −dV/dt (3.90 ± 0.49 vol/s versus 3.28 ± 1.34 vol/s, $p < 0.05$) and peak +dV/dt (3.95 ± 0.88 vol/s versus 2.54 ± 0.89 vol/s, $p < 0.01$) were greater in the normal subjects than in the patients. In addition, the ratio of peak +dV/dt to peak −dV/dt was similar in the 2 groups after atropine (0.91 ± 0.11 versus 0.81 ± 0.21 in the infarct patients) and the time to peak filling/time to peak emptying was also not different (2.56 ± 0.47 versus 2.55 ± 0.67).

End-diastolic volume index decreased in both normal subjects (3.12 ± 1.60 versus 3.90 ± 0.83 units/$m^2$, $p < 0.05$) and in the infarct patients (3.86 ± 1.46 versus 4.33 ± 1.29 units/$m^2$, $p < 0.05$). In addition, stroke volume declined in the normal subjects (2.03 ± 0.43 versus 2.59 ± 9.8, $p < 0.05$) and infarct patients (1.89 ± 0.9 versus 2.25 ± 1.0, $p < 0.05$), although cardiac output increased (180.3 ± 30.1) in the normal subjects and in the infarct patients (157.6 ± 24.2).

**Peak phenylephrine infusion data (Tables I to III):** The total increase in systolic pressure was similar in both groups (43.4 ± 7.2 mm Hg for the normal subjects and 40.3 ± 8.6 mm Hg for the coronary patients). At the peak pressure point, ejection fraction declined in the normal subjects (0.56 ± 0.08, $p < 0.05$ versus atropine and control) but did not decrease markedly in the infarct patients (0.45 ± 0.17 versus 0.49 ± 0.17 atropine and 0.52 ± 0.18 control, peak pressure $p < 0.05$ versus control). Peak −dV/dt and peak + dV/dt both declined significantly but, as before, the ratio of velocity indexes and the ratio of the times of peak filling to peak emptying did not significantly differ between the 2 groups.

End-diastolic volume increased in both groups when compared with the atropine data point (4.43 ± 0.69 versus 3.12 ± 1.60 units/$m^2$ in the normal subjects, $p < 0.01$; and 5.04 ± 1.81 versus 3.86 ± 1.46 in the infarct patients, $p < 0.01$). Stroke volume increased significantly in both groups ($p < 0.05$), resulting in a significant increase in cardiac output ($p < 0.05$).

In general, the time to peak ejection occurred somewhat earlier in the normal subjects than in the infarct patients, when estimated as a measure of absolute time or as a percentage of the left ventricular ejection. This tended to be less evident when phenylephrine was infused. Nonetheless, the differences were small, the overlap was relatively large, and the clinical utility minimal.

## Discussion

Variations in systemic arterial pressure have been demonstrated to have direct effect on measurements of a variety of indexes of left ventricular performance.[1–8,27–29,37] The effects of sequentially induced alterations in afterload have recently received sub-

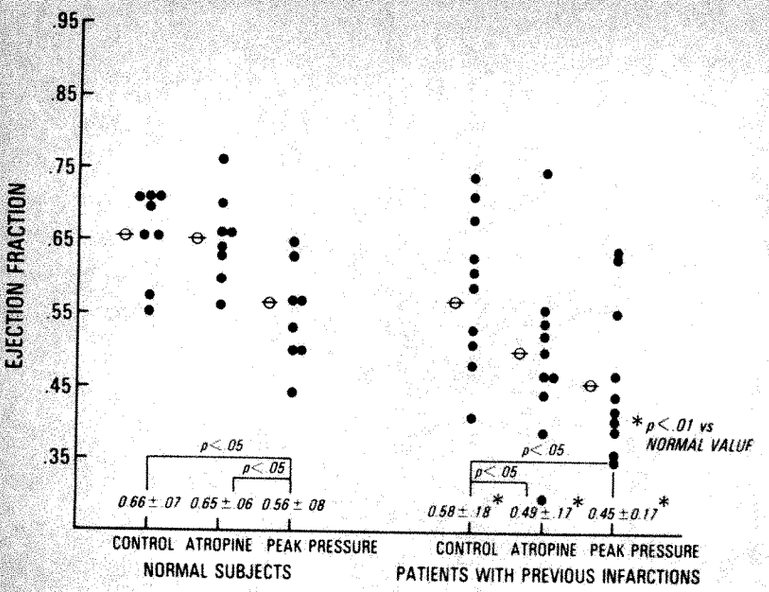



**FIGURE 3.** Response to pressure overload. The response of ejection fraction to atropine and afterload are given for both groups studied.

stantial attention,[27–29] particularly its effects on measures of left ventricular function in patients with asynchronous left ventricular contraction patterns. In the present study, the utility of an index of mid-ventricular systolic contractile events was examined,[38–40] as was an index of left ventricular diastolic filling.[23–25]

Peak ejection rate behaved in a fashion similar to ejection fraction, and was, by itself, neither more useful nor discriminating at rest or during interventions than ejection fraction alone. This is similar to the report of Bianco et al,[41] and corresponds to similar results from others.[42–46] In the present study, afterload stress induced delays in the timing of peak ejection rate in both normal subjects and infarct patients. Whether this represents the limits of preload reserve,[47] and an inability to generate velocity as quickly at greater left ventricular wall stress, remains unclear.

Similar to Hammermeister et al,[15] we found that peak normalized ejection rate occurred somewhere near the mid-portion of ejection. Normal subjects reach their peak ejection rate slightly earlier in systole than infarction patients, though not substantially so or with great enough uniformity to be a clinically useful finding. The effect of aortic compliance might substantially alter outflow impedance and aortic flow rates, as well as ventricular emptying rates.[9–14]

With afterload elevation, ejection time increased, in all likelihood due to reduced ejection rates and increased stroke volumes. In previous phenylephrine infusion studies using radionuclide angiography, we

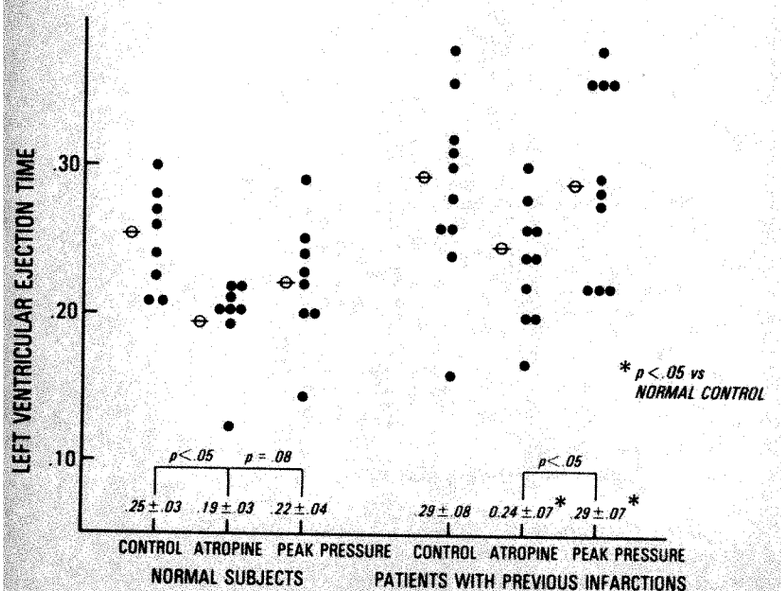



**FIGURE 4.** Response to pressure overload. The change in ejection time during atropine and phenylephrine administration is given.

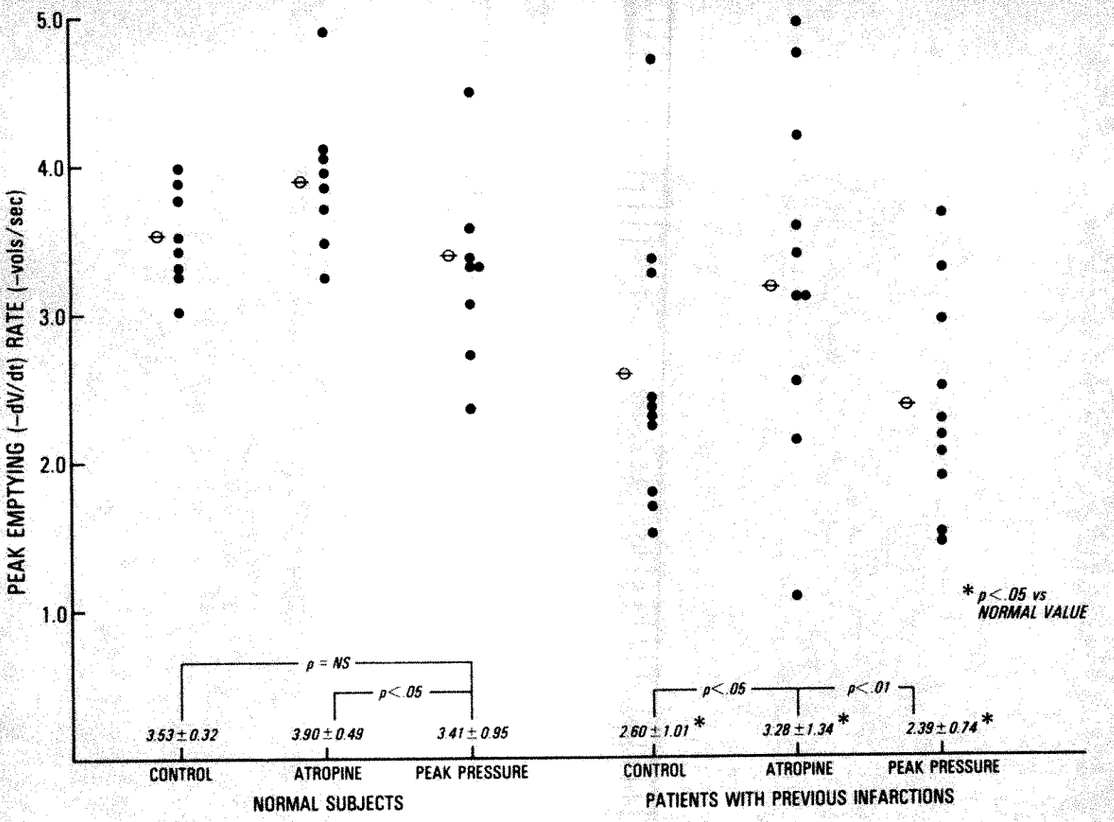



**FIGURE 5.** Response to pressure overload. The response of peak ejection rate to atropine and pressure overload in both groups.

found it uncommon to demonstrate an actual reduction in stroke volume with increases in arterial pressures.[27–29] This probably reflected adequate Frank-Starling reserve capacity in these subjects. Ejection rates have been known to decline with afterload elevations.[6]

Bonow et al[23] described ejection rates and times to peak ejection rate in normal subjects and patients with coronary heart disease at rest. They found that both time to peak ejection rate and ejection time were similar in normal subjects and coronary patients. However, heart rates were not available to review, and data are not given as a percentage of the R-R interval or ejection time. In any event, our coronary population was composed of patients with previous myocardial infarctions, who might be expected to differ from patients with ischemic disease without previous infarctions.

The pressure-volume relation of the normal ventricle in diastole is curvilinear, such that in the normal ventricle at low volumes, moderate changes in volume are associated with small pressure changes, whereas at larger volumes, small volume increases produce substantial changes in pressure. Thus, the ventricle is relatively compliant at low volumes but becomes progressively less so as volumes increase. Thus, it might be expected that as left ventricular volumes increase, filling rates might slow. In addition, patients with coronary disease may manifest both acute and chronic alterations in the diastolic pressure-volume relation. In some patients, elevation in diastolic pressure is noted despite normal left ventricular volumes.[47–49]

Radionuclide techniques only approximate measures of diastolic function. Noninvasive data were not related to intraventricular pressures in the present study. In addition, it is well-known that mere changes in ventricular volumes without ischemia can increase chamber stiffness without implying a change in muscle stiffness.[50] Furthermore, the mechanisms involved in abnormalities of timing of events during various phases of the cardiac cycle cannot be specifically delineated without knowing the timing of valvular opening and closing. This is not provided by analysis of the time-activity curve alone. The time from the peak of the QRS to peak −dV/dt includes isovolumic contraction time, and the time to peak +dV/dt includes both isovolumic relaxation and contraction time. Anomalies in these intervals may be difficult to interpret not only because of the combination of these 2 distinct phases of the cardiac cycle, but also because changes in the velocity of chamber blood flow may be affected by aberrations of myocardial relaxation.[51] Nevertheless, these methods provide an attractive qualitative approach to the measurement of diastolic function.

Relatively little data exist presently on the radionuclide assessment of diastolic function in normal subjects and coronary patients at rest and during alterations in afterload. Our determination of peak left ventricular filling rates using gated equilibrium radionuclide an-

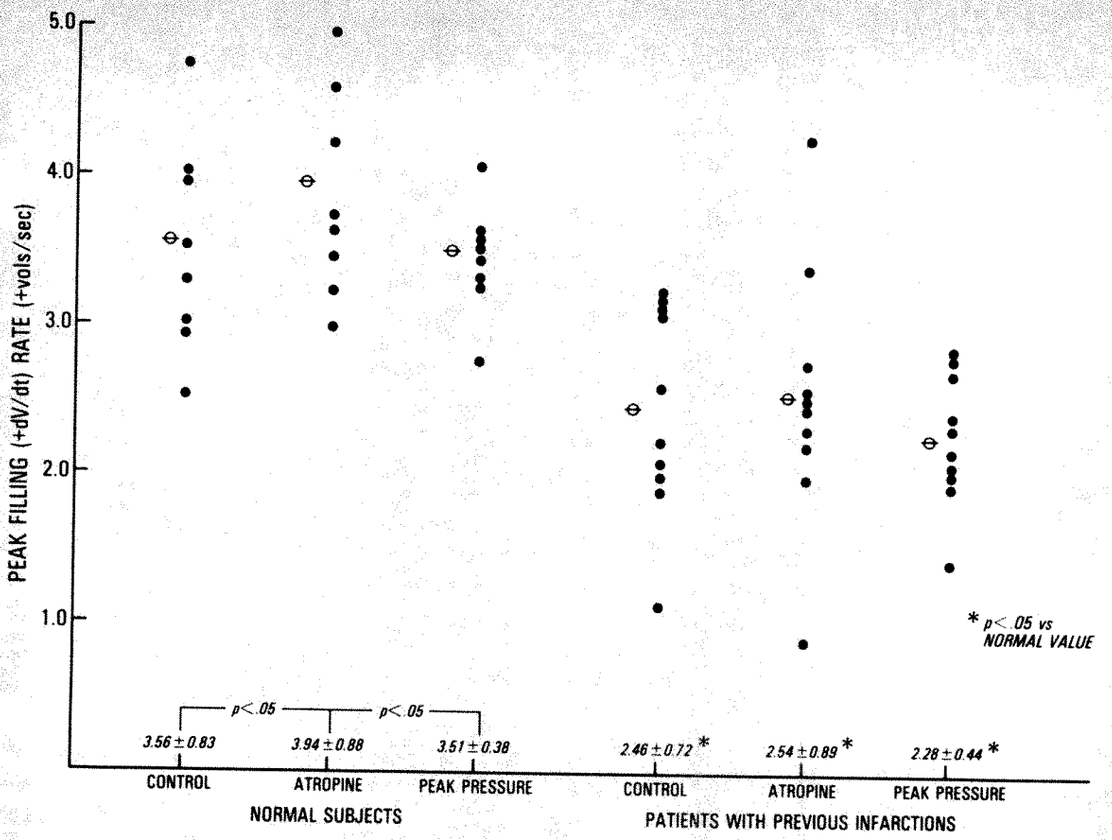



**FIGURE 6.** Response to pressure overload. The change in peak filling rate is shown in all subjects at control, atropine, and peak pressure points.

giography at rest is in close agreement with that of Bonow et al[23] and Reduto et al[5] and comparable to the angiographic results reported by Hammermeister et al.[15] The peak filling rate at rest in the coronary patients was lower than in the normal subjects, even when systolic function at rest was normal.

It appears that peak filling rate is a sensitive marker of cardiac dysfunction due to coronary disease in patients with a previous myocardial infarction. However, when a systolic variable employing differentiation is assessed, such as peak ejection rate, it appears to also be abnormal and has behavior which is similar to filling rates during acute alteration in afterload. This is in agreement with the work of Hammermeister et al,[15] who noted that in the absence of valvular disease, peak rate of volume change was similar in both systole and diastole and both were lower in coronary patients when compared with normal subjects.

We conclude that the normal left ventricle shows a decrease in ejection fraction and peak ejection and filling rates with increases in arterial pressure. This occurs in association with a slight but significant prolongation of ejection time and the times to peak ejection and filling rate. Similar findings occurred in patients with previous infarctions. Global indexes of mid- and total systole appeared to be of similar discriminatory value for normal subjects versus infarct patients at rest and during pressure intervention, as emphasized recently by others.[41–46,52] Diastolic portions of the cardiac cycle, as well as patterns of left ventricular emptying, can be easily evaluated during acute hemodynamic interventions.

## References


1. **Nutter D, Noble RJ, Hurst J III.** Peak aortic flow and acceleration as indices of ventricular performance in the dog. J Lab Clin Med 1971;77:307–318.
2. **Noble MIM, Trechard D, Guz A.** Left ventricular ejection in conscious dogs. 1. Measurement and significance of the maximum acceleration of blood from the left ventricle. Circ Res 1966;19:139–147.
3. **Noble MIM.** The contribution of blood momentum to left ventricular ejection in the dog. Circ Res 1968;23:663–670.
4. **Gabe I, Gault J, Ross J Jr, Mason D, Mills C, Schillingford J, Braunwald E.** Measurement of instantaneous blood flow velocity and pressure in conscious man with a catheter-tip velocity probe. Circulation 1969;40:603–614.
5. **Peterson K, Uther J, Shabetai R, Braunwald E.** Assessment of left ventricular performance in man: instantaneous tension-length relations obtained with the aid of an electromagnetic velocity catheter in the ascending aorta. Circulation 1973;47:924–935.
6. **Mills C, Gabe I, Gault J, Mason D, Ross J Jr, Braunwald E, Schillingford J.** Pressure-flow relationships and vascular impedance in man. Cardiovasc Res 1970;4:405–417.
7. **Snell P, Clements J, Patel D, Fry D, Luchsinger P.** Instantaneous blood flow in the human aorta. J Appl Physiol 1965;20:691–695.
8. **Noble MIM.** Left ventricular load, arterial impedance and their interrelationship. Cardiovasc Res 1979;13:183–198.
9. **Simonson E, Nakagawa K.** Effect of age on pulse wave velocity and "aortic ejection time" in healthy men and in men with coronary artery disease. Circulation 1960;22:126–129.
10. **Learoyd B, Taylor M.** Alterations with age in the viscoelastic properties of human arterial walls. Circ Res 1966;28:278–292.
11. **O'Rourke M, Blazek J, Morreels C, Krovetz LJ.** Pressure wave transmission along the human aorta: changes with age and in arterial degenerative disease. Circ Res 1968;28:567–579.
12. **Eliakim M, Sapoznikov D, Weinman J.** Pulse wave velocity in healthy subjects and in patients with various disease states. Am Heart J 1971;

82:448–457.
13. **Urschel C, Covell J, Sonnenblick E, Ross J Jr, Braunwald E.** Effect of decreased aortic compliance on performance of the left ventricle. Am J Physiol 1968;214:298–304.
14. **Elzinga G, Westerhof N.** Pressure and flow generated by the left ventricle against difference impedances. Circ Res 1973;32:178–186.
15. **Hammermeister K, Brooks R, Warbasse J.** The rate of change of left ventricular volume in man. I. Validation and peak systolic ejection rate in health and in disease. Circulation 1974;49:729–747.
16. **Peterson K, Skioven D, Ludbrook P, Uther J, Ross J Jr.** Comparison of isovolumic and ejection phase indices of myocardial performance in man. Circulation 1974;49:1088–1101.
17. **Lindquist V, Spangler R, Blount SG.** A comparison between the effects of dynamic and isometric exercise as evaluated by the systolic time intervals in normal man. Am Heart J 1973;85:227–236.
18. **Yamamoto H, Arakawa K, Yamashita T, Murakami H, Sakai T, Toril S, Nakamura M.** A new pharmacologic phonocardiography by the use of angiotension. Am Heart J 1971;81:29–37.
19. **Bhargava V, Slutsky R, Costello D.** Peak rate of left ventricular ejection by gated radionuclide techniques: correlation with contrast ventriculography. J Nucl Med 1981;22:506–609.
20. **Bacharach S, Green M, Borer J, Ostrow H, Redwood D, Johnson G.** ECG-gated scintillation probe measurement of left ventricular function. J Nucl Med 1977;18:1176–1182.
21. **Bhargava V, Slutsky R, LeWinter M.** Contrast angiographic validation of forward reverse break-up techniques for estimation of radionuclide volume curves (abstr). Circulation 1981;64:Suppl IV:IV-74.
22. **Mancini GBJ, Slutsky R, Norris S, Bhargava V, Ashburn W, Higgins C.** Radionuclide analysis of peak filling rate, filling fraction, and time to peak-filling rate: response to supine bicycle exercise in normal subjects and patients with coronary disease. Am J Cardiol 1983;51:43–51.
23. **Bonow RO, Bacharach SL, Green MV, Kent KM, Rosing DR, Lipson LC, Leon MB, Epstein SE.** Impaired left ventricular diastolic filling in patients with coronary artery disease: assessment with radionuclide angiography. Circulation 1981;64:315–323.
24. **Kemper AJ, Polack J, Bianco JA, Parisi AF, Tow DE.** Resting left ventricular early diastolic filling in normal subjects and patients having coronary artery disease (abstr). J Nucl Med 1981;22:84.
25. **Reduto LA, Wickemeyer WJ, Young JB, Del Ventura LA, Reid JW, Glaeser DH, Quinones MA, Miller RR.** Left ventricular diastolic performance at rest and during exercise in patients with coronary artery disease: assessment with first-pass radionuclide angiography. Circulation 1981;63:1228–1237.
26. **Smith TD, Richards P.** A simple kit for the preparation of 99m Tc-labelled red blood cells. J Nucl Med 1976;17:126–132.
27. **Slutsky R, Watkins J, Peterson K, Karliner J.** The effect of volume loading, atrial pacing and afterload stress on left ventricular function and size in patients with coronary heart disease. Circulation 1981;63:864–871.
28. **Watkins J, Slutsky R, Tubau J, Karliner J.** Scintigraphic analysis of systolic pressure-volume relations in response to changes in heart rate and afterload in normal and coronary patients. Br Heart J 1982;48:39–47.
29. **Slutsky R, Watkins J, Costello D.** The systolic blood pressure/end-systolic volume relationship: response to pharmacologic agents in patients with coronary artery disease. Am Heart J 1983;105:53–61.
30. **Dehmer G, Lewis S, Hillis L, Twelg D, Falkoff M, Parkey Willerson J.** A nongeometric method for scintigraphic determination of left ventricular volumes from gated cardiac blood pool scans. Am J Cardiol 1980;45:923–929.
31. **Links J, Becker J, Schindledecker J, Guzman P, Burow R, Nickoloff E, Alderson P, Wagner H.** Measurement of absolute left ventricular volume from gated blood pool studies. Circulation 1982;65:82–89.
32. **Konstam M, Wynne J, Holman B, Brown E, Neill J, Kozlowski J.** Use of equilibrium (gated) radionuclide ventriculography to quantitate left ventricular output in patients with and without left-sided valvular regurgitation. Circulation 1981;64:578–589.
33. **Massie B, Kramer B, Gertz E, Henderson S.** Radionuclide measurement of left ventricular volume: comparison of geometric and counts-based methods. Circulation 1982;65:725–734.
34. **Clements I, Brown M, Smith H.** Radionuclide measurement of left ventricular volume. Mayo Clin Proc 1981;56:733–742.
35. **Parrish M, Graham T, Born M, Jones J, Boucek R, Partain C.** Radionuclide ventriculography for assessment of absolute right and left ventricular volumes in children. Circulation, in press.
36. **Winer BJ.** Statistical Principles in Experimental Design. New York: McGraw-Hill, 1971:570–590.
37. **Ross J Jr, Braunwald E.** The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotension. Circulation 1964;29:739–745.
38. **Slutsky R, Karliner J, Battler A, Peterson K, Ross J Jr.** Comparisons of early systolic and holosystolic ejection phase indexes by contrast ventriculography in patients with coronary artery disease. Circulation 1980;61:1083–1090.
39. **Johnson L, Ellis K, Schmidt D, Weiss M, Cannon P.** Volume ejected in early systole: a sensitive indicator of left ventricular performance in coronary artery disease. Circulation 1975;52:378–389.
40. **Slutsky R, Gordon D, Karliner J, Battler A, Walaski S, Verba J, Pfisterer M, Peterson K, Ashburn W.** Assessment of left ventricular systole by first-pass radionuclide angiography: useful method for detection of left ventricular dysfunction at rest in patients with coronary artery disease. Am J Cardiol 1979;44:459–463.
41. **Bianco J, Makey D, Laskey W, Shafer R.** Radionuclide left ventricular dV/dt for the assessment of cardiac function in patients with coronary disease. J Nucl Med 1979;20:1–6.
42. **Hoshino T, Tomonanga G, Motomura M, Shimonono Y, Kinoshita M, Kusukawa R.** Quantitative analysis of left ventricular ejection phase by means of left ventricular cineangiography. Jpn Circ J 1977;41:1085–1094.
43. **Denenberg B, Makler T, Bove A, Maimud L, Charles D, Spann J.** Inability to detect coronary artery disease at rest by patterns of ventricular emptying using contrast angiography and radionuclide angiography (abstr). J Cardiol 1980;45:409.
44. **Jones A, Goodyer A, Cohen L, Langou R.** Lack of sensitivity of the resting first-third ejection fraction for identifying patients with coronary artery disease (abstr). Circulation 1980;Suppl III:III-78.
45. **Yamashina A, Roistacher M, Friedman R, Pierson R.** First-third ejection fraction: are radionuclide measurements accurate (abstr). J Nucl Med 1981;22:74.
46. **Kemper A, Bianco J, Swerdlow P, Folland E, Shulman R, Parisi A, Tow A.** Insensitivity of the interval ejection fraction to differentiate normals from patients with coronary artery disease (abstr). J Nucl Med 1980;21:P52.
47. **Ross J Jr.** Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. Prog Cardiovasc Dis 1976;43:255–269.
48. **Diamond G, Forrester JS.** Effect of coronary artery disease and acute myocardial infarction on left ventricular compliance in man. Circulation 1972;45:11–19.
49. **Bristow JD, Van Zee BE, Judkins MP.** Systolic and diastolic abnormalities of the left ventricle in coronary artery disease: studies in patients with little or no enlargement of ventricular volume. Circulation 1970;42:219–228.
50. **Covell JW, Ross J Jr.** Nature and significance of alterations in myocardial compliance. Am J Cardiol 1973;32:455–499.
51. **Grossman W, McLaurin LP.** Diastolic properties of the left ventricle. Ann Intern Med 1976;84:316–336.
52. **Slutsky RA, Mancini GBJ, Gerber K, Carey PH, Ashburn WL, Higgins CB.** Radionuclide analysis of ejection time, peak ejection rate, and time to peak ejection rate. Response to supine bicycle exercise in normal subjects and patients with coronary heart disease. Am Heart J, in press.

# Serial Changes in Left Ventricular Function After Correction of Chronic Aortic Regurgitation

## Dependence on Early Changes in Preload and Subsequent Regression of Hypertrophy

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**Surgical correction of chronic aortic regurgitation generally results in a substantial decrease in left ventricular (LV) volume and mass. To assess the functional significance of these structural changes, serial noninvasive tests of LV function from 23 patients were examined after aortic valve replacement. Three independent tests of LV function were used: (1) the ratio of the LV preejection period (PEP) to the LV ejection time (LVET), (2) the echocardiographic fractional increase in LV wall thickness (FT), and (3) the mitral E point to septal separation (ESS). Studies were performed before surgery and at 0.3 (early), 3 to 6 (mid), and 9 to 12 (late) months after surgery.**

**In the early postoperative studies, LV end-diastolic dimension decreased to normal or near-normal and the PEP/LVET ratio increased substantially in 17 patients. Ten of the 17 (group 1) had complete regression of LV hypertrophy and the average values for all 3 indexes of LV function were normal at the time of the late postoperative study (PEP/LVET = 0.41 ± 0.05, FT = 73 ± 14%, ESS = 6.2 ± 0.9 mm). Seven patients (Group 2) with incomplete regression of LV hypertrophy showed borderline to moderately abnormal function indexes at the late study. Six patients had persistent LV enlargement and no postoperative regression of hypertrophy (Group 3). These patients did not show the substantial early changes in the function indexes observed in Groups 1 and 2; moreover, the indexes remained markedly abnormal at the time of the late postoperative study (PEP/LVET = 0.52 ± 0.10, FT = 47 ± 13%, ESS = 22.3 ± 7.2 mm). Patients in Group 3 had preoperative evidence of abnormal LV function which was more marked than that observed in Groups 1 and 2. Thus, the early postoperative changes in LV preload and the subsequent regression of LV hypertrophy are associated with evidence of early LV dysfunction and subsequent improvement. Postoperative LV enlargement and persistent LV hypertrophy are associated with persistent LV dysfunction. These serial data provide a framework for the rational timing and interpretation of postoperative ventricular function tests.**

Left ventricular chamber size and myocardial mass usually decrease after the surgical correction of chronic aortic regurgitation.[1–24] Perhaps the most dramatic of these changes is the marked reduction in LV *volume* which is seen within a week of surgery. Over the subsequent 6 months, a gradual decrease in LV *mass* may occur, but the regression of LV hypertrophy is incomplete in many patients. Studies of LV *function* in the weeks and months after aortic valve replacement indicate variable results; some patients appear to have normal or borderline LV function while others show persistent postoperative LV enlargement and depressed function. Much of the reported data on postoperative LV function have not been obtained serially, and for this reason the time course of such changes has not been fully appreciated. Moreover, it is not known whether or not postoperative regression of LV hypertrophy has significant functional consequences: that is, whether the patient with complete regression of LV hypertrophy has a better functional result than the patient with incomplete regression of hypertrophy.

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The present study was designed to define the functional changes associated with the structural changes known to follow surgical correction of chronic aortic regurgitation. We made serial postoperative measurements of 3 independent noninvasive indexes of LV function and examined these data relative to the observed changes in LV size and myocardial mass; we especially emphasized the time course of these changes during the first year after aortic valve replacement. In addition, we examined the preoperative data in an attempt to identify noninvasive variables that might be useful in predicting the results of surgery.

## Methods

Twenty-three patients who underwent aortic valve replacement for chronic aortic regurgitation between January 1975 and December 1980 were invited to participate in the study. Admission to the study required high-quality echocardiographic LV studies and externally recorded systolic time intervals. Before surgery, all patients had typical clinical and hemodynamic findings of significant aortic regurgitation. Echocardiograms were obtained with a Smith Kline ultrasonoscope and a 2.25 MHz transducer. LV end-diastolic dimension was measured at the R wave of the electrocardiogram and the end-systolic dimension was measured as the smallest vertical dimension between left septal echocardiogram and the posterior wall echocardiogram at end-systole. Relative wall thickness was determined as one-half the end-diastolic dimension divided by the wall thickness.[9] Markedly abnormal septal motion was a uniform finding in the early postoperative studies, and for this reason fractional shortening of the LV internal dimension was not used as an index of LV function in postoperative studies. The fractional increase in LV posterior wall thickness (FT) from end-diastole to end-systole was calculated as follows: $FT = [(Th_{ed} - Th_{es})/Th_{ed}] \cdot 100$, where $Th_{ed}$ is end-diastolic posterior wall thickness and $Th_{es}$ is end-systolic wall thickness.[9,25–27] Fractional thickening is expressed as a percentage.

Echocardiographic estimation of LV muscle mass is known to be dependent on several assumptions regarding ventricular geometry. To avoid these potential problems, we used muscle cross-sectional area (CSA) as an index of LV myocardial mass which does not require major geometric assumption.[9,15] This index (in $cm^2/m^2$) was calculated from the echocardiographic dimension and wall thickness data, as follows: $CSA = \pi [(EDD/2) + Th_{ed}]^2 - \pi (EDD/2)^2$, where EDD = end-diastolic dimension.

The distance between the E point of the mitral valve anterior leaflet to the LV edge of the interventricular septum was used as an index of global LV function. ESS was measured according to the technique described by Massie et al.[28] This variable reflects global ejection fraction and is only minimally influenced by heart size.[28–30]

Systolic time intervals were obtained at the same time as the echocardiographic studies. They were derived from an electrocardiogram (lead II), a carotid pulse tracing (Statham P23Db), and a phonocardiogram. Total electromechanical systole ($QS_2$), preejection period (PEP), and LV ejection time (LVET) were measured and corrected for heart rate as described by Lewis et al[31] and Weissler.[32] The ratio of PEP to LVET was calculated for all patients. Four patients were excluded from this portion of the study due to left bundle branch block (n = 2) and permanent right ventricular endocardial pacing (n = 2).

Preoperative studies were performed in all patients. Postoperative studies were performed at 7 to 10 days after surgery (early), at 3 to 6 months postoperative (mid), and again at 9 to 12 months (late).

The 23 patients were divided into 3 groups for data analysis. Group 1 patients (n = 10) had a very satisfactory surgical result which we defined as a normal end-diastolic dimension (decreasing to within 2 standard deviations of normal, that is, $<3.3$ cm/m$^2$) and normal LV mass (cross-sectional area $<10$ $cm^2/m^2$). Group 2 patients (n = 7) attained a normal end-diastolic dimension postoperatively, but still had evidence of LV hypertrophy (cross-sectional area $>10$ $cm^2/m^2$). Group 3 patients (n = 6) had persistent postoperative LV enlargement (end-diastolic dimension $>3.3$ cm/m$^2$) and lack of regression of LV hypertrophy. None of our patients had paraprosthetic regurgitation.

Systolic time intervals, ESS, and FT data were analyzed within each group by analysis of variance for serial data; in this manner, we tested the hypothesis that significant temporal changes in LV function occurred postoperatively. Differences between groups at specific times were also tested by analysis of variance. Tabular data are presented as the mean ± 1 standard deviation.

## Results

The preoperative echocardiographic data are presented in Table I. The serial pre- and postoperative data are presented in Tables II to IV and Figures 1 to 4.

**LV end-diastolic dimension and muscle cross-sectional area:** Serial echocardiographic measurements of LV end-diastolic dimension and muscle cross-sectional area are presented in Table II and Figure 1. In Group 1, LV end-diastolic dimension and cross-sectional area decreased to normal levels in all 10 patients. The change in end-diastolic dimension at the time of the early postoperative study was highly significant (p

**TABLE I Preoperative Echocardiographic Data**

| | EDD ($cm/m^2$) | ESD ($cm/m^2$) | FS (%) | CSA ($cm^2/m^2$) | R/Th | P·R/Th (mm Hg) |
|---|---|---|---|---|---|---|
| Group 1 n = 10 | 3.6 ± 0.3 | 2.5 ± 0.3 | 33 ± 5 | 12.6 ± 2.7 | 3.5 ± 0.4 | 521 ± 88 |
| Group 2 n = 7 | 3.8 ± 0.5 | 2.6 ± 0.6 | 31 ± 7 | 14.9 ± 1.5 | 3.5 ± 0.4 | 562 ± 62 |
| Group 3 n = 6 | 4.3 ± 0.5 | 3.3 ± 0.4 | 26 ± 5 | 14.7 ± 1.2 | 4.1 ± 0.3 | 677 ± 56 |
| 1 versus 2 | NS | NS | NS | NS | NS | NS |
| 1 versus 3 | $p < 0.05$ | $p < 0.01$ | $p < 0.02$ | NS | $p < 0.05$ | $p < 0.02$ |
| 2 versus 3 | NS | $p = 0.05$ | NS | NS | $p < 0.05$ | $p < 0.01$ |

CSA = cross-sectional area; EDD = end-diastolic dimension; ESD = end-systolic dimension; FS = fractional shortening; NS = not significant; P·R/Th = product of systolic pressure and R/Th; R/Th = end-diastolic radius/thickness ratio.

**TABLE II LV End-Diastolic Dimension and Muscle Cross-Sectional Area in Chronic Aortic Regurgitation Before and After Valve Replacement**

| | | Postoperative Period | | |
|---|---|---|---|---|
| | Preop | Early | Mid | Late |
| Group 1 (n = 10) | | | | |
| EDD (cm/m$^2$) | 3.6 ± 0.3 | 2.9 ± 0.3 | 2.7 ± 0.3 | 2.6 ± 0.2 |
| CSA (cm$^2$/m$^2$) | 12.6 ± 2.7 | 12.9 ± 2.9 | 10.1 ± 1.4 | 9 ± 0.5 |
| Group 2 (n = 7) | | | | |
| EDD (cm/m$^2$) | 3.8 ± 0.5 | 3.2 ± 0.6 | 2.9 ± 0.3 | 2.8 ± 0.4 |
| CSA (cm$^2$/m$^2$) | 14.6 ± 1.5 | 14.7 ± 2.5 | 12.4 ± 1.6 | 11.7 ± 1.6 |
| Group 3 (n = 6) | | | | |
| EDD (cm/m$^2$) | 4.3 ± 0.5 | 3.9 ± 0.4 | 4.0 ± 0.3 | 3.7 ± 0.5 |
| CSA (cm$^2$/m$^2$) | 14.3 ± 0.9 | 14.4 ± 0.2 | 13.8 ± 1.2 | 13.2 ± 2.1 |

CSA = cross-sectional area; Early = 7 to 10 days; EDD = end-diastolic dimension; Late = 9 to 12 months; Mid = 3 to 6 months; Preop = preoperative.

<0.001), but the small changes thereafter did not achieve statistical significance. There was no significant change in muscle cross-sectional area at the time of the early postoperative study; cross-sectional area declined thereafter ($p < 0.01$ at 3 to 6 months after operation), and at the time of the late study was normal in all 10 patients in this group. In Group 2, end-diastolic dimension also declined postoperatively ($p < 0.05$ at the early study); there was an additional small decrease in end-diastolic dimension ($p < 0.01$) at the time of the late study so that end-diastolic dimension reached the normal range in all Group 2 patients. Although cross-sectional area declined postoperatively ($p < 0.01$ at the mid study), all 7 patients in this group had persistent LV hypertrophy (cross-sectional area greater than normal) at the time of the late postoperative study. Despite a modest reduction in end-diastolic dimension at the time of the late postoperative study ($p < 0.05$), all

**TABLE III Systolic Time Intervals in Chronic Aortic Regurgitation Before and After Valve Replacement**

| | | Postoperative Period | | |
|---|---|---|---|---|
| | Preop | Early | Mid | Late |
| Group 1 (n = 8) | | | | |
| PEPI (ms) | 111 ± 15 | 171 ± 14 | 153 ± 14 | 141 ± 9 |
| LVETI (ms) | 452 ± 33 | 377 ± 18 | 389 ± 14 | 397 ± 17 |
| QS2I (ms) | 563 ± 35 | 548 ± 22 | 542 ± 12 | 539 ± 14 |
| PEP/LVET | 0.25 ± 0.05 | 0.60 ± 0.06 | 0.47 ± 0.06 | 0.41 ± 0.05 |
| Group 2 (n = 7) | | | | |
| PEPI (ms) | 106 ± 21 | 159 ± 7 | 152 ± 18 | 156 ± 15 |
| LVETI (ms) | 441 ± 24 | 357 ± 33 | 377 ± 22 | 387 ± 16 |
| QS2I (ms) | 548 ± 22 | 517 ± 35 | 530 ± 23 | 542 ± 25 |
| PEP/LVET | 0.25 ± 0.08 | 0.61 ± 0.08 | 0.48 ± 0.11 | 0.47 ± 0.06 |
| Group 3 (n = 4) | | | | |
| PEPI (ms) | 109 ± 19 | 146 ± 32 | 157 ± 24 | 161 ± 9 |
| LVETI (ms) | 427 ± 27 | 392 ± 21 | 381 ± 21 | 390 ± 12 |
| QS2I (ms) | 535 ± 11 | 538 ± 19 | 538 ± 12 | 552 ± 10 |
| PEP/LVET | 0.26 ± 0.08 | 0.49 ± 0.21 | 0.50 ± 0.11 | 0.52 ± 0.10 |

LVETI = LV ejection time index; PEPI = preejection phase index; QS2I = electromechanical systole ($Q\text{-}S_2$); format and other abbreviations as in Table II.

**TABLE IV Fractional Change in LV Posterior Wall Thickness and Mitral E Point to Septal Separation (ESS)**

| | | Postoperative Period | | |
|---|---|---|---|---|
| | Preop | Early | Mid | Late |
| Group 1 | | | | |
| FT (%) (n = 10) | 60 ± 9 | 52 ± 9 | 62 ± 12 | 73 ± 14 |
| ESS (mm) (n = 10) | 11.9 ± 6.1 | 10.0 ± 1.7 | 7.8 ± 1.0 | 6.2 ± 0.9 |
| Group 2 | | | | |
| FT (%) (n = 7) | 56 ± 16 | 47 ± 17 | 56 ± 11 | 65 ± 14 |
| ESS (mm) (n = 6) | 17.8 ± 9.0 | 12.7 ± 4.0 | 10.5 ± 4.0 | 11.0 ± 4.2 |
| Group 3 | | | | |
| FT (%) (n = 6) | 60 ± 8 | 46 ± 18 | 48 ± 13 | 47 ± 13 |
| ESS (mm) (n = 6) | 23.0 ± 2.7 | 23.3 ± 3.7 | 23.8 ± 3.7 | 22.3 ± 7.2 |

FT = fractional thickening of the LV posterior wall; format and other abbreviations as in Table II.

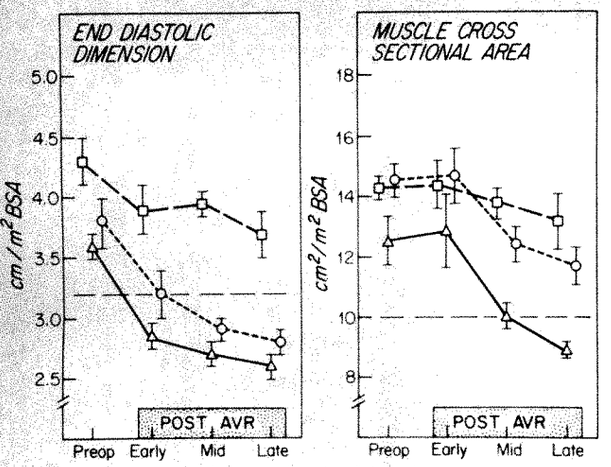



**FIGURE 1.** Serial changes in LV end-diastolic dimension and muscle cross-sectional area. The early, mid, and late postoperative studies were performed at 0.3, 3 to 6, and 9 to 12 months, respectively. All patients in Groups 1 (**triangles**) achieved a normal LV chamber dimension and a normal muscle cross-sectional area. Although LV end-diastolic dimension decreased to normal in Group 2 (**circles**) evidence of persistent LV hypertrophy was present at the late postoperative studies. The patients in Group 3 (**squares**) had persistent LV enlargement and no significant change in muscle cross-sectional area. The **broken horizontal line** indicates the upper limit of normal for these variables. AVR = aortic valve replacement; BSA = body surface area.

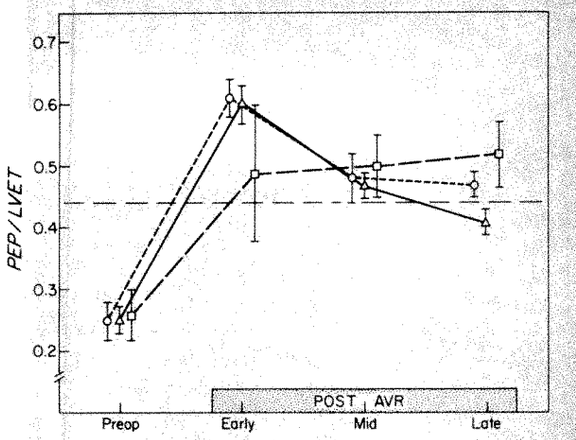



**FIGURE 2.** Serial changes in the LV PEP/LVET ratio. In the early postoperative study, the PEP/LVET ratio increased substantially in Groups 1 (**triangles**) and 2 (**circles**); this change was coincident with the early reduction in LV preload. With the regression of LV hypertrophy (mid to late), the PEP/LVET ratio decreased to normal values in Group 1 and remained moderately increased in Group 2. The PEP/LVET ratio in Group 3 (**squares**) progressively increased to markedly abnormal levels at the time of the late study. Thus, in addition to changes in the PEP/LVET ratio that are related to valve replacement alone, postoperative LV function is temporally related to the presence or absence of changes in preload and LV mass (see text). AVR = aortic valve replacement.

6 patients in Group 3 had persistent LV enlargement. Moreover, there were no significant postoperative changes in muscle cross-sectional area in this group.

**LV systolic time intervals:** The average values for the LV systolic time intervals are presented in Table III, and the serial measurements of the PEP/LVET ratio are shown graphically in Figure 2. Group 1 patients demonstrated an early postoperative increase in PEP ($p < 0.001$), a decrease in the LVET ($p < 0.01$), and an increase in the PEP/LVET ratio ($p < 0.001$). The marked increase in PEP/LVET which was observed at the time of the early study declined thereafter; it was significantly lower at the time of the mid versus early postoperative study ($p < 0.05$) and at the time of the late study ($p < 0.01$). The average values for the LV systolic

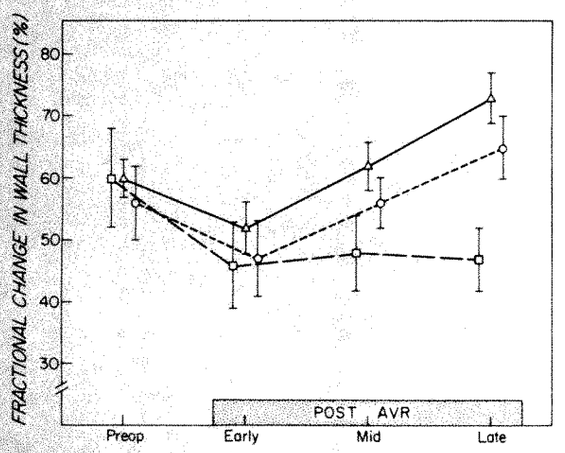



**FIGURE 3.** Serial measurements of the fractional increase in LV posterior wall thickness during systole. In the early postoperative period, there was a tendency for fractional thickening to decrease in all 3 groups. Thereafter, fractional thickening increased only in Groups 1 (**triangles**) and 2 (**circles**); fractional thickening remained low in Group 3 (**squares**). These data are consonant with the systolic time interval data; they indicate that patients with complete regression of LV hypertrophy (Group 1) show gradual improvement in fractional thickening, whereas those with persistent LV enlargement and no regression of LV hypertrophy show persistently depressed thickening.

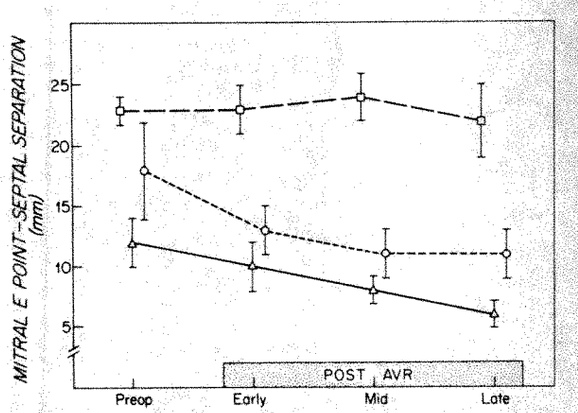



**FIGURE 4.** Serial changes in the echocardiographic ESS. In Group 1 (**triangles**), ESS declined to normal values at the time of the late postoperative study, while Group 3 (**squares**) showed a persistent and marked abnormality of ESS. Group 2 data (**circles**) were intermediate between 1 and 3. Thus, a postoperative normalization of chamber dimension and LV mass is associated with a normal ESS; however, with incomplete regression of LV hypertrophy, ESS may remain abnormal despite a significant decrease in LV size.

time intervals in Group 1 were all within the range of normal at the time of the late postoperative study. Group 2 patients had similar changes in the LV systolic time intervals at the early and mid postoperative studies (PEP, LVET, and PEP/LVET; all p = NS [not significant] versus Group 1). However, the average values for PEP remained above normal and LVET remained below normal at the time of the late postoperative study. The PEP/LVET ratio declined significantly by the time of the late versus early study ($p < 0.01$), but in contrast to the normal ratio achieved in the Group 1 patients, the average PEP/LVET in Group 2 remained above normal. In Group 3, the early increase in PEP and the decrease in LVET did not achieve statistical significance. The early increase in PEP/LVET ($p < 0.05$) was not as pronounced as that observed in Groups 1 and 2; 3 of the 4 patients in Group 3 had a PEP/LVET <0.45, while the ratio in all Group 1 and 2 patients was >0.47. There was a tendency for PEP/LVET to increase thereafter, and by the time of the late study the ratio was significantly higher ($p < 0.05$) than that seen in Group 2.

**Fractional change in LV wall thickness:** Fractional thickening data are shown in Table IV and Figure 3. All 3 groups demonstrated a small decrease in fractional thickening at the time of the early study (all p = NS versus preoperative values). Group 1 patients showed a tendency to increase thereafter so that the late postoperative values for fractional thickening were greater than those measured preoperatively ($p < 0.01$) and early postoperatively ($p < 0.05$). Fractional thickening also increased in Group 2 ($p < 0.01$ early versus late), but in contrast to Group 1, late fractional thickening was not significantly greater than preoperative levels. In Group 3, there was a tendency for fractional thickening to remain lower than preoperatively but this difference did not achieve statistical significance. The late postoperative fractional thickening in Group 3 was significantly lower than that observed in both Groups 1 and 2 (both $p < 0.05$), but the difference between Groups 1 and 2 did not reach statistical significance.

**Mitral E point to septal separation (ESS):** The ESS data are presented in Table IV and Figure 4. In Group 1, there was a gradual decrease in ESS which was statistically significant at the time of the late postoperative study ($p < 0.01$). Although a similar decrease was seen in Group 2, this trend did not reach statistical significance. The ESS was lower in Group 1 than in Group 2 ($p < 0.05$) at the time of the late postoperative study. There was no ESS change in the Group 3 patients, and this index remained markedly abnormal at the time of the late postoperative study.

**Preoperative differences between groups:** There was no significant difference between Groups 1 and 2 for any of the preoperative variables. In contrast, there were highly significant differences between most of the variables in Groups 1 and 2 versus Group 3 (see Table I).

## Discussion

LV function in chronic aortic regurgitation has been studied before and after surgery by a number of investigators, but with few exceptions, postoperative ventricular function has been assessed only at a single point in time. For this reason, time-dependent changes in postoperative function have not generally been appreciated. The serial postoperative data presented herein indicate that LV function is not stable in the first year after surgery and that the observed functional changes are not only related to the aortic valve replacement per se, but also to the 2 major structural changes which usually follow the surgical correction of chronic aortic regurgitation, namely a decrease in LV chamber size and a regression of LV hypertrophy. Our data and those of others indicate that most patients achieve a normal or near normal LV end-diastolic dimension or volume within 1 or 2 weeks of surgery. Subsequently, over the next 6 to 9 months, a significant regression of LV hypertrophy occurs; however, even in the late postoperative studies, many patients have evidence of persistent LV hypertrophy. It therefore appears that there are 3 major structural outcomes after the surgical correction of chronic aortic regurgitation: (1) a normal LV end-diastolic dimension or volume and a normal LV mass, (2) a normal end-diastolic dimension with incomplete regression of hypertrophy, or (3) persistent LV enlargement and no reduction in LV mass. The purpose of the present study was to define the changes in LV function which evolve during the development of these structural changes.

The early functional consequences of an abrupt postoperative decrease in LV end-diastolic dimension are evident in the Group 1 and Group 2 patients. The marked preload reduction which occurred in these 2 groups was associated with a prominent increase in the PEP/LVET ratio, whereas the increase was much less marked in the patients with persistent postoperative LV enlargement (Group 3). We interpret these data to suggest that the early increase in the PEP/LVET is related not only to correction of the valvular leak, but especially to a reduction in LV preload. Over the subsequent months, the PEP/LVET ratio declined in Group 1 and Group 2, while the Group 3 patients demonstrated a tendency to increase (Fig. 2). Thus, this early postoperative abnormality does not predict a poor outcome; in fact, the opposite seems to be true—patients with the highest early PEP/LVET ratio had the most satisfactory late result. Furthermore, our data suggest that the absence of an early postoperative increase in the PEP/LVET ratio might indicate persistent LV enlargement and a poor prognosis.

Externally recorded LV systolic time intervals have been used to assess LV function under a wide variety of clinical conditions, but these measurements have not previously been made serially after aortic valve replacement, as was done in the present study. Our data support the generally accepted idea that the PEP/LVET ratio is influenced by the presence of aortic valve disease independent of LV function. In fact, it appears that there is little relation between the preoperative PEP/LVET and preoperative LV function in chronic aortic regurgitation. However, in the postoperative period the ratio does appear to reflect the functional status of the left ventricle. Correction of aortic regurgitation directly increases aortic diastolic pressure and

decreases the LV stroke volume; consequently, the preejection period increases and the LV ejection time decreases.[33,34] Since the aortic regurgitation was corrected in all 3 groups, this mechanism cannot explain the observed differences between the groups. The effects of anesthesia, cardiopulmonary bypass, and myocardial ischemia have been implicated,[6] but our data indicate that the early postoperative changes in the systolic time intervals are due at least in part to a decrease in LV preload (end-diastolic dimension). Relative to Groups 1 and 2, the small change in preload in Group 3 was associated with relatively smaller changes in the systolic time intervals during the early postoperative period. Similarly, Boudoulas et al[35] suggested that an early postoperative decrease in LV preload contributes to early LV dysfunction after the surgical correction of mitral regurgitation; such changes did not occur after correction of mitral stenosis. These investigators also emphasized the benign nature of this temporary postoperative increase in the PEP/LVET ratio.

The systolic time interval data are supported by the mitral ESS and fractional thickening data which also indicate that early LV dysfunction should not be taken to indicate long-term functional abnormalities. In spite of a decrease in heart size in Groups 1 and 2, the mitral ESS remained abnormal in the early postoperative studies. While ESS as an index of global LV function has been said to be relatively independent of heart size,[28-30] it remains possible that the early ESS may have been greater if not for the early decrease in end-diastolic dimension. The fractional change in LV wall thickness showed a tendency to decline in the early studies, and in general these FT data tend to parallel the PEP/LVET data. All 3 indexes of LV function improved by the time of the late study. These findings are consonant with published radionuclide data that indicate a temporary decrease in the LV ejection fraction during the early postoperative period. Boucher et al[21] reported data from 7 patients in whom the systolic ejection fraction fell from a preoperative average of 56 to 42% at 2 to 4 weeks and subsequently increased to 52% at 1 to 2 years after surgery.[21]

The functional consequences of a gradual regression of LV hypertrophy are also apparent in the serial studies of these 3 groups of patients. As we and others have previously reported, there is no significant change in muscle cross-sectional area during the early postoperative period.[9,15] Thereafter, a significant decrease in cross-sectional area occurred only in Groups 1 and 2. Those patients who eventually achieved a normal muscle cross-sectional area (Group 1) achieved normal values for all 3 indexes of LV function. The patients with persistent LV enlargement and no regression of LV hypertrophy had marked and persistent abnormalities of all 3 indexes of LV function. The Group 2 values were intermediate. It appears, therefore, that a gradual regression of volume overload hypertrophy is associated with a parallel improvement in ventricular function.

Having thus defined the postoperative time course of changes in LV function in 3 distinct subgroups of patients, we then searched for differences in the preoperative data (Table I). There were no significant differences between the preoperative parameters in Group 1 versus those in Group 2. Because the muscle cross-sectional area tended to be higher in Group 2 than in Group 1, it is possible that the Group 2 patients had incomplete regression of LV hypertrophy simply because they started with higher values. However, we did not find a statistically significant difference in cross-sectional area between these 2 groups. In contrast, there were significant differences between several of the parameters in Group 1 versus 3 and Group 2 versus 3. In general, the Group 3 patients had larger values for end-diastolic and end-systolic dimension, higher values for relative wall thickness, and reduced values for fractional shortening. Our findings and those of others confirm the utility of echocardiography in the identification of high-risk patients with chronic aortic regurgitation.[9,18,19,36,37]

We conclude that the early postoperative LV dysfunction which is seen in many patients after correction of chronic aortic regurgitation is a temporary finding, due to an acute reduction in LV preload. The gradual improvement in LV function which occurs over the subsequent 6 to 9 months is at least partly related to the regression of LV hypertrophy. Since LV volume, mass, and function are not stable during most of the first year, the optimal assessment of LV function requires serial studies during this period.

## References


1. **Gault JH, Covell JW, Braunwald E, Ross J Jr.** Left ventricular performance following correction of free aortic regurgitation. Circulation 1970;42: 773–780.
2. **Lee SJK, Haraphongse M, Rossall RE, Fraser RS.** Circulatory changes in severe aortic regurgitation before and after surgical correction. Am J Cardiol 1971;28:442–448.
3. **Hirshfeld JW, Epstein SE, Roberts AJ, Glancy DL, Morrow AG.** Indices predicting long-term survival after valve replacement in patients with aortic regurgitation and patients with aortic stenosis. Circulation 1974;50: 1190–1199.
4. **Ross J Jr.** Adaptations of the left ventricle to chronic volume overload. Circ Res 1974;34:Suppl II:64–70.
5. **Burggraf GW, Craige E.** Echocardiographic studies of left ventricular wall motion and dimensions after valvular heart surgery. Am J Cardiol 1975; 35:473–479.
6. **Seabra-Gomes R, Sutton R, Parker DJ.** Left ventricular function after aortic valve replacement. Br Heart J 1976;38:491–496.
7. **Venco A, St. John Sutton MG, Gibson DG, Brown DJ.** Noninvasive assessment of left ventricular function after correction of severe aortic regurgitation. Br Heart J 1976;38:1324–1331.
8. **Kennedy JW, Doces J, Stewart DK.** Left ventricular function before and following aortic valve replacement. Circulation 1977;56:944–950.
9. **Gaasch WH, Andrias CW, Levine HJ.** Chronic aortic regurgitation: the effect of aortic valve replacement on left ventricular volume, mass, and function. Circulation 1978;58:825–836.
10. **Pantely G, Morton M, Rahimtoola SH.** Effects of successful, uncomplicated valve replacement on ventricular hypertrophy, volume, and performance in aortic stenosis and in aortic incompetence. J Thorac Cardiovasc Surg 1978;75:383–391.
11. **Schwarz F, Flameng W, Schaper J, Hehrlein F.** Correlation between myocardial structure and diastolic properties of the heart in chronic aortic valve disease: effects of corrective surgery. Am J Cardiol 1978;42:895–903.
12. **Schwarz F, Flameng W, Thormann J, Sesto M, Langebartels F, Hehrlein F, Schlepper M.** Recovery from myocardial failure after aortic valve replacement. J Thorac Cardiovasc Surg 1978;75:854–864.
13. **Borer JS, Rosing Dr, Kent KM, Bacharach SL, Green MV, McIntosh CJ, Morrow AG, Epstein SE.** Left ventricular function at rest and during exercise after aortic valve replacement in patients with aortic regurgitation. Am J Cardiol 1979;44:1297–1305.
14. **Krayenbuehl HP, Turina M, Hess OM, Rothlin M, Senning A.** Pre and postoperative left ventricular contractile function in patients with aortic valve disease. Br Heart J 1979;41:204–213.
15. **Schuler G, Peterson KL, Johnson AD, Francis G, Ashburn W, Dennish G, Baily P, Ross J.** Serial noninvasive assessment of left ventricular hypertrophy and function after surgical correction of aortic regurgitation. Am J Cardiol 1979;44:585–594.
16. **Schwarz F, Flameng F, Langebartels F, Sesto M, Walter P. Schlepper M.** Impaired left ventricular function in chronic aortic valve disease: survival and function after replacement by Bjork-Shiley prosthesis. Circulation

# Radionuclide Ventriculographic Study of Adaptations To Exercise in Aortic Regurgitation

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**Exercise-gated radionuclide ventriculography has been proposed as a method to evaluate cardiac reserve in patients with aortic regurgitation (AR). Characterization of ventricular function, however, in AR is complicated by the dynamic nature of the leak in individual patients and by variations in severity among patients. Twenty patients with isolated AR were studied to assess the effects of exercise on the regurgitant index. The regurgitant index (left ventricular ÷ right ventricular stroke counts) estimates the severity of the leak. The regurgitant index at rest was significantly higher in patients with AR than in patients without AR (3.46 ± 1.25 versus 1.08 ± 0.16, $p < 0.001$). In patients with AR, the regurgitant index decreased during exercise to 2.6 ± 0.8 ($p < 0.001$), whereas it did not change in the control group (1.16 ± 0.21, difference not significant). Further, in patients with AR, the greater the regurgitant index at rest, the greater the decrease during exercise ($y = 0.56x - 1.08$, $r = 0.78$, $p < 0.001$). End-diastolic counts and stroke count responses from rest to exercise were highly variable, but were explained in part by the decreasing regurgitant index. These data support previous catheterization studies and confirm gated radionuclide ventriculography as a useful tool for monitoring adaptations to exercise in AR.**

The timing of appropriate therapeutic intervention in aortic regurgitation is controversial.[1-3] Because ventricular dysfunction in AR is slowly progressive,[4,5] noninvasive technology capable of serial, comprehensive, and accurate evaluation of ventricular functional reserve would be helpful in resolving this controversy. Characterization of functional reserve is complicated by the dynamic nature of the volume load in individual patients and the variations in severity among patients. Gated blood pool scanning at rest has been applied to estimate ventricular volume, systolic function,[6,7] and the magnitude of regurgitation by means of the regurgitant index (left ventricular ÷ right ventricular stroke counts).[8-12] However, it is reasonable to assume that surgical intervention at a time when resting function is preserved but exercise reserve is somewhat diminished would be most appropriate.[13-15] To date, radionuclide studies during exercise in patients with AR have emphasized the ejection fraction response.[13,14] The present study was undertaken to characterize more completely the rest to exercise response in patients with AR with use of gated blood pool scanning.

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## Methods

The study group consisted of 20 consecutive patients referred for exercise radionuclide ventriculographic evaluation of isolated, chronic aortic regurgitation. The determination of an isolated valvular abnormality was determined in 10 patients with cardiac catheterization. No catheterized patient had >30% stenosis of a major coronary artery. The remaining 10 patients had isolated diastolic murmurs of aortic regurgitation, and diastolic fluttering of the mitral valve on echocardiography. Because these patients had no symptoms of chest discomfort, the maximal probability of coronary artery disease in any single patient was <4% based on age, sex, symptomatic status, and electrocardiographic stress testing.[16] Sinus rhythm was a prerequisite for entry into the study.

Six patients with chest pain syndromes but no structural or functional abnormalities at cardiac catheterization served as a normal control group for the radionuclide ventriculographic response to exercise.

Five patients with significant coronary artery disease and elevated resting left ventricular end-diastolic pressure at catheterization, but no valvular abnormalities, served as an additional control group for the effects of exercise on the regurgitant index.

**TABLE I Clinical Data**

| Case | Age (yr) & Sex | NYHA Clinical Class | Work Load (kpm) | Exercise End-Diastolic Count (% of Control) | Exercise Stroke Count (% of control) | Ejection Fraction | | Regurgitant Index | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Rest | Exercise | Rest | Exercise |
| 1 | 61 M | I | 450 | 101 | 98 | 59 | 57 | 3.17 | 1.37 |
| 2 | 49 F | III | 300 | 91 | 88 | 73 | 70 | 4.82 | 3.57 |
| 3 | 38 M | I | 900 | 107 | 124 | 68 | 79 | 2.74 | 2.66 |
| 4 | 64 F | III | 300 | 91 | 70 | 56 | 43 | 3.31 | 1.96 |
| 5 | 68 F | III | 225 | 96 | 87 | 69 | 63 | 2.64 | 1.90 |
| 6 | 28 F | I | 300 | 132 | 113 | 62 | 53 | 2.52 | 4.00 |
| 7 | 53 M | I | 450 | 108 | 110 | 59 | 60 | 2.02 | 2.02 |
| 8 | 67 M | II | 450 | 105 | 116 | 79 | 88 | 3.47 | 3.07 |
| 9 | 62 M | II | 300 | 96 | 77 | 64 | 52 | 5.97 | 3.98 |
| 10 | 54 M | I | 600 | 76 | 65 | 59 | 51 | 5.16 | 2.97 |
| 11 | 66 M | II | 600 | 101 | 92 | 39 | 36 | 1.27 | 1.28 |
| 12 | 37 M | I | 600 | 73 | 82 | 65 | 72 | 4.19 | 2.95 |
| 13 | 58 M | III | 300 | 90 | 81 | 48 | 43 | 3.46 | 2.46 |
| 14 | 50 F | III | 150 | 111 | 119 | 60 | 64 | 2.19 | 2.13 |
| 15 | 34 M | I | 900 | 98 | 102 | 79 | 82 | 4.81 | 3.38 |
| 16 | 33 M | II | 600 | 122 | 127 | 75 | 79 | 4.14 | 2.98 |
| 17 | 17 M | I | 900 | 93 | 106 | 69 | 79 | 3.02 | 2.07 |
| 18 | 43 F | III | 450 | 102 | 91 | 81 | 72 | 2.76 | 2.46 |
| 19 | 38 F | I | 300 | 64 | 68 | 75 | 80 | 5.20 | 3.02 |
| 20 | 53 M | I | 150 | 110 | 114 | 49 | 51 | 2.17 | 2.10 |
| Mean ± SD | 49 ± 15 | ... | 431 ± 215 | 98.3 ± 16 NS versus control | 96.5 ± 19 NS versus control | 64 ± 11 | 64 ± 15 NS | 3.46 ± 1.25 | 2.62 ± 0.78 p <0.001 |

NYHA = New York Heart Association.

## Radionuclide Determination of Left Ventricular Function

**Blood pool labelling with technetium-99m:** Red blood cells were labelled with 25 mCi of technetium-99m using an in vivo method. Percent labelling by this method was 69.8 ± 14.6 (mean ± standard deviation [SD]) and the effective half-life of the technetium-99m red blood cell complex was 4.5 hours.

**End-diastolic counts, end-systolic counts, stroke counts, count cardiac output, and ejection fraction:** Data were acquired using a mobile, standard field of view gamma camera with a high sensitivity collimator (Picker, North Ford, Connecticut) interfaced with a minicomputer dedicated to the acquisition and processing of nuclear medicine data (Digital Equipment, Marlborough, Massachusetts). Data were acquired in the modified left anterior oblique projection that best separated the left and right ventricles and left ventricular activity from left atrial activity. Studies from this laboratory[17] have shown that averaging the data from multiple, relatively brief acquisitions more effectively reduces statistical error than prolonging the time of a single acquisition, while maintaining high intra- and interobserver reproducibility. Therefore, for the present study, triplicate baseline and duplicate exercise acquisitions were obtained, and radionuclide data were averaged from these acquisitions. Each acquisition consisted of 28 frames per R-R cycle and a total of approximately $3 \times 10^6$ counts. Data were acquired in the zoom mode in 64 × 64 matrices. Typical acquisition times were 90 seconds per study depending on body habitus and labelling efficiency.

End-diastolic count data were determined by adding the first 3 frames of the 28-frame study. An end-diastolic region of interest was computer generated, and the minimal count rate in the time-activity curve from this region identified. The counts in this minimal frame, and those from frames immediately preceding and following it were summed and used as end-systolic count data. End-systolic and paraventricular regions of interest were then computer-generated and the unsmoothed data from within these 3 regions of interest plotted over the course of the cardiac cycle. Background-corrected end-diastolic and end-systolic count data were calculated from mathematically smoothed time-activity curves and corrected for frame duration and normalized to 20 ms. Stroke counts were determined as the difference between end-diastolic and end-systolic counts and count cardiac output was determined as the product of stroke counts and heart rate. All count data were then corrected for the 4.5 hour effective half-life of the technetium-99m red blood cell complex. In this way, all count data for each patient were referrable to the initial data acquisition. In this laboratory, in patients without valvular regurgitation, the correlation between

**TABLE II Exercise Testing**

| Group | Exercise Duration (min) | Work Load (kpm) | Heart Rate (beats/min) | | Systolic Blood Pressure (mm Hg) | | Diastolic Blood Pressure (mm Hg) | |
|---|---|---|---|---|---|---|---|---|
| | | | Rest | Exercise | Rest | Exercise | Rest | Exercise |
| Aortic regurgitation (n = 20) | 12 ± 7 | 431 ± 215 | 73 ± 17 | 137 ± 26* | 145 ± 16 | 211 ± 29* | 72 ± 14 | 89 ± 13* |
| Normals (n = 6) | 14.8 ± 7 | 500 ± 182 | 75 ± 11 | 140 ± 18* | 127 ± 9 | 195 ± 39* | 84 ± 12 | 100 ± 13† |
| Coronary artery disease (n = 5) | 10.4 ± 7 | 390 ± 171 | 89 ± 21 | 140 ± 20* | 124 ± 12 | 162 ± 10* | 84 ± 16 | 103 ± 15† |

* $p < 0.001$ versus rest; † $p < 0.02$ versus rest.

changes in stroke counts and in thermodilution stroke volume during intervention is r = 0.90, p <0.001.[18] Because gated radionuclide ventriculography measures total ventricular stroke volume, characterization of the rest-exercise response in AR also requires an estimate of the magnitude of the regurgitant volume.

Left ventricular ejection fraction was calculated according to the formula LVEF = (ED − ES)/ED, where ED = end-diastolic counts and ES = end-systolic counts, corrected for background. Correlation between left ventricular ejection fraction determined with this method and contrast cineangiography in this laboratory has been demonstrated to be r = 0.90, p <0.001.[19]

### Calculation of Regurgitant Index

The regurgitant index (LV ÷ RV stroke counts) was determined with use of operator-defined fixed end-diastolic regions of interest without background subtraction. This method estimates the regurgitant fraction determined with electromagnetic flow meter in an animal model and by catheterization techniques in patients with high intra- and interobserver reproducibility.[8,9,11] The correlation between radionuclide regurgitant index and catheterization regurgitant fraction for the patients in this study was r = 0.78, p <0.001.

### Exercise Protocol

Exercise was performed on a bicycle ergometer imaging table combination (Nuclear Associates, Carle Place, New York), which allowed the subject to exercise vigorously while maintaining a stable position under the gamma camera. For exercise patients are placed in the supine position with their feet up in pedals so that their legs are held approximately 15 cm above the level of the heart. We have found no consistent difference in end-diastolic counts, end-systolic counts, stroke counts, cardiac output, or ejection fraction with feet up when compared with positioning of the legs at the level of the heart. Ten minutes after the patient was in this starting position, triplicate baseline data were acquired. Bicycle exercise was then begun at 150 kpm. Pedal speed was held constant at 60 to 70 rpm. One minute after the onset of exercise, duplicate consecutive gated studies were acquired. Immediately on completion of the second acquisition, the work load was increased by 150 kpm. One minute later an acquisition was again initiated. Exercise levels were increased until termination of the study. Criteria for terminating the study were extreme fatigue, severe angina, shortness of breath, complex ventricular arrhythmias, or a decrease in systolic blood pressure. Care was taken to exercise each patient to his or her symptomatic maximum. Pulse, blood pressure, and electrocardiograms were recorded each minute throughout exercise.

### Statistical Analysis

All data are presented as means ± 1 standard deviation. Changes in count data are expressed as percent of supine rest. Comparisons among groups were done using a grouped *t* test. Comparisons in individual subjects from rest to peak exercise were done using paired *t* tests. Relations between variables were tested with linear regression and the significance of these relations were tested by one-way analysis of variance.[20] A p value ≤0.05 was considered significant.

## Results

**Patient group:** There were 13 men and 7 women (aged 49 ± 15 years) in the study group. Ten patients were in New York Heart Association[21] clinical class I, 4 patients were in class II, and 6 patients were in class III (Table I). At the time of the study, 8 patients were receiving digitalis preparations, and 3 were taking antiarrhythmic agents. All other cardioactive drugs were discontinued for the purpose of testing.

The 6 subjects (4 men and 2 women) with chest pain but no demonstrable coronary or valvular abnormalities at cardiac catheterization averaged 44 years of age. All 5 patients with coronary artery disease (4 men and 1 woman), mean age 51 years, had previous myocardial infarctions, elevated left ventricular end-diastolic pressures at rest (18 ± 4 mm Hg), and multivessel coronary artery disease. No control subject was taking medication at the time of the test.

**Exercise testing (Table II):** For the study group, exercise duration averaged 12 ± 7 minutes and peak work load 431 ± 215 kpm. Eighteen patients stopped exercising because of leg fatigue, whereas 2 stopped because of shortness of breath. Heart rate increased significantly with exercise from 73 ± 17 to 137 ± 26 beats/min (p <0.001) or to 84 ± 13% of maximal predicted heart rate. Systolic blood pressure increased significantly from 145 ± 16 to 211 ± 29 mm Hg (p <0.001) as did diastolic pressure (72 ± 14 to 89 ± 13, p <0.001).

For the normal control group, the heart rate was 75 ± 11 beats/min at rest and increased to 140 ± 18 beats/min (p <0.001) or 85 ± 4% of maximal predicted heart rate with exercise. Systolic blood pressure increased from 127 ± 9 to 195 ± 39 mm Hg (p <0.001) as did diastolic blood pressure, from 84 ± 12 to 100 ± 13 mm Hg (p <0.02). Exercise duration averaged 14.8 ± 6.7 minutes and peak work load 500 ± 182 kpm.

For the patients with coronary artery disease, the heart rate was 89 ± 21 beats/min at rest and increased significantly with exercise to 140 ± 20 beats/min (p <0.001) or to 83 ± 11% of the maximal predicted heart rate. Systolic blood pressure was 124 ± 12 mm Hg at rest and increased to 162 ± 9.6 mm Hg (p <0.001). Diastolic blood pressure also increased from 84 ± 16 to 103 ± 15 mm Hg (p <0.02). Exercise duration averaged 10.4 ± 7 minutes and peak work load 390 ± 171 kpm.

### Radionuclide Count Data

**Normal control:** With exercise, end-diastolic counts increased to 123 ± 20% of control values (p <0.05). Stroke counts and count cardiac output increased for all subjects (p <0.001), averaging 148 ± 28 and 252 ± 47% of control values. Ejection fraction also increased in all subjects, on the average from 72 ± 10 to 82 ± 11% (p <0.02).

**Aortic regurgitation (Table I):** The end-diastolic count response to exercise in patients with aortic regurgitation was highly variable, averaging 98.3 ± 16% of the resting value (p = NS [not significant], range 64 to 132%). Similarly, stroke count response was variable, averaging 96.5 ± 19% (p = NS, range 65 to 127%) of control values. Ejection fraction at rest was 64 ± 11 and 64 ± 16% at peak exercise (p = NS). Again responses were variable, ranging from an 11 unit increase to a 12 ejection fraction unit decrease. Count cardiac output increased in all patients, on average 89 ± 57% (p <0.001, range 123 to 316% of control values).

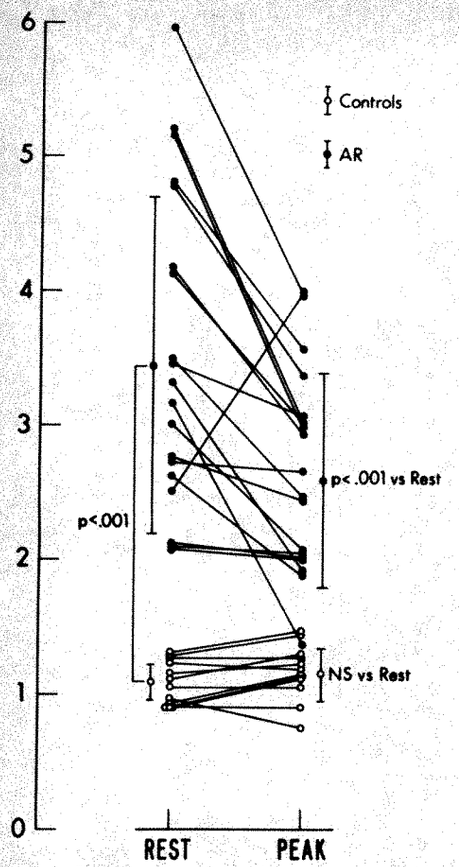



**FIGURE 1.** Regurgitant index at rest and during peak exercise in patients with aortic regurgitation (AR) and in the normal and coronary disease control group. At rest, the regurgitant index was significantly greater ($p < 0.001$) in patients with AR than in the control patients. With exercise, the regurgitant index decreased ($p < 0.001$) in patients with AR but did not change in the control group.

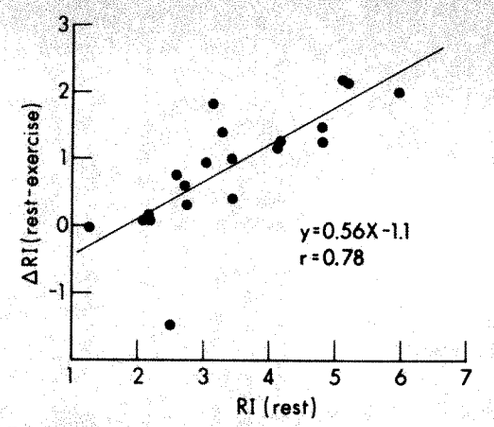



**FIGURE 2.** Relation between the regurgitant index (RI) at rest and its response to exercise. The greater the RI at rest, the greater the decrease with exercise ($r = 0.78$, $p < 0.001$).

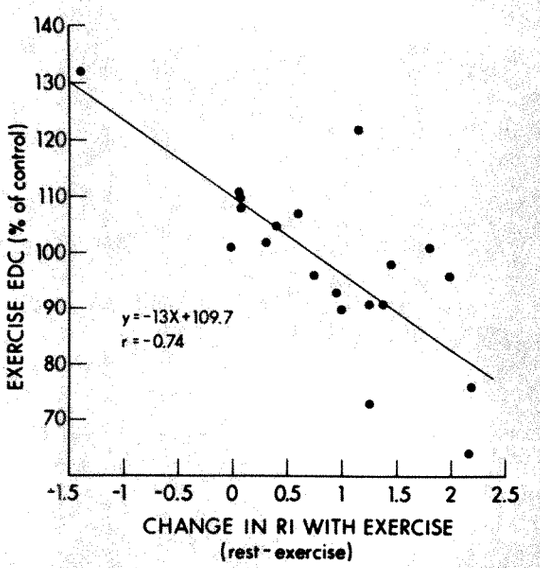



**FIGURE 3.** Relation between the decrease in the regurgitant index (RI) and the end-diastolic count (EDC) response. As the regurgitant index decreased (or increased in 1 patient) so did end-diastolic counts ($p < 0.001$).

**Regurgitant index:** As the regurgitant index at rest and during exercise was similar in normal subjects and patients with coronary disease, the 2 groups of patients were combined for analysis. The regurgitant index was $1.08 \pm 0.16$ at rest, and with exercise did not differ significantly: $1.16 \pm 0.21$.

In contrast, in patients with AR, the regurgitant index at rest was greater than in the control group ($3.46 \pm 1.25$, $p < 0.001$) and decreased with exercise to $2.6 \pm 0.8$ ($p < 0.001$) (Fig. 1, Table I). The magnitude of the decrease in the regurgitant index was directly related to the regurgitant index at rest as described by the equation $y = 0.56x - 1.08$, $r = 0.78$, $p < 0.001$ (Fig. 2).

**Impact of changing regurgitant index during exercise on radionuclide ventriculographic count data and ejection fraction in patients with AR:** With exercise the percent change in end-diastolic counts was directly related to changes in the regurgitant index (Fig. 3) as given by the equation $y = -13x + 110$, $r = -0.74$, $p < 0.001$; that is, as the regurgitant index decreased, so did the end-diastolic counts, explaining in part the variability in the end-diastolic count response in this group. Furthermore, the stroke count response to exercise was related to the end-diastolic count response. Linear regression analysis revealed a correlation of $r = 0.81$, $y = 0.98x - 0.22$, $p < 0.001$ (Fig. 4). However, changes in ejection fraction with exercise did not correlate with the end-diastolic count response.

## Discussion

The purpose of this study was to examine in detail the ventricular response to exercise in AR using gated radionuclide ventriculography. The most striking finding was great interpatient variability resulting in no change in mean end-diastolic counts, stroke counts, or ejection fraction with exercise.

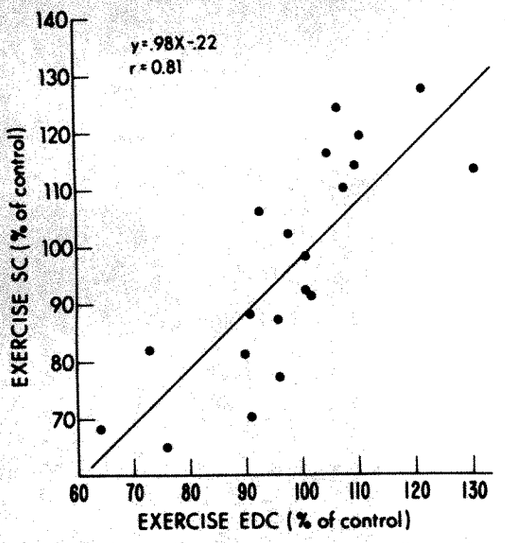



**FIGURE 4.** Relation between changes in end-diastolic counts and total ventricular stroke counts with exercise in patients with aortic regurgitation. Changes in stroke counts (SC) were related to changes in end-diastolic counts (EDC) ($p < 0.001$).

In normal subjects, all 3 radionuclide variables increase with exercise, as shown in this and other studies.[22,23] The observed variability in stroke counts and end-diastolic counts in patients with AR[24] may in part represent physiologic adaptations to varying degrees of regurgitation. The greater the regurgitant index at rest, the greater the decrease with exercise. The decrease in regurgitant index with stress partly accounted for the changes in end-diastolic counts. The stroke count changes were, in turn, related to changes in the end-diastolic counts. For the group, because the regurgitant index decreased and stroke counts did not change, forward stroke output per beat necessarily increased, a "normal" response to exercise.[25,26] Therefore, a more complete understanding of the response to exercise in AR should include an estimation of the regurgitant volume both at rest and during exercise.

Gated radionuclide ventriculography is being increasingly applied to the study of patients with AR. In addition to the variables of end-diastolic volume, stroke volume, and ejection fraction, several groups have reported on the regurgitant index, an estimate of the severity of valvular regurgitation.[8–12] In our study, in the control group at rest the regurgitant index was 1.08 ± 0.16, similar to values previously reported for groups without left heart regurgitant lesions or left to right shunts.[10–12] Values greater than unity reflect the inability of the method to completely separate atrial from ventricular activity. During exercise in the control group, there was no significant change in the regurgitant index. In contrast, in patients with AR, the regurgitant index averaged 3.46 at rest (compatible with moderate to severe regurgitation[10]), and decreased significantly with stress. In a preliminary report, Horowitz et al[27] also noted that the regurgitant index decreases during isotonic exercise in patients with AR.

The decrease in the regurgitant index with a consequent decrease in end-diastolic volume has been suggested clinically for more than a century as the mechanism behind preservation of exercise tolerance[28] and has previously been demonstrated with use of catheterization techniques. Levinson et al[29] used indocyanine green dye to show that the regurgitant fraction decreased from rest to exercise in patients with AR. Similar results have been reported in patients with combined aortic stenosis and regurgitation.[30] Bristow et al[31] used thermal techniques to demonstrate a reduction in end-diastolic volume during exercise in most patients with AR. Borer et al,[13] using gated radionuclide techniques, noted a 6% reduction on average in end-diastolic volume in patients with severe AR. Recently, Dehmer et al[24] reported highly variable gated radionuclide end-diastolic volume responses to supine exercise in patients with AR, with several patients showing a marked decrease.

Thus, using divergent methods several groups have demonstrated that left ventricular end-diastolic volume can decrease during exercise in patients with AR. The shortened diastolic filling period during exercise coupled with a lowered peripheral resistance are postulated mechanisms leading to decreased backflow and diastolic volumes.[29] Judge et al[32] used rapid atrial pacing to shorten the diastolic filling period and demonstrated decreases in end-diastolic volume (contrast angiographic), end-diastolic pressure, and regurgitant flow per beat in most patients. The ejection fraction also decreased. More recently, Firth et al[33] studied the effects of increments in atrial pacing rate among patients with AR. The regurgitant volume was calculated as the difference between gated radionuclide ventriculographic total stroke volume and simultaneously measured thermodilution forward stroke volume. Progressive increases in heart rate resulted in progressive decreases in regurgitant flow per stroke and end-diastolic volume. However, ejection fraction and regurgitant fraction responses were highly variable and unchanged for the group.

We have no ready explanation for the 1 patient in our series who showed an increase in end-diastolic volume and regurgitant index with stress. Noninvasive data suggested the presence of isolated AR, and she remains in clinical class I at 1 year of follow-up. Theoretically, an increase in regurgitant valve area with exercise could explain these findings.[32]

As noted earlier, the phenomenon of decreasing regurgitant index during exercise provides an explanation for the dramatic changes in end-diastolic counts seen in our patients with AR. Although not dictating the ejection fraction response (no correlation in this study or that of Dehmer et al[24]), large changes in end-diastolic counts may compromise the ejection fraction as an index of contractility.[34,35] In normal hearts, the tachycardia and increased afterload of exercise tend to decrease the ejection fraction. These effects are offset by increased venous return and enhanced contractility, resulting in an increase in ejection fraction.[36] In patients with AR, the effect of tachycardia may be greatly exaggerated if end-diastolic volume decreases precipi-

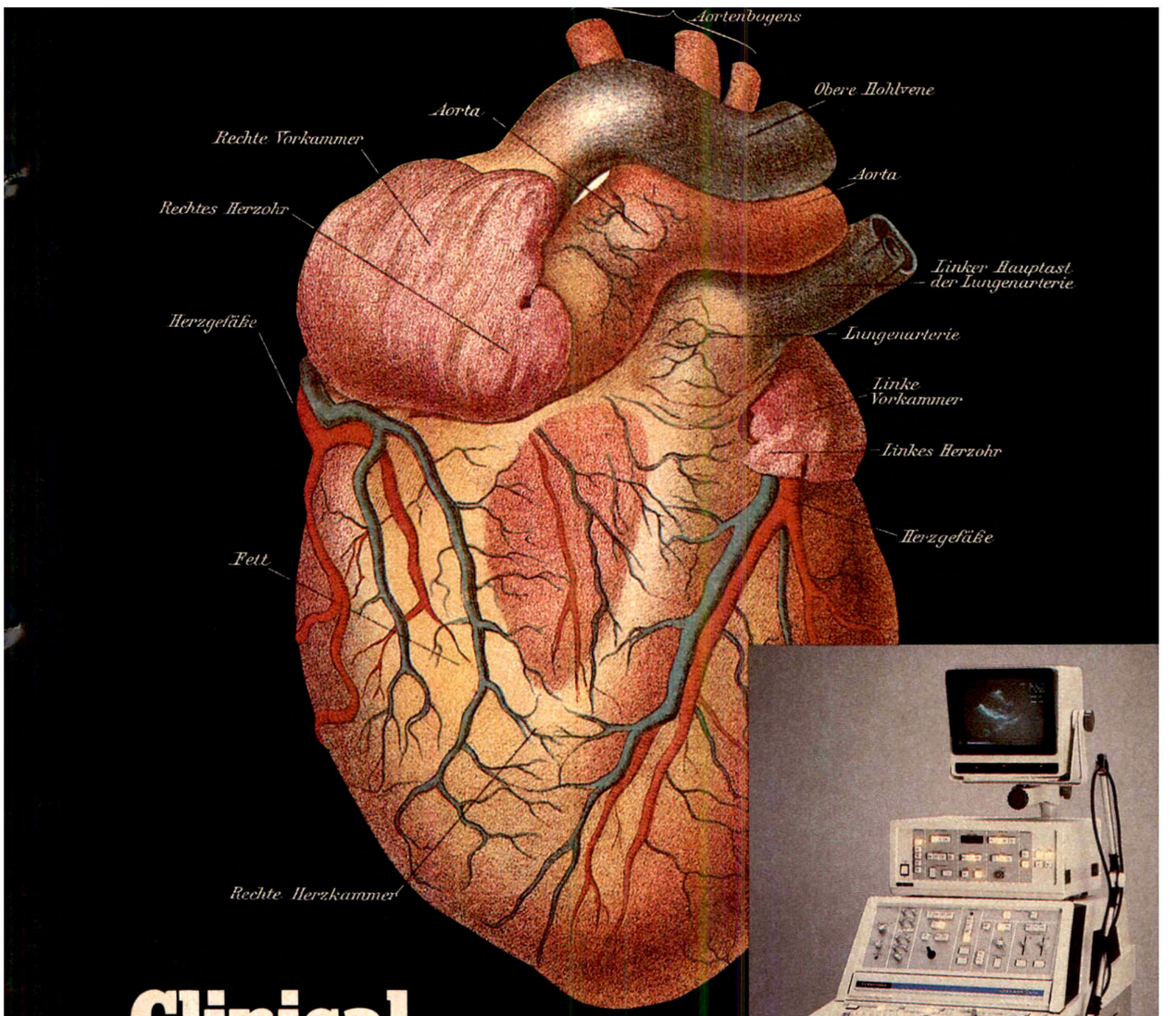
tously, as might be anticipated in patients who have large regurgitant indexes at rest. With such large volume loads at rest, when gross ventricular stroke volume is nearly maximized, failure of the ejection fraction to increase or even a frank decrease with exercise may reflect the influence of decreasing end-diastolic volume rather than decreased contractility as such.

*In summary*, we have shown that radionuclide ventriculography can evaluate the physiology of the ventricular response to exercise in AR, as previously demonstrated with more invasive techniques. Measurement of radionuclide regurgitant index at rest and during exercise and tracking the end-diastolic volume and ejection fraction responses will help to characterize these patients more completely.

**Acknowledgment:** We thank Nancy Nelson for her help in preparing this manuscript.

## References

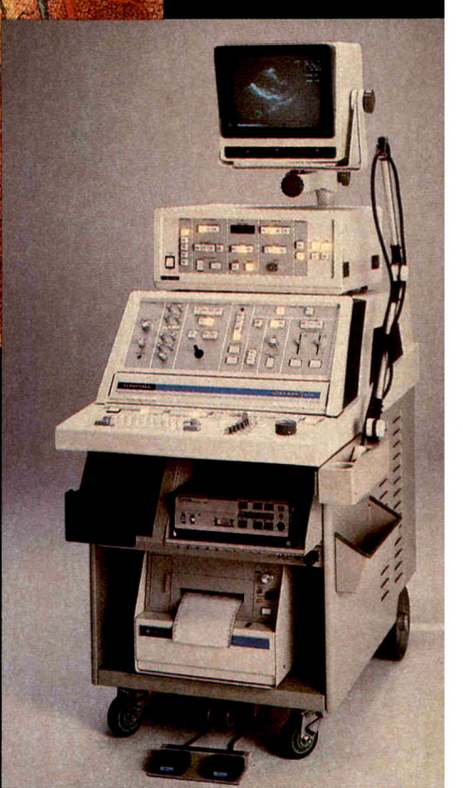

1. **Selzer A.** Cardiac valve replacement: an unanswered question. Am J Cardiol 1976;37:322–324.
2. **Rahimtoola SH.** Early valve replacement for preservation of ventricular function? Am J Cardiol 1977;40:472–475.
3. **O'Rourke RA, Crawford MH.** Timing of valve replacement in patients with chronic aortic regurgitation. Circulation 1980;61:493–495.
4. **Spagnuolo M, Kloth H, Taranta A, Doyle E, Pasternack B.** Natural history of rheumatic aortic regurgitation. Criteria predictive of death, congestive heart failure and angina in young patients. Circulation 1971;44:368–380.
5. **Henry WL, Bonow RO, Rosing DR, Epstein SE.** Observations on the optimum time for operative intervention for aortic regurgitation. II. Serial echocardiographic evaluation of asymptomatic patients. Circulation 1980;61:484–492.
6. **Bacharach SL, Green MV, Borer JS, Douglas MA, Ostrow HG, Johnston GS.** A real-time system for multi-image gated cardiac studies. J Nucl Med 1977;18:79–84.
7. **Slutsky R, Karliner J, Ricci D, Kaisir R, Pfisterer M, Gordon D, Peterson K, Ashburn W.** Left ventricular volumes by gated equilibrium radionuclide angiography: a new method. Circulation 1979;60:556–564.
8. **Rigo P, Alderson PO, Robertson RM, Becker LC, Wagner HN.** Measurement of aortic and mitral regurgitation by gated cardiac blood pool scans. Circulation 1979;60:306–312.
9. **Baxter RH, Becker LC, Alderson PO, Rigo P, Wagner HN, Weisfeldt ML.** Quantification of aortic valvular regurgitation in dogs by nuclear imaging. Circulation 1980;61:404–410.
10. **Lam W, Pavel D, Byrom E, Sheikh A, Best D, Rosen K.** Radionuclide regurgitant index: value and limitations. Am J Cardiol 1981;47:292–298.
11. **Urquhart J, Patterson RE, Packer M, Goldsmith SJ, Horowitz SF, Litwak R, Gorlin R.** Quantification of valve replacement surgery. Am J Cardiol 1981;47:287–291.
12. **Bough EW, Gandsman EJ, North DL, Shulman RS.** Gated radionuclide angiographic evaluation of valve regurgitation. Am J Cardiol 1980;46:423–428.
13. **Borer JS, Bacharach SL, Green MV, Kent KM, Henry WL, Rosing DR, Seides SF, Johnston GS, Epstein SE.** Exercise-induced left ventricular dysfunction in symptomatic and asymptomatic patients with aortic regurgitation: assessment with radionuclide cineangiography. Am J Cardiol 1978;42:351–357.
14. **Borer JS, Rosing DR, Kent KM, Bacharach SL, Green MV, McIntosh CJ, Morrow AG, Epstein SE.** Left ventricular function at rest and during exercise after aortic valve replacement in patients with aortic regurgitation. Am J Cardiol 1979;44:1297–1305.
15. **Wexler J, Steingart RM, Blaufox D.** Assessment of ventricular function: physiological interventions. Sem Nucl Med 1981;11:68–79.
16. **Diamond GA, Forrester JS.** Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300:1350–1358.
17. **Ganz W, Wexler J, Rabinowitz A, Brenner AI, Steingart R, Blaufox D.** Methods of improving the precision of left ventricular volume and ejection fraction determination (abstr). J Nucl Med 1980;21:48.
18. **Steingart RM, Gross R, Wexler J, Greenberg M, Weinstein L.** Validation of stroke volume determinations by radionuclide ventriculography during intervention (abstr). Circulation 1981;64:Suppl IV:IV-106.
19. **Ganz W, Wexler J, Brenner AI, Bontemps R, Steingart R, Blaufox D.** Variability of resting gated ejection fraction (abstr). J Nucl Med 1980;21:163.
20. **Zar JH.** Biostatistical Analysis. Englewood Cliffs, NJ: Prentice-Hall, 1974:101–227.
21. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for the Diagnosis of Diseases of the Heart and Great Vessels. 8th ed. Boston: Little, Brown, 1979:290.
22. **Bar-Shlomo BZ, Druck MN, Morch JE, Jablonsky G, Hilton JD, Feiglin DH, McLaughlin PR.** Left ventricular function in trained and untrained healthy subjects. Circulation 1982;65:484–488.
23. **Pollner LR, Dehmer GJ, Lewis SE, Parkey RW, Blomqvist CG, Willerson JT.** Left ventricular performance in normal subjects: a comparison of the response to exercise in the upright and supine position. Circulation 1980;62:528–534.
24. **Dehmer GJ, Firth BG, Hillis LD, Corbett JR, Lewis SE, Parkey RW, Willerson JT.** Alterations in left ventricular volumes and ejection fraction at rest and during exercise in patients with aortic regurgitation. Am J Cardiol 1981;48:17–27.
25. **Gorlin R, Cohen LS, Elliott WC, Klein MD, Lane FJ.** Effect of supine exercise on left ventricular volume and oxygen consumption in man. Circulation 1965;32:361–371.
26. **Chapman CB, Fisher JN, Sproule BJ.** Behavior of stroke volume at rest and during exercise in human beings. J Clin Invest 1960;39:1208–1213.
27. **Horowitz S, Goldman M, Kukin M, Patterson R, Urquhart J, Teichholz LE, Armas R, Goldsmith S, Gorlin R.** Scintigraphic quantitation of regurgitant index during multi-intervention studies in aortic regurgitation (abstr). Circulation 1981;64:Suppl IV:IV-1:247.
28. **Corrigan DJ.** On permanent patency of the mouth of the aorta, or inadequacy of the aortic valves. Edinburgh Med & Surg J 1832;37:707–727.
29. **Levinson GE, Frank MJ, Schwartz CJ.** The effect of rest and physical effort on the left ventricular burden in mitral and aortic regurgitation. Am Heart J 1970;80:791–801.
30. **Ettinger PO, Frank MJ, Levinson GE.** Hemodynamics at rest and during exercise in combined aortic stenosis and insufficiency. Circulation 1972;65:267–276.
31. **Bristow JD, Kloster FE, Farrehi C, Brodeur MTH, Lewis RP, Griswold HE.** The effects of supine exercise on left ventricular volume in heart disease. Am Heart J 1966;71:319–329.
32. **Judge TP, Kennedy JW, Bennett LF, Wills RE, Murray JA, Blackmon JR.** Quantitative hemodynamic effects of heart rate in aortic regurgitation. Circulation 1971;64:355–367.
33. **Firth BG, Dehmer GJ, Nicod P, Willerson JT, Hillis LD.** Effect of increasing heart rate in patients with aortic regurgitation. Am J Cardiol 1982;49:1860–1867.
34. **Sonnenblick EH, Strobeck JE.** Derived indexes of ventricular and myocardial function. N Engl J Med 1977;296:978–982.
35. **Nixon JV, Murray RG, Leonard PD, Mitchell JH, Blomqvist CG.** Effect of large variations in preload on left ventricular performance characteristics in normal subjects. Circulation 1982;65:698–703.
36. **Braunwald E, Ross J, Sonnenblick EH.** Mechanisms of contraction of the normal and failing heart. 2nd ed. Boston: Little, Brown, 1976:292–308.




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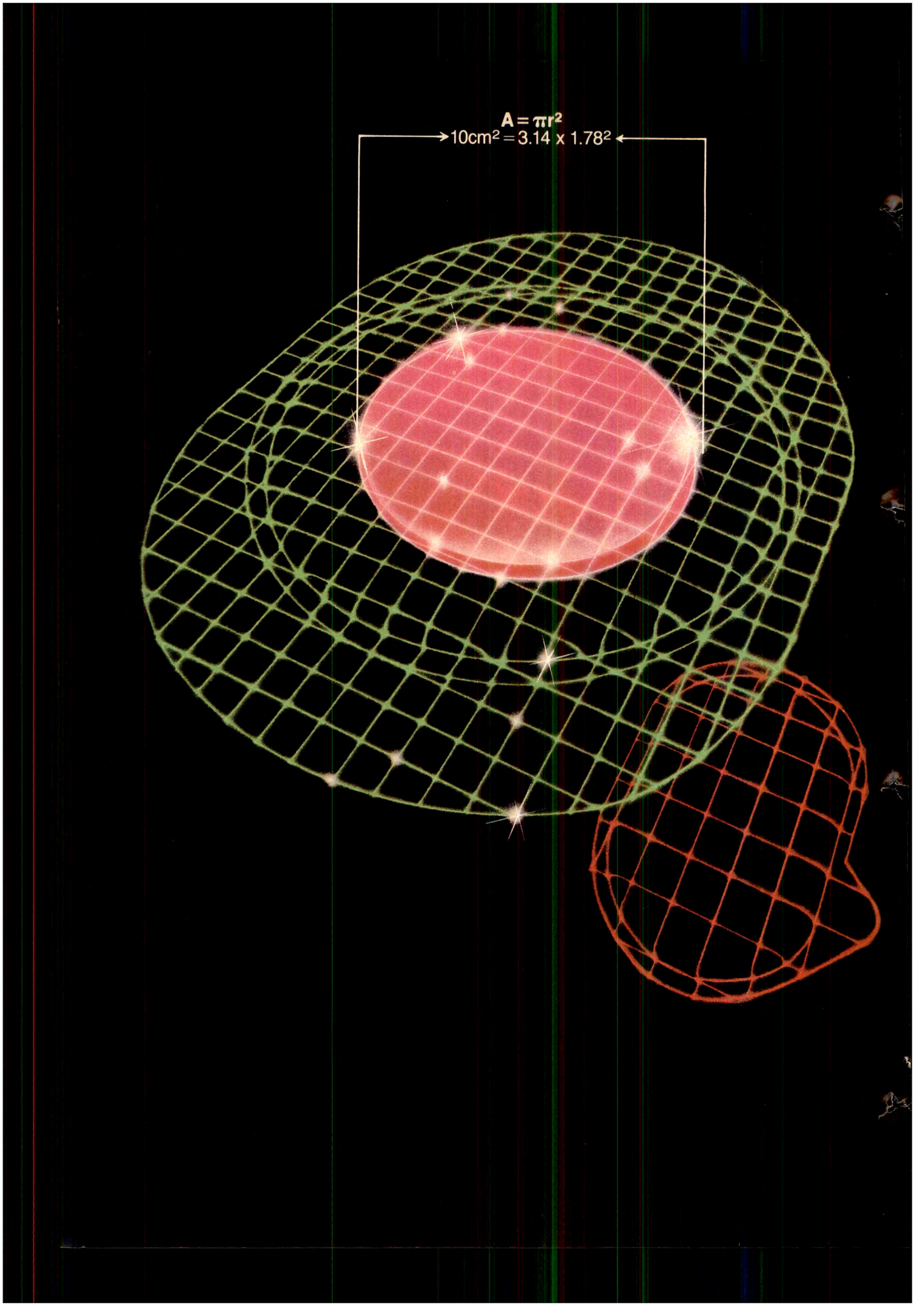


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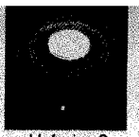
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# Nitro-Dur™
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**DESCRIPTION:** The Nitro-Dur Transdermal Infusion System contains nitroglycerin in a gel-like matrix composed of glycerin, water (purified), lactose, polyvinyl alcohol, povidone and sodium citrate to provide a continuous source of the active ingredient. Nitro-Dur is available in dosage sizes 5cm², 10cm², 15cm² and 20cm², containing 26 mg, 51 mg, 77 mg and 104 mg of nitroglycerin, respectively, thereby providing precise dosing levels of nitroglycerin. Nitro-Dur has a rated release *in vivo* of approximately 0.5mg/cm²/24 hours. Each unit is sealed in a polyester-foil-polyethylene laminate. The bandage portion consists of a medical grade non-woven, heat sealable, microporous tape.

**CLINICAL PHARMACOLOGY:** When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies[2] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

**INDICATIONS AND USAGE:** Prevention and treatment of angina pectoris due to coronary artery disease.

**CONTRAINDICATIONS:** Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

**WARNINGS:** The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

**PRECAUTIONS:** Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

**ADVERSE REACTIONS:** Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

**HOW SUPPLIED:** Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28.

**CAUTION:** Federal law prohibits dispensing without a prescription.

**PATIENT INSTRUCTIONS FOR APPLICATION:** Patient instructions are furnished with each unit dose package.

*For complete prescribing information, please see package insert.*

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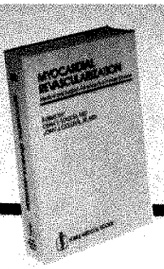
**References**


1. Pharmacy acquisition cost (AWP), *Drug Topics Red Book*, 1982 (assuming a 50% markup).
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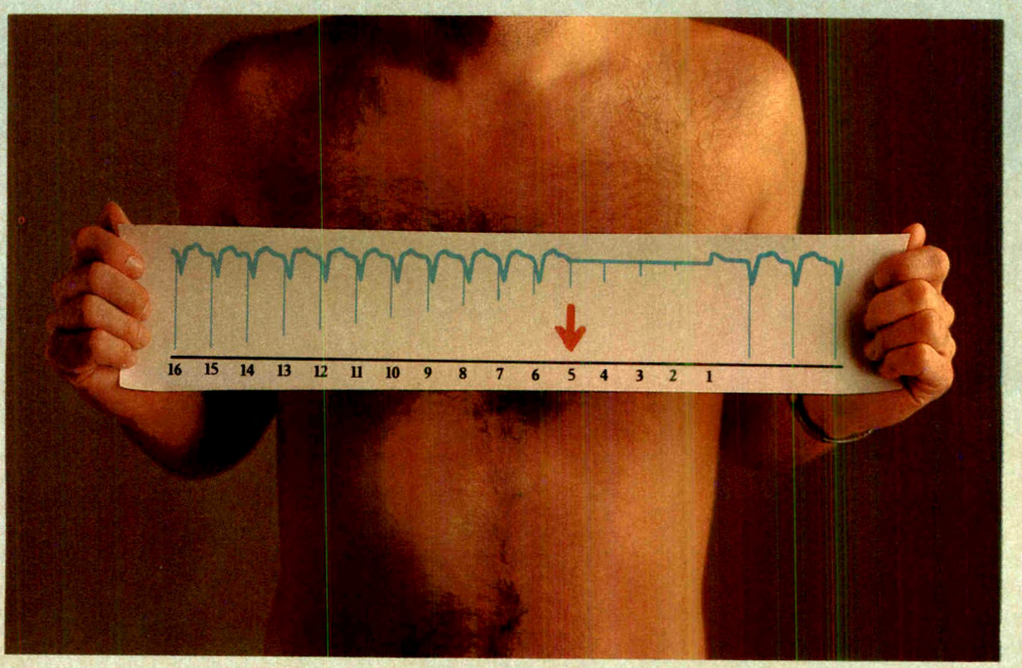
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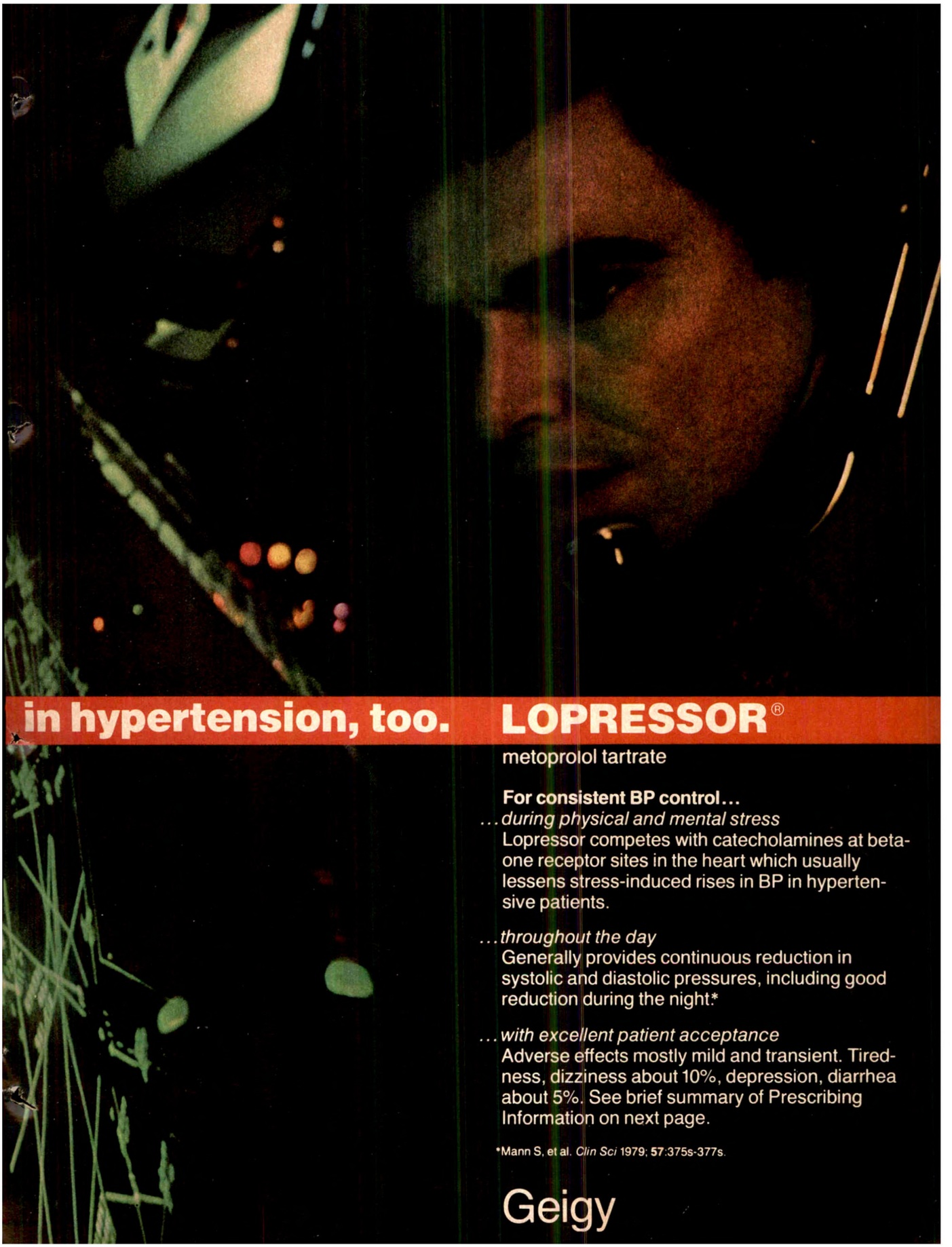
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**Warnings** ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.
***In Patients Without a History of Cardiac Failure:*** Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.
***Ischemic Heart Disease:*** Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.
***Bronchospastic Diseases:*** **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**
***Major Surgery:*** The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.
***Diabetes Mellitus:*** Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.
***Thyrotoxicosis:*** Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.
**Precautions** ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.
***Drug Interactions:*** Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.
***Long-Term Animal Studies:*** Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.
***Usage In Pregnancy:*** Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.
***Nursing Mothers:*** It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.
***Usage in Children:*** Safety and effectiveness in children have not been established.
**Adverse Reactions** Most adverse effects have been mild and transient.
***Central Nervous System:*** Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.
***Cardiovascular:*** Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**
***Respiratory:*** Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**
***Gastrointestinal:*** Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.
***Allergic:*** Pruritus has occurred in less than 1 of 100 patients.
***Miscellaneous:*** Peyronie's disease has been reported in less than 1 of 100,000 patients. The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.
***Potential Adverse Effects:*** In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.
*Central Nervous System:* Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.
*Cardiovascular:* Intensification of AV block (see **Contraindications**).
*Hematologic:* Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
*Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.
*Miscellaneous:* Reversible alopecia.
*Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.
**Dosage and Administration** Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.
This drug should be stored at controlled room temperature and protected from moisture.
**How Supplied** Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.
Store at controlled room temperature and protect from moisture.
*Dispense in tight, light-resistant container (USP).*

C80-82 (12/80)

*Consult complete product literature before prescribing.*

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# Indexes of Intravascular Hemolysis, Quantification of Coagulation Factors, and Platelet Survival in Patients With Porcine Heterograft Valves

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**Ten patients with porcine heterograft valves who were not receiving anticoagulant agents were evaluated to determine the effect of the valve on red blood cell survival and on platelet activation and consumption as measured by (1) quantification of the coagulation mechanism, (2) platelet function studies, and (3) 51-chromium platelet survival time. There was no evidence of significant intravascular hemolysis as determined by the reticulocyte count, serum iron and iron binding capacity, serum bilirubin level, or lactic dehydrogenase activity. The coagulation profile and the platelet function studies were normal. No statistically significant difference was found in the platelet survival time in the 10 patients with porcine heterograft valves (half-life 3.2 ± 0.8 days) and the 11 normal control subjects (half-life 3.6 ± 0.6 days) ($p > 0.2$). The finding of a normal platelet survival time in patients with porcine heterograft valves is consistent with clinical experience indicating that this device is associated with a low incidence of systemic embolization, approximating 3% per year.**

Embolic and hemolytic complications after cardiac valve replacement represent a substantial cause of morbidity and mortality.[1–6] Since 1970, approximately 75,000 patients have undergone bioprosthetic valve replacement with the glutaraldehyde-preserved porcine valve. The major advantage of the porcine valve is the low incidence of intravascular hemolysis and systemic embolization.[7] This study evaluates the effect of the porcine heterograft valve on red blood cell destruction as measured by indexes of intravascular hemolysis, and its effect upon platelet activation and consumption as measured by (1) quantification of the coagulation mechanism, (2) platelet function studies, and (3) 51-chromium platelet survival time. The latter allows estimation of the thrombogenic potential of a prosthetic valve.[8,9]

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## Methods

All 10 patients had Hancock porcine heterograft valve (Vascor, Anaheim, California) replacement 7 to 49 months before participation in the study: 8 had mitral valve replacement alone (model 342) and 2 had mitral and aortic valve replacements (model 242). Eight were in sinus rhythm at study (Table I). The bioprosthetic valve or valves were functioning normally without evidence of regurgitation or stenosis. Congestive heart failure and a history of systemic embolization, either before or after valve replacement, were not present. No patient was receiving the anticoagulant agent warfarin or any drug known to affect platelet function at study.

The following variables were used to judge the extent of intravascular hemolysis: hemoglobin, hematocrit, reticulocyte count, serum iron and iron binding capacity, serum haptoglobin, and lactic dehydrogenase activity, the latter 2 being the most sensitive and specific (Table II).[10,11]

Coagulation profiles, assays of coagulation factors, and platelet function studies were performed in 9 patients (Tables III to V). These studies were performed using previously described or standard methods.[12–14] A modification of the method described by Saltzman[15] was used to determine the glass bead retention index.

Platelet survival studies were carried out in 11 normal volunteers and the 10 patients utilizing autologous 51-chromium–labeled platelets. The platelets were obtained by manual plasmapheresis, and the survival studies were performed in accordance with the report of the International Committee for Standardization in Hematology.[16] The platelet survival times in the patients were compared with those determined in 11 normal volunteers. Student's $t$ test was used for statistical analysis.[17]

**TABLE I Patient Profile**

| Patient | Age (yr) & Sex | Valve Age (mo) | Rhythm | Valve Replaced | Platelet Survival (Days Half-Life) |
|---|---|---|---|---|---|
| 1 | 29M | 7 | S | A/M | 3.0 |
| 2 | 66F | 11 | S | M | 2.4 |
| 3 | 57M | 12 | S | M | 3.2 |
| 4 | 62M | 14 | S | M | 2.0 |
| 5 | 47F | 15 | S | M | 3.7 |
| 6 | 34F | 16 | S | M | 3.4 |
| 7 | 47M | 22 | AF | M | 2.5 |
| 8 | 66F | 31 | S | M | 3.0 |
| 9 | 51M | 39 | AF | A/M | 4.7 |
| 10 | 52M | 49 | S | M | 3.8 |

A = aortic; AF = atrial fibrillation; M = mitral; S = sinus rhythm.

## Results

The results are summarized in the accompanying tables. There was no evidence of significant intravascular hemolysis (Table II). The screening tests of coagulation (Table III) gave normal results. Likewise, there was no evidence of intravascular coagulation. Assays of coagulation factors (Table IV) and platelet function studies (Table V) gave normal findings.

The platelet half-life in 11 normal control subjects was 3.6 ± 0.6 days. In the 10 patients with porcine heterograft valves who were not receiving anticoagulant therapy, the platelet half-life was 3.2 ± 0.8 days (Table I). No statistically significant difference was observed in the platelet survival time in the patients with porcine heterograft valves and in the normal control subjects ($p > 0.2$).

## Discussion

Intravascular hemolysis as a result of trauma to red blood cells is a common complication of prosthetic heart valves.[18–20] In evaluating patients for intravascular hemolysis, the most sensitive and specific indexes are serum lactic dehydrogenase activity >500 IU and a depressed level of serum haptoglobin.[10,11] No patient with a porcine bioprosthesis in this study had evidence of significant intravascular hemolysis. The degree of intravascular hemolysis associated with the porcine bioprosthesis is comparable to that demonstrated for the newer tilting disc-type valves (Björk-Shiley) and is of no clinical significance.[21]

Study of the effects of artificial heart valves on the coagulation profile has been limited due to the necessity for long-term anticoagulant therapy. Patients with porcine bioprostheses have not required anticoagulation; hence, a study of their coagulation and platelet activity is feasible. The tests of the plasma coagulation mechanism were normal and suggested no abnormality resulting from the prosthetic device. Platelet function has been studied in patients with prosthetic heart valves by several investigators and also was reported to be normal.[8,9,22] Platelet function studies, in contrast to

**TABLE II Evaluation of Intravascular Hemolysis**

| | Normal | Mean | Range |
|---|---|---|---|
| Hemoglobin (g/dl) | >13 | 15.1 | 13.1–17.6 |
| Reticulocyte count (%) | 2 | 1.95 | 0.3–4 |
| Serum iron (μg/dl) | 80–160 | 127 | 57–201 |
| Iron binding capacity (μg/dl) | 250–420 | 325 | 294–411 |
| Haptoglobin (mg/dl) | 30–170 | 103 | 45–225 |
| Bilirubin (mg/dl) | <1.4 | 1.09 | 0.5–1.8 |
| Lactic dehydrogenase (IU) | <170 | 175 | 122–276 |

**TABLE III Coagulation Tests**

| | Normal Range (seconds) | Mean | Range |
|---|---|---|---|
| Prothrombin time | 10.8–13.0 | 10.8 | 9.6–11.8 |
| Activated partial thromboplastin time | 26–34 | 30.5 | 27.5–35.4 |
| Thrombin time | 13–18 | 15.6 | 15.1–16.1 |
| Ethanol/protamine gel | 0 | 0 | 0 |
| Fibrin split products | 0 | 0 | 0 |

**TABLE IV Coagulation Factor Assay**

| Factor | Normal Range | Mean | Range |
|---|---|---|---|
| I | 150–450 mg/dl | 330.00 | 215–565 |
| II | 0.5–1.5 U/ml | 1.06 | 0.75–1.3 |
| V | 0.5–1.5 U/ml | 1.01 | 0.73–1.4 |
| VII | 0.5–1.5 U/ml | 1.07 | 0.62–1.4 |
| VIII | 0.5–1.5 U/ml | 1.37 | 0.68–2.2 |
| IX | 0.5–1.5 U/ml | 1.12 | 0.72–1.4 |
| X | 0.5–1.5 U/ml | 0.95 | 0.56–1.3 |
| XI | 0.5–1.5 U/ml | 1.04 | 0.50–1.25 |
| XII | 0.5–1.5 U/ml | 1.12 | 0.86–1.3 |
| Fletcher | 0.5–1.5 U/ml | 0.99 | 0.82–1.35 |
| AT III | 80–120 U/ml | 105.29 | 86–122 |

**TABLE V Platelet Function**

| | Normal | Mean | Range |
|---|---|---|---|
| Platelet count ×1,000 $mm^3$ | 150–450 | 238 | 120–417 |
| Platelet aggregation | | | |
| ADP 4 × $10^{-5}M$ | >60% | 99.4 | 95–100 |
| ADP 4 × $10^{-6}M$ | >60% | 81.1 | 60–100 |
| Collagen | >60% | 100 | 100 |
| Ristocetin | >60% | 100 | 100 |
| Thrombin | 50–100% | 98.8 | 90–100 |
| Glass Bead Retention Index | >20% | 69 | 61–80 |

ADP = adenosine diphosphate.

platelet survival studies, are not predictive of future thromboembolism in patients with prosthetic heart valves.[8,9]

Kinetic platelet survival studies have been useful in predicting future thromboembolic events.[8,9] Platelet survival (half-life 3.2 ± 0.8 days) in our 10 patients with Hancock porcine valves who were not receiving anticoagulant therapy did not differ significantly from the platelet survival time determined in 11 normal subjects (half-life 3.6 ± 0.6 days) ($p > 0.2$). Lee et al[23] determined the platelet half-life in 10 patients with the Hancock porcine valve who were not receiving anticoagulant agents to be 2.9 ± 0.6 days, which was significantly shorter than the platelet half-life of 5.1 ± 0.5 days observed in 7 normal control subjects ($p < 0.05$). The statistical differences observed in these 2 reports may be explained by the relatively small number of subjects in each study. The finding of a normal platelet survival time in patients with Hancock porcine heterograft valves complements the normal platelet survival time found in patients with homograft prosthetic valves.[8,9] The similarities in tissue composition between the homograft valve and the Hancock valve lends credence to this observation and is consistent with clinical experience indicating this device is associated with a low incidence (approximately 3% per year) of systemic embolization.[7]

## References


1. **Duvoisin GE, Brandenburg RO, McGoon DC.** Factors affecting thromboembolism associated with prosthetic heart valves. Circulation 1967;35:Suppl I:I-70–I-76.
2. **Javier RP, Hildner FJ, Berry W, Greenberg JJ, Samet P.** Systemic embolism and the Beall mitral valve prosthesis. Ann Thorac Surg 1970;10: 20–26.
3. **Hylen JC.** Mechanical malfunction and thrombosis of prosthetic heart valves. Am J Cardiol 1972;30:396–404.
4. **Andersen MN, Gabrieli E, Zizzi JA.** Chronic hemolysis in patients with ball-valve prostheses. J Thorac Cardiovasc Surg 1965;50:501–510.
5. **Walsh JR, Starr A, Ritzmann LW.** Intravascular hemolysis in patients with prosthetic valves and valvular heart disease. Circulation 1966;39:Suppl I:I-140–I-151.
6. **Eyster E, Rothchild J, Mychajliw O.** Chronic intravascular hemolysis after aortic valve replacement. Long-term study comparing different types of ball-valve prostheses. Circulation 1971;44:657–665.
7. **Angell WW, Angell JD.** Porcine valves. Prog Cardiovasc Dis 1980;23: 141–166.
8. **Welly HS, Steele PP, Davies H, Pappas G, Genton E.** Platelet survival in patients with substitute heart valves. N Engl J Med 1974;290:534–537.
9. **Manohithajarah SM, Rahman AN, Donnelly RJ, Deverall PB, Watson DA.** Platelet survival in patients with homograft and prosthetic heart valves. Correlation with incidence of thromboembolism. Thorax 1974;29:639–642.
10. **Owen JA, deGruchy GC, Smith H.** Serum haptoglobins in haemolytic states. J Clin Pathol 1960;13:478–482.
11. **Myhre E, Rasmussen K, Andersen A.** Serum lactic dehydrogenase activity in patients with prosthetic heart valves: a parameter of intravascular hemolysis. Am Heart J 1970;80:463–468.
12. **Lewis JH, Spero JA, Hasiba U.** Diagnostic Methods: Laboratory Tests, Bleeding Disorders. Garden City, NY: Medical Examination, 1978:22–34.
13. **Lewis JH.** Comparative hematology: studies on goats. Am J Vet Res 1976;37:601–605.
14. **Ragni MV, Lewis JH, Spero JA, Hasiba U.** Bleeding and coagulation abnormalities in alcoholic liver disease. Alcoholism: Clin Exp Res 1982;6, in press.
15. **Saltzman EW.** Measurement of platelet adhesiveness. J Lab Clin Med 1963;62:724–735.
16. International Committee for Standardization in Hematology, Panel on Diagnostic Application of Radioisotopes in Hematology. Recommended methods for radioisotope platelet survival studies. Blood 1977;50:1137.
17. **Snedecor GW, Cochran WG.** Statistical Methods. Ames, IA: Iowa State University Press, 1967:59.
18. **Kloster FE.** Diagnosis and management of complications of prosthetic heart valves. Am J Cardiol 1975;35:872–885.
19. **Williams JC Jr, Vernon CR, Daicoff GR, Bartley TD, Wheat MW Jr, Ramsey HW.** Hemolysis following mitral valve replacement with the Beall valve prosthesis. J Thorac Cardiovasc Surg 1971;61:393–396.
20. **Santinga JT, Kirsh MM.** Hemolytic anemia in Series 2300 and 2310 Starr-Edwards prosthetic valves. Ann Thorac Surg 1972;14:539–544.
21. **Nitter-Hauge S, Sommerfelt SC, Hall K-V, Froysaker T, Efskind L.** Chronic intravascular haemolysis after aortic disc valve replacement. Br Heart J 1974;36:781–785.
22. **Dale J, Myhre E, Rootwelt K.** Effects of dipyridamole and acetylsalicylic acid on platelet functions in patients with aortic ball-valve prostheses. Am Heart J 1975;89:613–618.
23. **Lee G, Joye JA, Rose A, DeNardo S, Kozina JA, Mason DT.** Evaluation of platelet kinetics following porcine and mechanical valve replacement. Clin Cardiol 1981;4:11–14.


The evil that men do
lives after them;
The good is oft interred
with their bones....

William Shakespeare

# Rheumatic Tricuspid Valve Disease: Two-Dimensional Echocardiographic, Hemodynamic, and Angiographic Correlations

STEVEN J. DANIELS, MD, GARY S. MINTZ, MD, and MORRIS N. KOTLER, MD

**From March 1977 through April 1982, 2-dimensional echocardiography detected 372 patients with rheumatic mitral valve disease. Of these patients, 23 (6%) had tricuspid valve involvement. Two-dimensional echocardiographic criteria of rheumatic tricuspid valve disease included thickened leaflets with restriction in motion, diastolic doming, and encroachment of the leaflet tips on the ventricular inlet. These criteria provided a sensitivity of 100%, a specificity of 90%, a predictive accuracy of 21%, and a negative predictive value of 100% in diagnosing hemodynamically significant tricuspid stenosis.**

**Hemodynamic variables in patients with rheumatic tricuspid valve disease (Group I) were compared with those in patients with no rheumatic tricuspid disease (Group II). The only significant difference was mean right atrial pressure (15 ± 7 mm Hg versus 11 ± 5 mm Hg, p <0.02). Both groups were classified into patients with (A) and without (B) significant tricuspid regurgitation (TR). There was no significant difference in any hemodynamic variable when Group IA was compared with Group IIA. In addition, there was no difference in any hemodynamic variable when patients with functional TR (Group IIA) were compared with those with rheumatic mitral valvular disease without TR (Group IIB). Two-dimensional echocardiography and cardiac catheterization provide complementary diagnostic information in these patients.**

In patients with rheumatic heart disease, the reported incidence of tricuspid valve involvement varies, ranging from 3.5[1] to 67%.[2] Most reports are from the preantibiotic era and from underdeveloped nations. One recent report[3] claims that finding a thickened and restricted tricuspid valve on 2-dimensional echocardiographic study is predictive of hemodynamically significant tricuspid stenosis (TS). In this report we attempt to (1) define the incidence of rheumatic tricuspid valve disease in the present era, (2) determine the sensitivity, specificity, predictive accuracy, and negative predictive value of the 2-dimensional echocardiographic criteria of rheumatic TS, (3) evaluate the hemodynamic consequences of rheumatic tricuspid valve disease, and (4) determine whether hemodynamic variables can differentiate primary rheumatic TR from secondary TR in patients with rheumatic mitral valve disease.

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## Methods

The 2-dimensional echocardiographic reports from Hahnemann University and Hospital from March 1977 through April 1982 were reviewed. Of 372 patients with rheumatic mitral valve disease, 23 also had rheumatic tricuspid valve involvement. An additional 7 patients with prosthetic mitral valves had rheumatic tricuspid valve disease. The echocardiographic, hemodynamic, and angiographic findings in these patients were reviewed retrospectively.

**Echocardiography:** Two-dimensional echocardiographic studies were performed with the patient in the supine or left lateral decubitis position. These patient studies were done using either a Grumman Health Systems RT 400 or Varian V 3000, 3000R, or 3400 phased array sector scanner. A complete study consisted of the parasternal long- and short-axis views, the apical 2- and 4-chamber views, and the parasternal right ventricular inflow tract view. Images were recorded on videotape for analysis. Illustrations were obtained from Polaroid® photographs of stop-action single frame images made from the videotape recordings.

Rheumatic mitral valve disease was defined as increased thickening of the mitral valve leaflets, restricted leaflet motion, encroachment of the leaflet tips into the left ventricular inlet, and diastolic doming of the leaflets (particularly an obtuse angular bend of the anterior leaflet). Similar findings of increased thickening, restricted motion, encroachment of leaflets on the right ventricular inlet, and diastolic doming defined rheumatic tricuspid valve disease. The 2-dimensional

echocardiographic criteria were compared with hemodynamic and angiographic findings.

**Catheterization techniques and interpretation:** Of the 379 patients, 151 underwent cardiac catheterization. The hemodynamic and angiographic findings were reviewed. Hemodynamic data were available for all 151 patients, but patients with a mitral prosthesis or an echocardiographically normal tricuspid valve and no right ventriculography were excluded from hemodynamic analysis. These exclusions left 50 patients: 15 with 2-dimensional echocardiographic features of rheumatic tricuspid valve involvement (Group I), 31 with rheumatic mitral valvular disease and no echocardiographic tricuspid valve involvement who had undergone right ventriculography during catheterization (Group II), and 4 with a prosthetic mitral valve and echocardiographic rheumatic tricuspid valve disease. There were 7 men and 43 women, aged 22 to 72 years (mean ± standard deviation 55 ± 12). The patients in Groups I and II were subdivided according to the presence (A) or absence (B) of significant TR. Eight patients in Group I had right ventriculography performed as part of the catheterization; 7 had significant TR and formed Group IA. (The other 7 patients in Group I did not have a right ventriculogram. Whether or not they had TR is not known. Therefore, they are excluded from this part of the data analysis.) All patients in Group II had right ventriculography. Eleven of the 31 patients in Group II had significant TR, and, thus, formed Group IIA. Twenty patients in Group II had no or insignificant TR and formed Group IIB. Right atrial, right ventricular, pulmonary artery, pulmonary capillary wedge or left atrial, and left ventricular pressures were recorded using Bentley Transtec or Statham P23DP transducers. Cardiac output was determined using the indocyanine green dye dilution. Pulmonary vascular resistance was calculated. Mitral stenosis was considered hemodynamically significant if the calculated mitral valve area was $\leq 1.5$ cm$^2$. Right atrial and right ventricular pressures were measured simultaneously. TS was considered hemodynamically significant if there was at least a 2 mm Hg diastolic gradient across the tricuspid valve, regardless of the presence of TR.

Left ventriculography was performed using either biplane (right anterior oblique and left anterior oblique views) or single plane (right anterior oblique view) technique. Right ventriculography was performed using either biplane (right anterior oblique and left anterior oblique views) or single plane (right anterior oblique) techniques. If the procedure was performed by way of the transfemoral route, a pigtail catheter with a preformed curve was used so that the catheter coursed from a superior to inferior direction across the tricuspid valve. If the procedure was performed by brachial cutdown, a model 7 NIH catheter was used for right ventriculography. The degree of mitral insufficiency or TR was classified according to the following scale, suggested by Grossman[4]: 1+ (regurgitant contrast material essentially clears with each beat and never opacifies the entire atrium), 2+ (regurgitant contrast does not clear with 1 beat and generally opacifies the entire atrium after several beats, but the degree of opacification does not equal that of the ventricle), 3+ (regurgitant dye completely opacifies the atrium and equals opacification with the ventricle), and 4+ (opacification of the atrium occurs in 1 beat and becomes progressively more dense with each beat). Valvular insufficiency (either mitral or tricuspid) of ≥2+ was considered significant.

Using the data from the 151 patients who had hemodynamic study, the sensitivity, specificity, predictive accuracy, and negative predictive value of the 2-dimensional echocardiographic diagnosis of hemodynamically significant TS were calculated as follows: Sensitivity = [true positive/(true positive + false negative)] × 100; Specificity = [true negative/(true negative + false positive)] × 100; Predictive accuracy = [true positive/(true positive + false positive)] × 100; Negative predictive value = [true negative/(true negative + false negative)] × 100.

Statistical analysis was performed using the Student's $t$ test. Probability values $<0.05$ were considered significant.

## Results

**Echocardiographic findings:** Of 372 patients with 2-dimensional echocardiographic features of rheumatic mitral valve disease, 23 patients also had echocardiographic features of rheumatic tricuspid valve disease (incidence = 6.2%). Simultaneous right ventricular and right atrial pressure measurements were recorded in 19 patients with echocardiographic tricuspid valve involvement (15 patients from Group I and 4 patients with a mitral prosthesis), 4 patients (21%) had TS (Fig. 1 and 2); and 15 patients had no diastolic tricuspid valve gradients. Hemodynamic data were available in 132 patients without echocardiographic tricuspid valve involvement; no patient had hemodynamic TS. Thus,

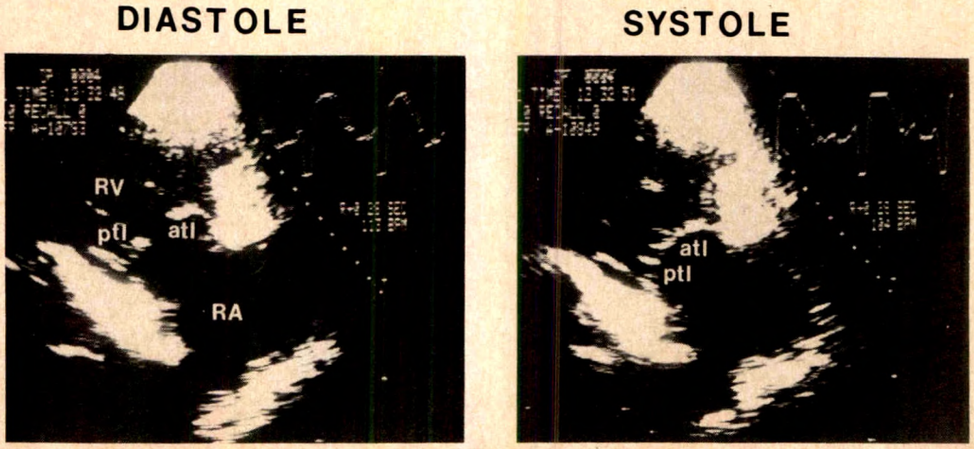



**FIGURE 1.** Two-dimensional echocardiographic study of a patient with rheumatic tricuspid valve disease. The right ventricular inflow tract view is shown. The anterior and posterior tricuspid leaflets (atl, ptl) are thickened and restricted in motion during diastole. The patient had pure TS. RA = right atrium; RV = right ventricle.

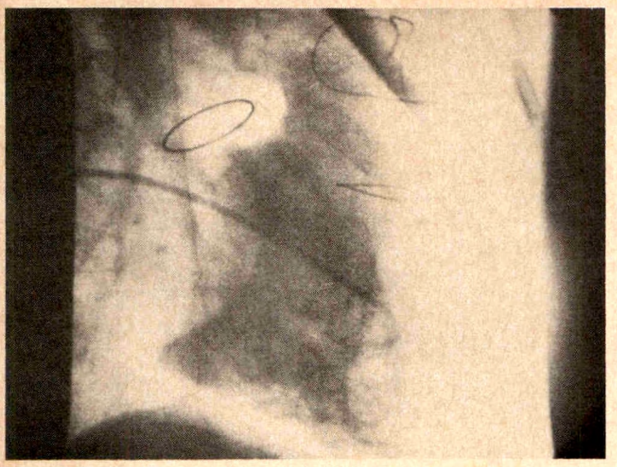


**FIGURE 2.** Right ventriculogram (from the patient in Fig. 1) showing no TR.

**TABLE I Hemodynamic Values in Patients With (Group I) and Without (Group II) Rheumatic Tricuspid Valve Disease**

| | Group I (n = 15) | Group II (n = 31) | p |
|---|---|---|---|
| Mean PCWP (mm Hg) | 26 ± 9 | 25 ± 8 | NS |
| PA systolic (mm Hg) | 60 ± 26 | 52 ± 19 | NS |
| PA mean (mm Hg) | 40 ± 16 | 37 ± 13 | NS |
| RVDP (mm Hg) | 13 ± 6 | 11 ± 5 | NS |
| RA mean (mm Hg) | 15 ± 5 | 11 ± 5 | <0.02 |
| PVR (dynes s $cm^{-5}$) | 409 ± 316 | 262 ± 204 | NS |

NS = not significant; PA mean = mean pulmonary arterial pressure; PA systolic = pulmonary arterial systolic pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA mean = right atrial mean; RVDP = right ventricular end-diastolic pressure.

**TABLE II Hemodynamic Values in Patients With "Primary" (Group IA) and "Secondary" (Group IIA)**

| | Group IA (n = 7) | Group IIA (n = 11) | p |
|---|---|---|---|
| Mean PCWP | 25 ± 6 | 28 ± 11 | NS |
| PA systolic (mm Hg) | 59 ± 28 | 55 ± 21 | NS |
| PA mean (mm Hg) | 39 ± 17 | 39 ± 16 | NS |
| RA mean (mm Hg) | 16 ± 8 | 11 ± 5 | NS |
| PVR (dynes s $cm^{-5}$) | 400 ± 397 | 283 ± 227 | NS |

Abbreviations as in Table I.

2-dimensional echocardiography has a sensitivity of 100%, a specificity of 90%, a predictive accuracy of 21%, and a negative predictive value of 100% in identifying patients with hemodynamically significant TS. Twelve patients with echocardiographic rheumatic tricuspid valve involvement had right ventriculography performed during cardiac catheterization. Nine patients (75%) had significant TR (Fig. 3 and 4).

**Hemodynamic variables (Fig. 5):** Analysis of the hemodynamic variables in patients with rheumatic tricuspid valve disease (Group I) showed a significantly higher mean right atrial pressure than in patients without rheumatic tricuspid valve disease (Group II) (Table I). However, there was no significant difference between the groups in mean pulmonary capillary wedge pressure, pulmonary arterial systolic pressure, mean pulmonary arterial pressure, right ventricular end-diastolic pressure, or pulmonary vascular resistance. There was no significant difference in any of the hemodynamic variables when patients with rheumatic TR (Group IA) were compared with those with functional (Group IIA) (Table II), nor when patients with functional TR (Group IIA) were compared with those with rheumatic mitral valvular disease and no functional TR (Group IIB) (Table III).

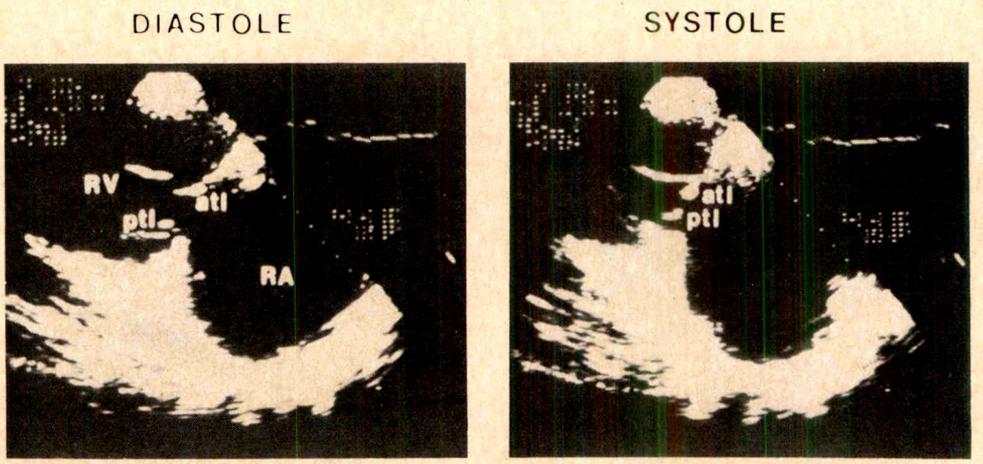



**FIGURE 3.** Two-dimensional echocardiographic study of a patient with rheumatic tricuspid valve disease. The right ventricular inflow tract view is shown. The anterior and posterior tricuspid leaflets (atl, ptl) are thickened and restricted. The patient had pure TR. RA = right atrium; RV = right ventricle.

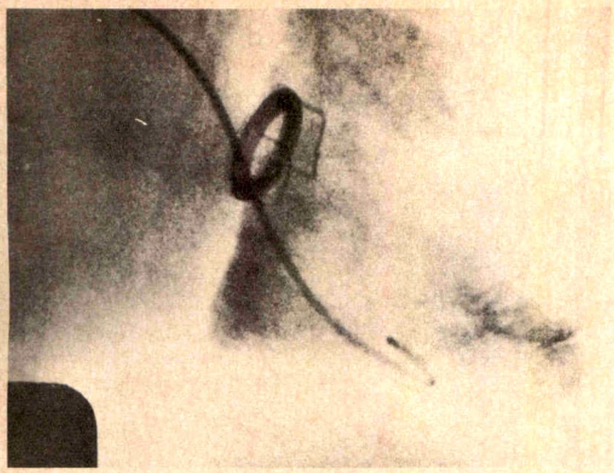


**FIGURE 4.** Right ventriculogram (from the patient in Fig. 3) showing severe TR.

**TABLE III Hemodynamic Values in Patients With (Group IIA) and Without (Group IIB) "Secondary" TR**

| | Group IIA (n = 11) | Group IIB (n = 20) | p |
|---|---|---|---|
| Mean PCWP (mm Hg) | 28 ± 11 | 24 ± 7 | NS |
| PA systolic (mm Hg) | 55 ± 21 | 50 ± 18 | NS |
| PA mean (mm Hg) | 39 ± 16 | 34 ± 14 | NS |
| RVDP (mm Hg) | 10 ± 5 | 12 ± 5 | NS |
| RA mean (mm Hg) | 11 ± 5 | 11 ± 5 | NS |
| PVR (dynes s $cm^{-5}$) | 283 ± 227 | 251 ± 195 | NS |

Abbreviations as in Table I.

## Discussion

In our 2-dimensional echocardiographic study, the incidence of rheumatic tricuspid valve involvement in patients with rheumatic mitral valve disease is 6.2%. This incidence is somewhat different from that noted in previous studies. Autopsy studies have shown the incidence of rheumatic tricuspid valve involvement in patients with rheumatic heart disease to range from 3.5%[1] (in a series published in 1940) to 67%[2] (in a series published in 1923). However, most pathologic series[5–11] have shown tricuspid valve involvement in approximately 30 to 50% of people with rheumatic heart disease. Although these incidences are higher than ours, 2 factors must be considered. First, we diagnosed rheumatic tricuspid valve disease by 2-dimensional echocardiography, not morphologically. Gross pathologic disease was probably necessary since most patients had hemodynamically significant TS or TR; and, thus, 2-dimensional echocardiography may underestimate the actual incidence of anatomic rheumatic tricuspid valve involvement. Second, most previous studies were done in the preantibiotic era, when the incidence and severity of rheumatic fever was greater than it is now. Therefore, the actual incidence of tricuspid valve involvement may be lower today.

Recently, Guyer et al[3] suggested that 2-dimensional echocardiography is a sensitive and specific method of evaluating patients with suspected TS. They found the sensitivity of 2-dimensional echocardiography to be 100%, the specificity to be 91%, the predictive accuracy to be 70%, and the negative predictive value to be 100% in diagnosing hemodynamically significant TS. Although our figures for sensitivity, specificity, and negative predictive value are similar, we do not find the predictive accuracy of 2-dimensional echocardiography to be as high (70 versus 21%). When 2-dimensional echocardiography showed rheumatic tricuspid valve disease, hemodynamically significant TS occurred in

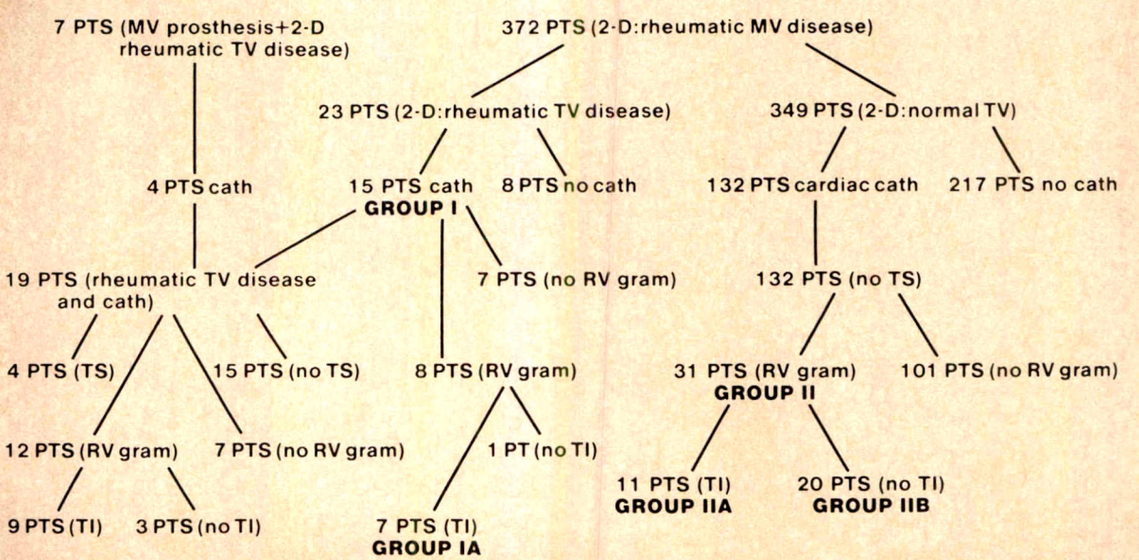



**FIGURE 5.** Flow diagram of the echocardiographic, hemodynamic, and angiographic analysis in this study. Cath = catheterization; MV = mitral valve; PTS = patients; RV = right ventricle; TI = tricuspid insufficiency; TS = tricuspid stenosis; TV = tricuspid valve; 2-D = 2-dimensional.

only a small proportion of our patients. Significant TR was more common.

Braunwald[12] suggested that in patients with rheumatic TR, pulmonary artery systolic pressures >60 mm Hg favor secondary or functional TR while pulmonary arterial systolic pressures <40 mm Hg favor organic tricuspid disease.

We compared patients with TR and rheumatic tricuspid involvement to patients with functional TR (Table II). There were no significant differences in the hemodynamic parameters studied. Pulmonary arterial systolic pressure, mean pulmonary arterial pressure, and pulmonary vascular resistance did not distinguish organic TR from functional TR. A high percentage of patients with significant organic rheumatic tricuspid valve disease have elevated pulmonary arterial pressures. In this population, the elevated pressures merely reflect the severity of the mitral valvular disease. In fact, 5 of 7 patients with rheumatic tricuspid valve disease with TR had pulmonary arterial systolic pressures >40 mm Hg, while 7 of 11 patients with "secondary" TR had pulmonary arterial systolic pressures <60 mm Hg. In patients with rheumatic tricuspid valve disease and pulmonary hypertension, TR may be partly "primary" and partly "secondary." Previous studies have examined the hemodynamics of secondary TR. Lichtlen[13] found higher right ventricular pressures, Schwartz[14] found higher right atrial and right ventricular end-diastolic pressures, and Sepulveda[15] found higher pulmonary vascular resistance, mean right atrial pressure, and right ventricular pressures in patients with rheumatic mitral valvular disease and secondary TR compared with patients with rheumatic mitral valvular disease and no TS or TR. We found no significant difference in any hemodynamic variable when we examined these 2 groups (Table III). The pathophysiology of secondary TR may be more complex and not merely secondary to pulmonary hypertension.

Thus, 2-dimensional echocardiography and cardiac catheterization provide complementary information in evaluating tricuspid valve involvement and function in patients with rheumatic mitral valvular disease. Two-dimensional echocardiographic findings of thickened tricuspid leaflets with restriction in motion and diastolic doming are not predictive of finding a tricuspid valve gradient. Hemodynamic variables do not appear to differentiate organic from functional TR in patients with rheumatic mitral valve disease. Two-dimensional echocardiography is useful in deciding whether the tricuspid valve is structurally involved by the rheumatic process. This becomes clinically important when mitral valve replacement is being considered. Patients with organic tricuspid valve disease require tricuspid valve replacement if the TR is severe, whereas patients with secondary TR may require only tricuspid anuloplasty or may not need any repair if the mitral valve lesion is corrected.

## References


1. **Clausen BJ.** Rheumatic heart disease: an analysis of 796 cases. Am Heart J 1940;20:454–474.
2. **Libman E.** Characterization of various forms of endocarditis. JAMA 1923;80:813–818.
3. **Guyer D, Gillam L, Dinsmore R, Clark MC, Block P, Palacios I, Weyman AE.** Detection of tricuspid stenosis by two-dimensional echocardiography (abstr). Am J Cardiol 1982;49:104.
4. **Grossman W, Dexter L.** Profiles in valvular heart disease. In: Grossman W, ed. Cardiac Catheterization and Angiography. 2nd ed. Philadelphia: Lea & Febiger, 1980:305–335.
5. **Smith JA, Levine SA.** The clinical features of tricuspid stenosis. Am Heart J 1942;23:739–760.
6. **Aceves S, Carral R.** The diagnosis of tricuspid valve disease. Am Heart J 1947;34:114–130.
7. **Chopra P, Tandon HD.** Pathology of chronic rheumatic heart disease with particular reference to tricuspid valve involvement. Acta Cardiol 1975; 32:423–434.
8. **Cook WT, White PD.** Tricuspid stenosis with particular reference to diagnoses and prognoses. Br Heart J 1941;3:147–165.
9. **Bland EF, White PD, Jones TD.** The development of mitral stenosis in young people. Am Heart J 1935;10:995–1004.
10. **Van Glahn WC.** Rheumatic disease of the heart. Arch Pathol Lab Med 1927;3:355–356.
11. **Thayer WS.** Notes on acute rheumatic heart diseases of the heart. Bull Johns Hopkins 1925;36:99–104.
12. **Braunwald E.** Valvular heart disease. In: Braunwald E, ed. Heart Disease. 1st ed. Philadelphia: WB Saunders, 1980:1095–1165.
13. **Lichtlen PR, Simon R.** Incidence, severity and mechanisms of tricuspid regurgitation in patients with rheumatic mitral valve disease analysed by right ventricular angiography (abstr). Circulation 1976;53,54:Suppl II:II-104.
14. **Schwartz F, Manthey J, Schuler G, Maurer W, Mehmel A, Kubler W.** The effect of tricuspid insufficiency on right ventricular performance in patients with valvular heart disease. Z Kardiol 1981;70:466–471.
15. **Sepulveda G, Lukas DS.** The diagnosis of tricuspid insufficiency. Clinical features in 60 cases with associated mitral valve disease. Circulation 1955;11:552–563.

# Calcium Phosphorus Metabolism in Dialysis Patients With and Without Mitral Anular Calcium

## Analysis of 30 Patients

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**To test the hypothesis that accelerated metastatic calcification in the mitral anulus results from abnormalities in calcium phosphorus and parathyroid hormone, 10 patients with end-stage renal disease having echocardiographically proven mitral anular calcium (MAC) (Group I) and 20 patients without MAC (Group II) were evaluated over 12 consecutive months. Serum levels of total calcium, phosphorus, intact and carboxyl-terminal parathyroid hormone, serum ionized calcium, and total calcium-phosphorus product were compared for both groups. In addition, other variables such as sex, supine systolic and diastolic blood pressure, age, duration of hemodialysis, type of renal disease, and diabetes also were compared in both groups.**

**Although both groups had elevated intact and carboxyl-terminal parathyroid hormone levels. Group I did not differ significantly from Group II. Total serum calcium levels were within normal limits in both groups and were not significantly different. However, the serum ionized calcium level was significantly higher in Group I with MAC versus Group II without MAC ($p < 0.05$). The serum phosphorus level and calcium phosphorus product were significantly higher in the group with MAC compared to the group without MAC ($p < 0.01$ and $p < 0.001$, respectively). No significant differences were found in the other clinical variables analyzed.**

**It is concluded that MAC in patients with chronic renal failure occurs in the setting of secondary hyperparathyroidism. However, it is found more often in patients with increased ionized calcium and serum phosphorus levels and significantly higher calcium-phosphorus product levels. In chronic renal failure, MAC does not appear to be the result of a degenerative process and high ventricular systolic pressure as has been previously described.**

Mitral anular calcification (MAC), a known complication of progressive renal insufficiency, was detected in 9 to 26% of patients with chronic renal disease.[1,2] Degenerative processes associated with high ventricular systolic pressure are widely assumed to predispose to calcification of the anulus.[3] Recently, rapidly progressive acquired mitral anular and valvular calcification with resultant calcific mitral stenosis was described in a patient with chronic renal failure and elevated calcium-phosphorus product.[4] Roberts and Waller[5] recently emphasized the important role of metabolic factors, namely, hypercalcemia, in cardiac valvular anular calcific deposits in secondary hyperparathyroidism of renal origin.[5] This report evaluates the role of total calcium, ionized calcium, and phosphorus levels and calcium-phosphorus product in patients with end-stage renal disease with MAC.

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### Methods

Thirty patients with chronic renal failure receiving maintenance hemodialysis (3 times/week) were evaluated. No patient was on vitamin D or calcium supplementation. The 10 consecutive patients of Group I with MAC and 20 patients of Group II without MAC were identified by echocardiographic technique. Echocardiographic recordings of all patients were obtained using standard techniques with an Irex System II ultrasonograph using a 1.27 cm, 2.25 MHz medium internally focused transducer with a repetition rate of 1,000 pulses/second. Calcium in the mitral anulus or submitral anulus was recognized echocardiographically as a uniform dense band of

echoes posterior to the posterior mitral leaflet and anterior to the left ventricular wall[6] (Fig. 1). Frequently, the band of echoes moved similarly to the left ventricular wall.

Both serum immunoactive intact parathyroid hormone[7] and serum carboxyl-terminal parathyroid hormone[8] were measured by radioimmunoassay. Ionized calcium levels were obtained using the ion specific electrode method.[9] These measurements were performed at the final month (12th) of the study for each patient. Total serum calcium levels were measured by atomic absorption spectrophotometry[10] and serum phosphorus levels were measured by semiautomated determination of phospholipids.[11] In addition, the outpatient monthly medical records were reviewed. The average supine systolic and diastolic predialysis blood pressure over the preceding 12-month period was recorded. In every patient, the total serum calcium and phosphorus values were determined each month before dialysis. The average phosphorus, calcium, and calcium-phosphorus product were calculated for each patient over the 12 months preceding the echocardiographic study. Length of time on hemodialysis, age, and presence of diabetes were recorded and the data subjected to statistical analysis. The Yates corrected chi-square test was used for comparison of differences in proportions, and differences in means were analyzed by Student's unpaired *t* test.[12]

## Results

**Clinical data:** The data are summarized in Tables I and II. The 10 patients with MAC (Group I, Table I) and 20 patients without MAC (Group II, Table II) did not differ in mean age (59.3 ± 9.5 and 53.5 ± 15.0 years, respectively), sex (70% male versus 50% female), length of time on hemodialysis (4.7 ± 2.8 and 4.5 ± 3.2 years), level of systolic blood pressure (147 ± 19 and 139 ± 20 mm Hg), level of diastolic pressure (81 ± 8.7 and 79 ± 8 mm Hg), or presence of diabetes (4 of 10 in Group I and 6 of 20 in Group II). Hypertensive nephrosclerosis accounted for 50% of patients in both groups followed by diabetic nephrosclerosis as the cause of chronic renal failure. None of the patients had a history or echocardiographic findings consistent with Marfan's syndrome, mitral and aortic valvular disease, or hypertrophic cardiomyopathy. Precordial systolic murmurs were heard in 13 patients (8 with and 5 without MAC).

**Laboratory data:** The data are summarized in Tables I and II. Mean intact parathyroid hormone (normal 163 to 347 pgEq/dl) was elevated in both groups but did not differ significantly between Group I (542 ± 438 pgEq/dl) and Group II (433 ± 306 pgEq/dl). Similarly, mean carboxyl-terminal parathyroid hormone levels (normal up to 375 pgEq/dl) were elevated in the MAC group (13,116 ± 19,730 pgEq/dl) versus the control group (6,233 ± 8,443 pgEq/dl), but this difference was not significant. The ionized calcium level was higher in Group I compared with Group II (3.77 ± 0.48 versus 3.36 ± 0.52 mg/dl, $p < 0.05$). Normal values for ionized calcium were 3.70 to 4.50 mg/dl.

The average serum phosphorus value (normal 2.5 to 4.5 mg/dl) measured monthly over a 12-month period was elevated at 5.4 ± 0.8 mg/dl in Group I and 4.1 ± 1.1 mg/dl in Group II ($p < 0.01$). The average total serum calcium (normal 8.5 to 10.5 mg/dl) over the same period was 9.1 ± 0.7 mg/dl in Group I and 8.7 ± 0.7 mg/dl in Group II (difference not significant [NS]). The average calcium-phosphorus product over 12 months was elevated at 50 ± 9 in Group I and normal at 35 ± 11 in Group II ($p < 0.001$). Analysis of laboratory data at the 12th month (when serum ionized calcium and parathyroid hormone were drawn) revealed no significant difference in total calcium (8.7 ± 0.8 in Group I and 8.4 ± 1.0 in Group II), but significant differences in phosphorus (5.7 ± 1.6 in Group I and 4.3 ± 1.7 in Group II, $p < 0.01$) and calcium-phosphorus product (49.6 ± 15.4 in Group I and 36.5 ± 15.0 in Group II, $p < 0.001$).

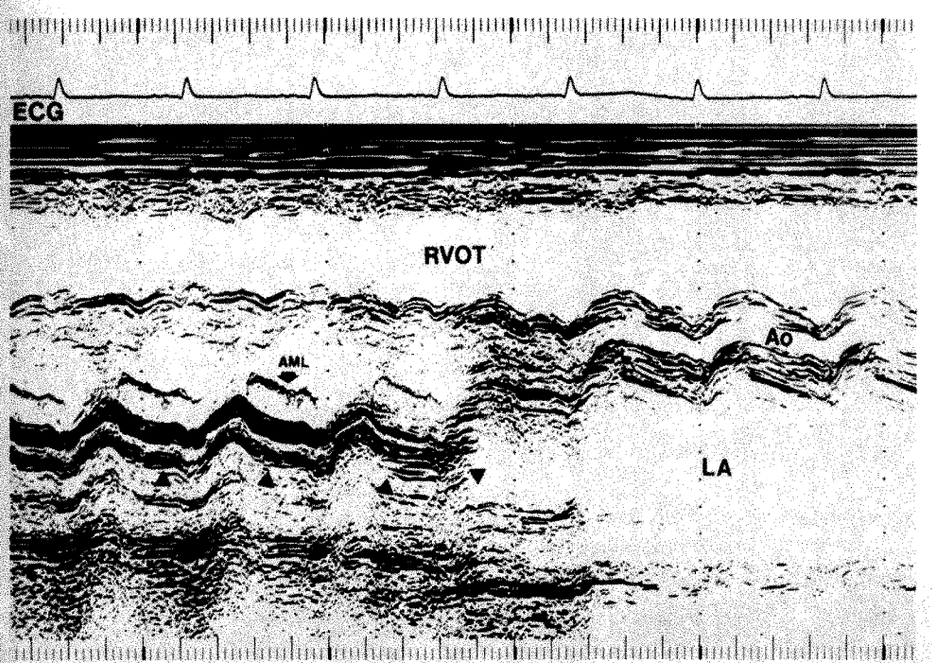



**FIGURE 1.** M-mode echocardiogram in a patient (Patient 5, Table I) with mitral anular calcification. Dense linear band of echoes (**lower triangular arrows**) starting at the atrioventricular groove and extending into the body of the left ventricle is seen. Marked mitral anular calcification is detected echocardiographically in a plane between the posterior mitral leaflet and the left ventricular posterior wall. AML = anterior mitral leaflet; Ao = aorta; ECG = electrocardiogram; LA = left atrium; RVOT = right ventricular outflow tract.

**TABLE I Clinical and Laboratory Data in 10 Patients With Chronic Renal Failure and MAC (Group I)**

| | Clinical Data | | | | | Laboratory Data | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Case | Sex & Age (yr) | HD (yr) | SAP (mm Hg) | DAP (mm Hg) | Renal Disease | C-PTH (pgEq/dl) | I-PTH (pgEq/dl) | I-$Ca^{++}$ (mg/dl) | P (mg/dl) | Ca (mg/dl) | CaxP |
| 1 | M36 | 1.0 | 137 | 88 | D | 3,091 | 149 | 3.72 | 6.20 | 9.66 | 59.8 |
| 2 | M59 | 4.8 | 168 | 94 | H | 1,677 | 262 | 3.66 | 5.16 | 9.67 | 50.0 |
| 3 | F70 | 1.9 | 122 | 80 | D | 66,060 | 979 | 3.58 | 4.75 | 9.82 | 46.8 |
| 4 | F63 | 9.7 | 169 | 92 | H | 6,765 | 267 | 4.29 | 4.35 | 8.65 | 37.2 |
| 5 | F64 | 8.5 | 131 | 70 | C | 3,737 | 612 | 3.11 | 6.30 | 9.30 | 58.6 |
| 6 | F58 | 3.8 | 124 | 68 | D | 2,723 | 272 | 3.50 | 4.00 | 8.65 | 34.7 |
| 7 | F68 | 3.4 | 143 | 76 | H | 23,388 | 1,588 | 4.72 | 6.00 | 10.00 | 62.0 |
| 8 | M63 | 5.9 | 166 | 77 | H | 6,946 | 390 | . . . | 6.15 | 8.25 | 50.7 |
| 9 | F53 | 3.0 | 161 | 80 | H | 3,665 | 356 | 3.58 | 5.79 | 8.17 | 47.4 |
| 10 | F67 | 4.6 | 121 | 62 | D | 42,150 | 240 | 4.65 | 3.84 | 9.90 | 38.1 |
| Mean | 59.3 | 4.7 | 147 | 81 | . . . | 13,116 | 542 | 3.77* | 5.41† | 9.12 | 49.7‡ |
| ±SD | 9.5 | 2.8 | 19 | 8.7 | . . . | 19,730 | 438 | 0.48 | 0.82 | 0.66 | 9.0 |

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, Group I versus Group II.
C = chronic glomerulonephritis; Ca = calcium (normal 8.5 to 10.5 mg/dl); CaxP = mean calcium phosphorus product (normal 40); C-PTH = carboxyl-terminal parathyroid hormone level (normal up to 375 pgEq/dl); D = diabetic nephrosclerosis; DAP = diastolic arterial pressure; H = hypertensive glomerulonephritis; HD = hemodialysis; I = interstitial nephritis (chronic); I-$Ca^{++}$ = ionized calcium (normal 3.70 to 4.50 mg/dl); I-PTH = intact parathyroid hormone level (normal 163 to 347 pgEq/dl); L = lupus nephritis; P = phosphorus (normal 2.5 to 4.5 mg/dl); SAP = systolic arterial pressure.

## Discussion

The pathogenesis of MAC in patients with chronic renal failure is probably multifactorial. Systemic hypertension is often found in this subset of patients. Disturbed calcium-phosphorus metabolism was proposed by Jain et al[13] as another possible predisposing factor. However, patients with MAC in that study underwent hemodialysis for a longer time than did the control group.[13] Our patients showed no differences in length of time on hemodialysis, blood pressure levels, age, and associated disorders such as aortic or mitral valvular disease. We found no significant difference in intact and carboxyl-terminal parathyroid hormone levels between the group with MAC and the control group, although both groups did have elevated intact and carboxyl-terminal parathyroid hormone levels. Values for ionized calcium were statistically higher in the group with MAC than in the control group. Values for mean serum phosphorus level and mean calcium-phosphorus product over a 1 year period and for the final month were statistically higher in the group with MAC than in those without MAC.

Because only a single parathyroid hormone level was obtained, it would be inappropriate to assume that parathyroid hormone did not play an important role in the MAC group, as it is known that parathyroid hormone levels change with dialysis over time.[14] Similarly, although ionized calcium was statistically significantly higher in the MAC group, differences in protein con-

**TABLE II Clinical and Laboratory Data in 20 Patients With Chronic Renal Failure With No MAC (Group II)**

| | Clinical Data | | | | | Laboratory Data | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Case | Sex & Age (yr) | HD (yr) | SAP (mm Hg) | DAP (mm Hg) | Renal Disease | C-PTH (pgEq/dl) | I-PTH (pgEq/dl) | I-$Ca^{++}$ (mg/dl) | P (mg/dl) | Ca (mg/dl) | CaxP |
| 1 | M70 | 6.9 | 132 | 80 | H | 3,938 | 360 | 3.36 | 3.83 | 9.28 | 35.0 |
| 2 | M73 | 4.2 | 114 | 75 | D | 2,779 | 296 | . . . | 3.4 | 8.83 | 29.9 |
| 3 | F62 | 13.0 | 182 | 87 | C | 16,551 | 486 | 3.18 | 4.91 | 8.61 | 42.4 |
| 4 | F45 | 2.1 | 132 | 76 | H | . . . | 1,007 | 3.95 | 3.00 | 8.87 | 26.6 |
| 5 | F40 | 3.4 | 130 | 84 | H | 3,213 | 1,440 | 3.57 | 5.86 | 8.76 | 52.1 |
| 6 | M64 | 8.6 | 178 | 92 | H | . . . | 233 | 3.70 | 5.48 | 10.23 | 56.4 |
| 7 | F50 | 1.0 | 117 | 70 | I | 1,888 | 318 | 3.80 | 3.41 | 8.13 | 27.7 |
| 8 | M60 | 9.2 | 142 | 80 | C | 2,183 | 270 | 4.18 | 4.46 | 9.52 | 19.4 |
| 9 | F29 | 3.2 | 145 | 86 | D | 1,641 | 240 | 3.83 | 2.10 | 9.40 | 19.5 |
| 10 | M61 | 4.2 | 120 | 66 | H | 733 | 277 | 2.62 | 3.85 | 7.45 | 28.7 |
| 11 | M29 | 1.4 | 133 | 80 | D | 7,195 | 418 | 2.81 | 5.50 | 7.17 | 38.9 |
| 12 | F63 | 7.8 | 173 | 94 | H | 780 | 234 | 2.57 | 4.18 | 8.88 | 37.3 |
| 13 | F30 | 4.0 | 130 | 82 | L | 4,208 | 883 | 3.53 | 3.90 | 9.30 | 36.2 |
| 14 | F41 | 1.1 | 134 | 81 | H | 36,206 | 400 | 3.35 | . . . | . . . | . . . |
| 15 | M40 | 1.3 | 131 | 78 | D | 2,451 | 301 | 3.21 | 3.05 | 8.30 | 25.0 |
| 16 | M63 | 1.8 | 139 | 72 | D | 11,076 | 322 | 3.52 | 2.48 | 7.89 | 19.3 |
| 17 | F76 | 3.2 | 164 | 91 | H | 2,680 | 287 | 3.55 | 4.14 | 8.46 | 34.5 |
| 18 | M61 | 2.6 | 131 | 67 | D | 3,546 | 240 | 3.73 | 4.83 | 8.73 | 42.2 |
| 19 | F60 | 1.5 | 124 | 70 | H | 4,896 | 391 | 2.0 | 5.34 | 9.22 | 49.3 |
| 20 | M51 | 7.5 | 154 | 90 | H | 3,277 | 254 | 3.52 | 3.32 | 8.72 | 29.0 |
| Mean | 53.5 | 4.5 | 139.5 | 79.5 | . . . | 6,233 | 433 | 3.36* | 4.09† | 8.72 | 34.4‡ |
| ± SD | 15 | 3.2 | 19.6 | 8.0 | . . . | 8,443 | 306 | 0.52 | 1.05 | 0.73 | 10.8 |

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, Group I versus Group II.
Abbreviations as in Table I.

centration or acid-base status (which were not determined) may have played a role. However, the data suggest that in patients with chronic renal failure accelerated MAC may be a complication of a disordered calcium-phosphorus balance. The significant feature of this imbalance is the elevated serum calcium-phosphorus product dependent on an elevated serum phosphorus in the presence of a background of secondary hyperparathyroidism. These coincident circumstances may result in the precipitation of calcium in the vulnerable tissue of the mitral anulus.

A prospective study in a group of patients with end-stage renal disease early in their dialysis program and before MAC has occurred would be helpful in clarifying the relations between parathormone, phosphorus, and calcium in the pathogenesis of MAC. However, the observation of an association between high serum phosphorus levels and MAC as well as other detrimental effects of hyperphosphatemia would prohibit performance of such a study, as therapy would have to be initiated for the elevated phosphorus level.

Biochemical factors are associated with accelerated deposition of calcium not only in the cardiac anuli but also in the valvular cusps, media, and intima of coronary arteries and individual myocardial fibers.[5] Therefore, acquired valvular heart disease[4] and accelerated coronary atherosclerosis are potential problems in patients with chronic renal failure. MAC is no longer considered a benign entity. Complications include mitral regurgitation, arterial emboli, atrioventricular block, and infective endocarditis.[3] In chronic hemodialysis patients, infective endocarditis has been reported in those with MAC.[15] Nonvisceral calcification can be prevented by reducing serum phosphorus concentration and, accordingly, the calcium-phosphorus product using dialysis and phosphate binding gels.[16] Therefore, aggressive phosphorus control may decrease the incidence of MAC in patients with end-stage renal disease. Serial echocardiograms may be useful in following up these patients to identify early MAC.

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## References

1. **Schott CR, Kotler MN, Segal BL, Parry W, Mahan J.** Echocardiographic spectrum in chronic renal failure (abstr). Circulation 1976;54:Suppl II:II-221.
2. **D'Cruz IA, Bhatt GR, Cohen HC, Blick G.** Echocardiographic detection of cardiac involvement in patients with chronic renal failure. Arch Intern Med 1978;138:720–724.
3. **Fulkerson PK, Beaver BM, Auseon JC, Graber HL.** Calcification of the mitral anulus: etiology, clinical association, complications and therapy. Am J Med 1979;66:967–977.
4. **DePace NL, Rohrer AH, Kotler MN, Brezin JH, Parry WR.** Rapidly progressive massive mitral anular calcification in a patient with chronic renal failure. Arch Intern Med 1981;141:1663–1665.
5. **Roberts WC, Waller BF.** Effect of chronic hypercalcemia on the heart: an analysis of 18 necropsy patients. Am J Med 1981;71:371–384.
6. **Dashkoff N, Karakushensky M, Fortuin NJ.** Echocardiographic features of mitral anulus calcification (abstr). Circulation 1975;52:Suppl II:II-34.
7. **Hawker CD.** Parathyroid hormone: radioimmunoassay and clinical interpretation. Ann Clin Lab Sci 1975;5:383–398.
8. **DiBella FP, Kehrwald JM, Laakso K, Zitzner L.** Parathyrin radioimmunoassay: diagnostic utility of antisera produced against carboxyl-terminal fragments of the hormone from the human. Clin Chem 1978;24:451–454.
9. **Schwartz HD.** Ionized calcium, serum by ion specific electrode (abstr). Clin Chem 1977;23:1126.
10. **Trudeau DL, Freier EF.** Determination of calcium in urine and serum by atomic absorption spectrophotometry (AAS). Clin Chem 1967;13:101–114.
11. **Kraml M.** A semi-automated determination of phospholipids. Clin Chem ACTA 1966;13:442–448.
12. **Colton T.** Statistics in Medicine. Boston: Little, Brown, 1974:99–188.
13. **Jain M, D'Cruz I, Kathpalia S, Goldbarg A.** Mitral anulus calcification as a manifestation of secondary hyperparathyroidism in chronic renal failure (abstr). Circulation 1980;62:Suppl III:III-133.
14. **Goldsmith RS, Johnson WJ.** Role of phosphate depletion and high dialysate calcium in controlling dialytic renal osteodystrophy. Kidney Intern 1973; 4:154–160.
15. **Goldblum SE, Reed WP.** Defenses and immunologic alterations associated with chronic hemodialysis. Ann Intern Med 1980;93:597–613.
16. **Contiguglia SR, Alfrey AC, Miller NL, Runnels DE, LeGeros RZ.** Nature of soft tissue calcification in uremia. Kidney Intern 1973;4:229–235.

# Quantitative Morphologic Findings of the Myocardium in Idiopathic Dilated Cardiomyopathy

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**This study assesses the relation between quantitative morphologic findings and left ventricular contractile function in patients with idiopathic dilated cardiomyopathy. Left ventricular endomyocardial catheter biopsy specimens were obtained from 73 patients during diagnostic heart catheterization. All patients had normal coronary arteriograms but abnormal electrocardiograms. Twenty-six patients had normal left ventricular function (ejection fraction ≥55%), whereas 47 patients had contractile dysfunction (ejection fraction ≤54%). Myocardial fiber diameter, volume fraction of interstitial fibrosis, and intracellular volume fraction of myofibrils were determined by light microscopic morphometry. Results of light microscopic morphometry were confirmed by electron microscopic morphometry in 12 patients. The coefficient of variation (analysis of several biopsies from the same patient) was 6% for determination of fiber diameter, 43% for interstitial fibrosis, and 3% for volume fraction of myofibrils. Fiber diameter ($r = -0.32$, $p < 0.01$) and fibrosis ($r = -0.47$, $p < 0.001$) showed a negative correlation, the volume fraction of myofibrils ($r = 0.55$, $p < 0.001$) and calculated myofibrillar mass per 100 g of myocardium ($r = 0.64$, $p < 0.001$) a positive correlation with the ejection fraction. Thus, (1) sampling error is low for determination of fiber diameter and myofibrils but high for evaluation of fibrosis, and (2) a reduction in the volume fraction of myofibrils and an increase in fibrosis are morphologic correlates of left ventricular dysfunction in patients with idiopathic dilated cardiomyopathy.**

Right and left ventricular biopsy techniques have extended our knowledge of the relation between morphologic findings and clinical aspects in various types of heart disease.[1-7] Several features of the myocardium in patients with idiopathic dilated cardiomyopathy have been described.[1-3] However, quantitative morphometric data have not been reported. Furthermore, the sampling error of data obtained from endomyocardial biopsy specimens is not well defined. This study aims to (1) determine the sampling error of morphometric data obtained from left ventricular endomyocardial biopsy in patients with idiopathic dilated cardiomyopathy, and (2) correlate the quantitative morphometric data with the contractile function of the left ventricle.

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## Methods

**Patients:** The study group consisted of 73 patients (61 men and 12 women) aged 23 to 55 years with idiopathic myocardial disease studied invasively between July 1978 and July 1980. At catheterization, each patient had 2 or more of the following clinical features: (1) symptoms of heart failure; (2) episodes of chest discomfort; (3) roentgenographic evidence of cardiomegaly (cardiothoracic ratio >0.5); (4) an electrocardiographic abnormality in the form of an intraventricular conduction defect (with a wide QRS complex >0.11 second), atrial arrhythmias, left ventricular hypertrophy (S wave in $V_1$ or $V_2$ plus R wave in $V_5$ or $V_6$ >35 mm), or S-T segment and T wave abnormalities. Table I lists the proportion of each clinical feature in the study population. Patients with coronary artery disease (diameter reduction of major coronary vessel of ≥25%), systemic hypertension, valvular heart disease, cor pulmonale, or systemic disease involving the heart muscle were excluded from the study.

**Catheterization:** All patients underwent left ventricular catheterization including selective coronary arteriography and left ventricular cineangiography. At catheterization, 52% of patients were taking digitalis or diuretics, or both. Single plane cineangiography was performed in the 30° right anterior

**TABLE 1 Clinical Features of the Study Population**

| Features | Patients (%) |
|---|---|
| Symptoms of heart failure | 74 |
| Episodes of chest discomfort | 37 |
| Cardiomegaly (cardiothoracic ratio >0.5) | 38 |
| Electrocardiographic abnormalities | |
| Intraventricular conduction defect | 29 |
| Atrial arrhythmias | 15 |
| Left ventricular hypertrophy | 23 |
| S-T segment and T wave abnormalities | 38 |

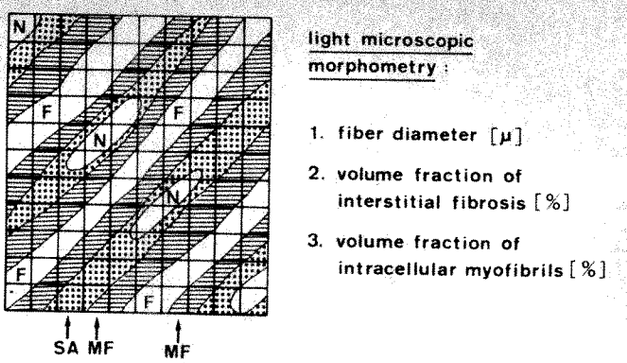



**FIGURE 1.** Schematic drawing illustrating the technique of light microscopic morphometry. The fiber diameter is determined from cross and oblique sections. The volume fraction of interstitial fibrosis and of intracellular myofibrils is determined from longitudinal sections by point counting technique, that is, intersections of the grid falling on fibrosis (F) or myofibrils (MF) are counted and expressed as a percentage of total points or points falling on myocardial cells. SA = sarcoplasm; N = nucleus.

oblique projection (50 to 60 ml of Urografin®-76, 35 mm cinefilm, 50 frames/s, Philips dual field 9-5 inch image intensifier system). Selective coronary arteriography was performed using the Judkins technique. Left ventricular volumes and ejection fraction were determined by the area length method.[8]

**Diagnosis:** Forty-seven patients had depressed left ventricular function as evaluated by a left ventricular ejection fraction of ≤54%. These patients were classified as having idiopathic dilated cardiomyopathy. Among these patients the following etiologic "risk factors" could be encountered: peripartal cardiomyopathy in 1 patient and increased alcohol intake (>2,000 ml of beer or an equivalent dose of wine per day for more than 10 years in 12 patients).[9] The remaining 26 patients had a normal ejection fraction (≥55%). Clinical features in most patients were episodes of chest pain and electrocardiographic abnormalities, and the patients were classified as having chronic myocarditis or latent cardiomyopathy.[4]

**Endomyocardial biopsy:** Endomyocardial biopsy specimens were taken with the King's College Bioptome using the retrograde transarterial route and a polyvinyl chloride (PVC) sheath.[10] At least 2 biopsy samples were obtained from the left ventricular anterior free wall. Biopsy from the left ventricular apex was carefully avoided. There were no serious complications in the 73 patients during and after biopsy. Immediately after biopsy, tissues were fixed in a mixture of 1.5% glutaraldehyde and 1.5% formaldehyde in 0.2 *M* phosphate buffer. The biopsy specimens were embedded in Araldit®, and thin sections (0.5 μm) were prepared and stained with alkaline toluidine blue and 3% paraphenylendiamine (combined staining) for light microscopic morphometry (magnification 160× for determination of fibrous tissue and 1,000× for determination of myofibrils). The area of tissue analyzed ranged from 1.2 to 6.5 $mm^2$ (mean 2.8 ± 1.7). Fiber diameter of myocardial cells was measured from 80 to 300 cross and oblique sections of myocardial cells using the light microscope (magnification 400×). When oblique sections were counted, the short diameter of the section profile was determined. The volume fraction of fibrous interstitial tissue[11] was measured by light microscopic morphometry. The volume fraction of fibrous interstitial tissue and of myofibrils was measured in randomly selected sections without respect for the direction of sectioning. Random test areas were evaluated to determine volume fractions, and we did not use different planes of the same biopsy. If cross-sections were unavailable for measurement of fiber diameter, we changed the direction of sectioning. The point counting method was performed with a Zeiss eyepiece containing a test grid with 36 intersections (test points). From each biopsy 5 to 20 areas were counted (each containing 36 points). Volume fraction of fibrous tissue is the number of points falling on fibrosis divided by the points falling on total tissue (Fig. 1). We carefully avoided counting the endocardium as fibrous tissue. The collagen-containing tissue component was counted without edema, blood vessels, and interstitial tissue cells. At the edge of the biopsy specimens a rim of about 100 μm was excluded from analysis to avoid areas with marked hypercontraction. Myofibrils were counted in 12 areas. Intracellular volume fraction of myofibrils is the number of points falling on myofibrils divided by points falling on total myocardial cells (Fig. 1). Analysis of biopsies was performed without knowledge of clinical data.

**Comparison of light and electron microscopic morphometry:** Because light microscopic morphometry was used to measure the volume fraction of myofibrils in the present study and all previous studies used electron micrographs as the source of data, it was necessary to compare light and electron microscopic morphometry. To get formal validation of the light microscopic method, we chose randomly 12 tissues out of the series studied (12 patients). Ultra- and semithin sections were cut from the same tissue block. Electron microscopic point counting was performed on 40 random test areas using a total number of about 3,200 test points (magnification 10,000). Total test area mounted to 12,000 $\mu m^2$. A monitor with a television camera connected to a Zeiss EM 10 was used for the counting procedure. Details of this method were described elsewhere.[12] Light microscopic morphometry was performed with the method just described herein (test area 15,000 $\mu m^2$).

**Sampling variability of endomyocardial biopsies:** To determine what changes in the measurement of different biopsy samples from the same heart should be considered significant, we estimated reproducibility in terms of sampling variability of endomyocardial biopsies (that is, how much each measurement varied when made from separate biopsy specimens in the same patient). The sampling variability was determined in 26 patients in whom 2 (n = 14) or 3 (n = 12) separate biopsy specimens were obtained. Variability was determined by the coefficient of variation, defined as the standard deviation of all repeated measurements in a given case divided by the mean of those measurements. Two standard deviations on either side of the mean were calculated from estimates of reproducibility and the 95% confidence interval was determined for each variable; the actual value by which each measurement can vary was then calculated. All biopsy samples were encoded and analyzed without knowing which biopsies were from the same patient.

**Statistical analysis:** The linear regression analysis and Student's $t$ test for paired and unpaired data were used.[13] Significance was accepted at the 5% probability level. Data are mean ± standard deviation. A combined index of myofibrils and fibrosis was calculated: myofibrillar mass/100 g of myocardium (that is, [100 minus volume fraction of fibrosis in %] multiplied by volume fraction of myofibrils in % divided by 100).

## Results

**Comparison of light and electron microscopic morphometry:** Figure 2 illustrates sections of myocardium of biopsy specimens obtained from a patient with idiopathic dilated cardiomyopathy using light (upper panel) and electron microscopy (lower panel). Myofibrils can easily be identified by light microscopy. Data obtained by light and electron microscopic morphometry were correlated using linear regression analysis, and the following equation was obtained: myofibrils (determined by light microscopy) = 1.01 myofibrils (determined by electron microscopy) + 2.26, r = 0.96. To test whether both methods are equivalent when normal and abnormal muscle cells are analyzed, we divided the data into 2 subgroups with a volume fraction of myofibrils ≥50% (normal myocardial cells) and ≤50% (abnormal myocardial cells). Table II lists the individual and mean data obtained by both methods. Light microscopic morphometry revealed similar values of volume fraction of myofibrils as compared with electron microscopic morphometry, although there was a slight overestimation of the myofibrillar volume fraction when using light microscopic morphometry. Nevertheless, both methods produced similar results on normal as well as abnormal myocardial tissue.

**Sampling variability of morphologic findings:** Data analyzing sampling variability of morphometric analysis are presented in Table III. The greatest scatter

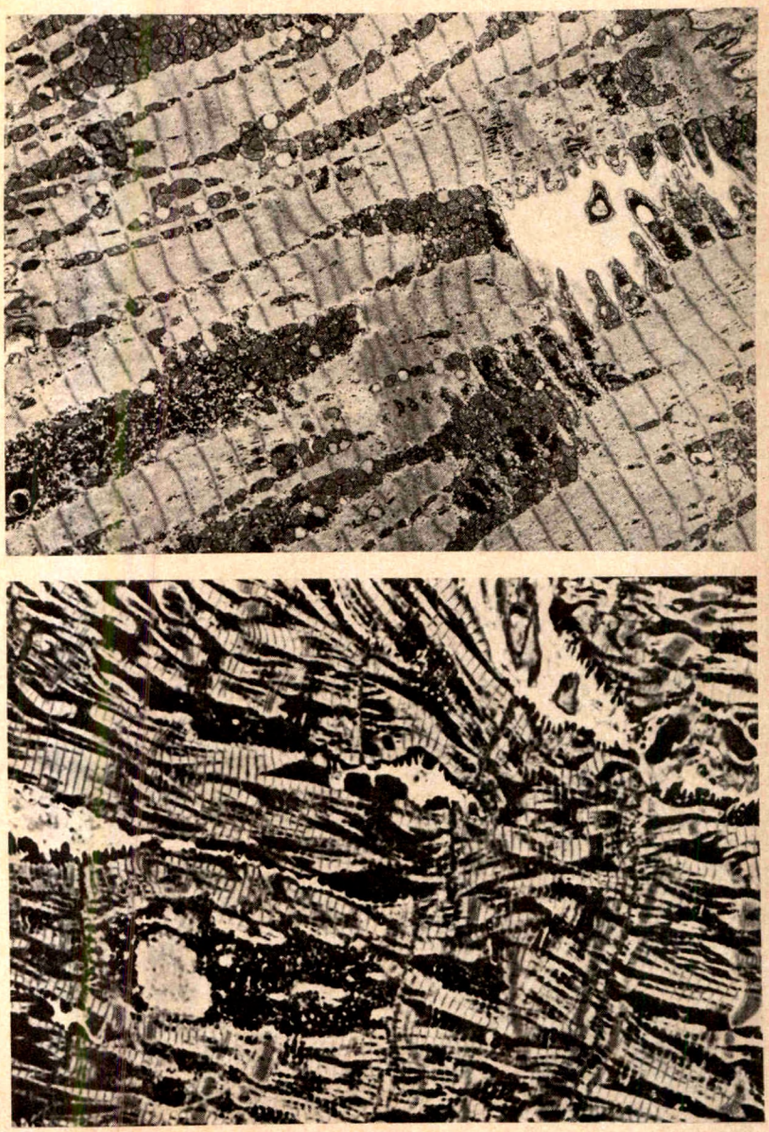


**FIGURE 2.** Endomyocardial biopsy obtained from a patient with idiopathic dilated cardiomyopathy. **Upper panel,** electron micrograph, magnification ×5,000. **Lower panel,** light micrograph, magnification ×1,000 for comparison. Both panels reduced 36%. Myofibrils are seen with the light microscope.

**TABLE II Comparison Between Determination of Volume Fraction of Myofibrils by H Electron and Light Microscopic Morphometry**

| Volume Fraction of Myofibrils (%) | |
|---|---|
| Electron Microscopy | Light Microscopy |
| Normal Myocardial Cells | |
| 53.8 | 55.8 |
| 52.9 | 60.2 |
| 54.0 | 55.6 |
| 56.6 | 57.0 |
| 57.4 | 59.5 |
| 54.3 | 60.6 |
| 50.9 | 51.5 |
| 54.3 ± 2.2* | 57.2 ± 3.2* |
| Abnormal Myocardial Cells | |
| 30.9 | 34.2 |
| 44.4 | 49.4 |
| 43.8 | 43.5 |
| 40.3 | 41.5 |
| 45.7 | 48.7 |
| 41.0 ± 6.0* | 43.5 ± 6.2* |

* Mean ± standard deviation.

of data is found for the determination of interstitial fibrosis, whereas evaluation of fiber diameter and volume fraction of myofibrils reveals less variability.

**Reduced volume fraction of myofibrils in the failing heart:** Figure 3 represents inverse correlations between left ventricular ejection fraction and fiber diameter (upper panel) and the volume fraction of fibrosis (lower panel). Both correlations reveal considerable scatter of data points. Figure 4 displays the correlations between left ventricular ejection fraction and volume fraction of myofibrils (upper panel) and myofibrillar mass (lower panel). The latter correlation revealed the highest correlation coefficient ($r = 0.64$).

## Discussion

**Light versus electron microscopic morphometry:** In the present study morphologic changes of the left ventricular myocardium were quantitated by light microscopic morphometry. With this technique we assessed (1) hypertrophy of myocardial fibers, (2) interstitial fibrosis, and (3) intracellular volume fraction of myofibrils. The volume fraction of myofibrils was not previously measured by light microscopy. This technique was equivalent to electron microscopic morphometry provided 3 prerequisites are fulfilled: (1) use of thin sections (0.5 $\mu$m), (2) combined staining with toluidine blue and paraphenylendiamine, and (3) use of phase contrast microscopy with oil immersion. The staining technique was found superior to standard toluidine blue staining, because paraphenylendiamine enhances the contrast between myofibrillar and nonmyofibrillar components of myocardial cells. As shown in Figure 2 myofibrils can easily be identified with this technique. Furthermore, as shown in Table II, light and electron microscopic morphometry revealed similar results on normal as well as abnormal myocardium. Light microscopy was preferred for quantification of myofibrils, because large test areas could be analyzed (about 30,000 $\mu m^2$ per biopsy).

**Sampling error in endomyocardial biopsy technique:** In previous studies using various grading systems to evaluate intracellular degenerative changes in left ventricular biopsies taken from patients with idiopathic dilated cardiomyopathy, the sampling error was not defined and hence not taken into account in the interpretation of results.[4–6] Table III illustrates that a considerable scatter of data was found when quantitative data obtained from 2 different myocardial biopsy specimens taken from the same heart were compared. The sampling error was greatest for quantification of interstitial fibrosis. Determination of fiber diameter and volume fraction of myofibrils revealed a significantly smaller sampling error. Thus, the degree of fibrosis can only be approximated in idiopathic dilated cardiomyopathy, but cannot be determined with accuracy when endomyocardial biopsy technique is used.

**Reduced volume fraction of myofibrils in the failing heart:** In the failing heart with idiopathic dilated cardiomyopathy, a slight increase in fiber diameter as well as an increase in fibrosis and a reduction in myofibrils and myofibrillar mass was observed when the ejection fraction declined. These findings document that quantitative data of morphologic evaluation correlate with left ventricular dysfunction. The inverse relation between ejection fraction and fibrosis may suggest that fibrosis determines contractile dysfunction in idiopathic dilated cardiomyopathy. However, because the degree of fibrosis can only be approximated by the technique used, this relation remains uncertain. In contrast, determination of myofibrils shows high accuracy and the relation incorporating volume fraction of myofibrils was close and therefore shows that a reduction in myofibrils reflects myocardial dysfunction. What causes the decrease in the volume fraction of

**TABLE III Sampling Variability of Endomyocardial Biopsies (Reproducibility of Morphometric Evaluation)**

| | Patients (n) | Measured Data H (Mean ± SD) | Coefficient of Variation (%) | 95% Confidence Interval (±2 SD) of Each Measurement |
|---|---|---|---|---|
| Fiber diameter ($\mu$m) | 26 | 24.5 ± 4.0 | 6 | ±2.9 |
| Volume fraction of interstitial fibrosis (%) | 25 | 10.7 ± 9.7 | 43 | ±9.2 |
| Volume fraction of intracellular myofibrils (%) | 26 | 55.9 ± 4.7 | 3 | ±3.4 |

SD = standard deviation.

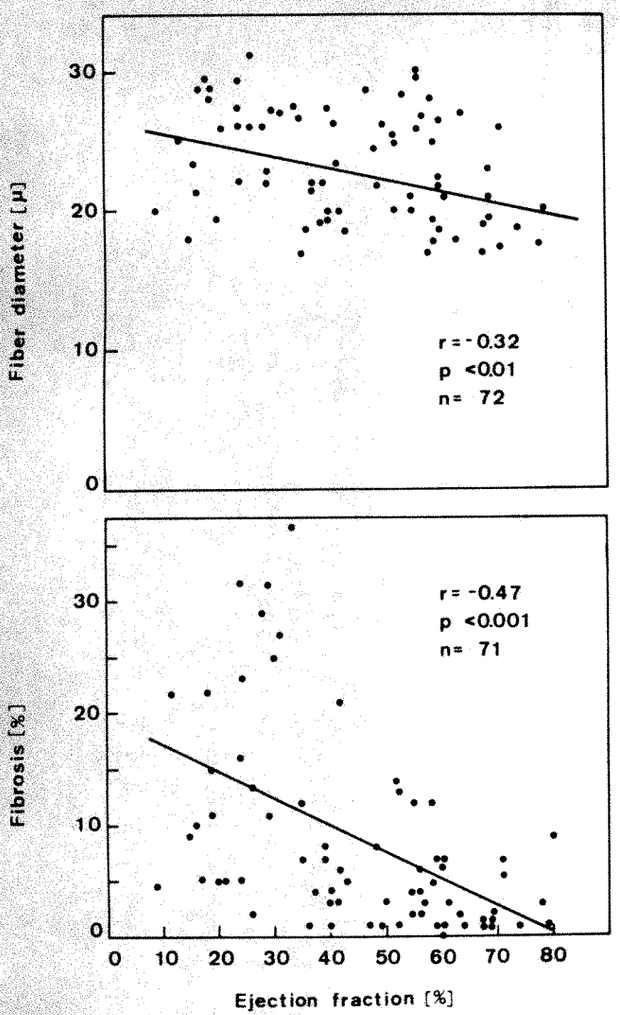



**FIGURE 3.** Inverse correlation between left ventricular ejection fraction and fiber diameter of myocardial cells (**upper panel**) and interstitial fibrosis (**lower panel**).

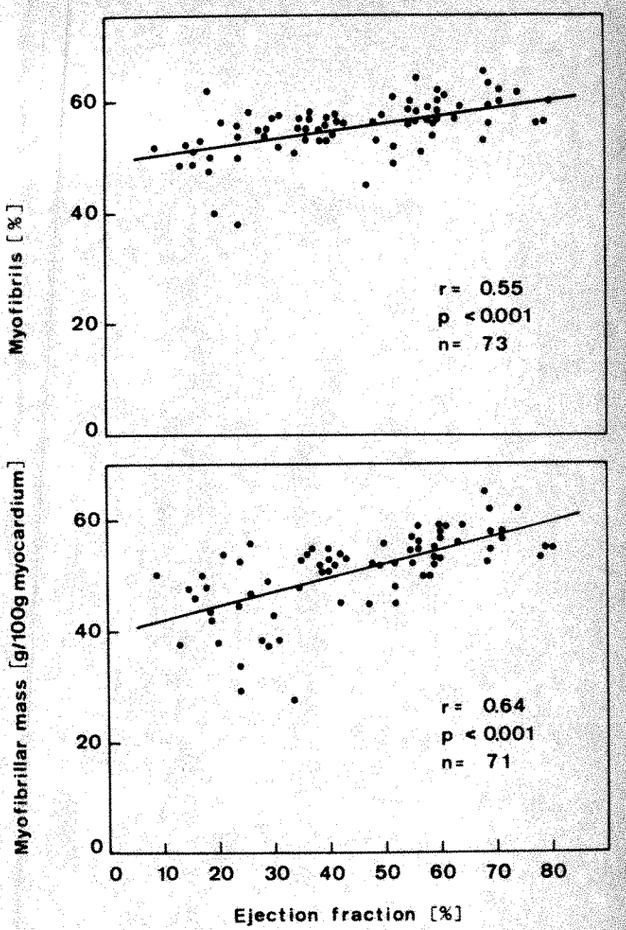



**FIGURE 4.** Correlation between left ventricular ejection fraction and intracellular volume fraction of myofibrils (**upper panel**) and myofibrillar mass (**lower panel**).

myofibrils? Is it a reflection of intracellular edema, proliferation of nonmyofibrillar components (mitochondria), or an absolute decrease in the number of myofibrils? Obviously, it is impossible to answer conclusively on the basis of morphometric data. Because we studied the biopsies by electron microscopy also (qualitatively), we believed that the decrease in the volume fraction of myofibrils is caused by a loss in myofibrils (myofibrillar lysis) or an impaired resynthesis of contractile proteins, or both. We interprete the reduction in volume fraction of myofibrils as a quantitative measure of the degeneration of myocardial fibers. Myofibrillar lysis was previously described by our group in patients with coronary artery disease.[14] An intracellular reduction in volume fraction of myofibrils (with or without an associated increase in interstitial fibrosis) is not pathognomonic for patients with idiopathic dilated cardiomyopathy, because similar findings were observed in patients with chronic aortic valve disease and in those with coronary artery disease.[7,14] Obviously, a uniform cellular response to various cardiac stresses occurs.

**Clinical implications:** From the data it can be concluded that the reduction in myofibrils is a consistent finding in myocardium in patients with idiopathic dilated cardiomyopathy. The degree of fibrosis cannot accurately be assessed by endomyocardial biopsy technique, although fibrosis seems to be augmented in cases with severe impairment of contractile function. Whether changes of myocardial structure are the cause or the effect of contractile dysfunction remains to be clarified.

## References

1. **Roberts WC, Ferrans VJ.** Pathologic anatomy of the cardiomyopathies. Human Pathol 1975;6:287–322.
2. **Roberts WC, Ferrans VJ.** Pathological aspects of certain cardiomyopathies. Circ Res 1974;35,36:Suppl II:II-128–II-141.
3. **Doerr W, Mall G.** Cardiomyopathie. Angeborene, erworbene und Differentialdiagnose. Pathologe 1979;1:7–35.
4. **Kuhn H, Breithardt G, Knieriem HJ, Loogen F, Both A, Schmidt WAK, Stroobandt R, Gleichmann U.** Die Bedeutung der endomyokardialen Katheter-Biopsie für die Diagnostik und die Beurteilung der Prognose der congestiven Kardiomyopathie. Dtsch Med Wochenschr 1975;100:717–

728.
5. **Kunkel B, Lapp H, Kober G, Kaltenbach M.** Correlations between clinical and morphological findings and natural history in congestive cardiomyopathy. In: Cardiomyopathy and Myocardial Biopsy. Kaltenbach M, Loogen F, Olsen EGJ, eds. Berlin: Springer Verlag, 1978:271–288.
6. **Noda S.** Histopathology of endomyocardial biopsies from patients with idiopathic cardiomyopathy; quantitative evaluation based on multivariate statistical analysis. Jpn Circ J 1980;44:95–121.
7. **Schwarz F, Schaper J, Kittstein D, Flameng W, Walter P, Schaper W.** Reduced volume fraction of myofibrils in myocardium of patients with decompensated pressure overload. Circulation 1981;63:1299–1302.
8. **Kasser IS, Kennedy JW.** Measurement of left ventricular volumes in man by single-plane cineangiography. Invest Radiol 1969;4:83–90.
9. **Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL.** The nature course of idiopathic dilated cardiomyopathy. Am J Cardiol 1981; 47:525–532.
10. **Richardson PJ.** King's endomyocardial bioptome. Lancet 1974;1:660–663.
11. **Weibel ER, Gonzagne SK, Walter F.** Practical stereological methods for morphometric cytology. J Cell Biol 1966;30:23–37.
12. **Mall G, Reinhard H, Kayser K, Rossner JA.** An effective morphometric method for electron microscopic studies on papillary muscles. Virchows Arch Path Anat Histol 1978;379:219–232.
13. **Sachs L.** Statistische Auswertungsmethoden. Berlin: Springer Verlag, 1972:386–392.
14. **Schwarz F, Flameng W, Thiedemann KU, Schaper W, Schlepper M.** Effect of coronary stenosis on myocardial function, ultrastructure and aortocoronary bypass graft hemodynamics. Am J Cardiol 1978;42:193–201.

# Significance of Ventricular Tachycardia in Idiopathic Dilated Cardiomyopathy: Observations in 35 Patients

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**To evaluate the significance of ventricular tachycardia (VT) in idiopathic dilated cardiomyopathy (IDC), 35 consecutive patients seen between 1976 and 1980 were studied. The criteria for diagnosis of IDC were based on clinical, laboratory, and cardiac catheterization findings. All patients had right and left heart catheterization, left ventriculography, and coronary cineangiography. Long-term ambulatory electrocardiograms (Holter) were obtained in all patients at the time of diagnosis. There were 24 male and 11 female patients aged 22 to 72 years (mean ± standard deviation [SD] 51 ± 12). Frequent ventricular premature beats (VPB) (30/h) were observed in 29 patients (83%): complex VPB (Lown grades 3, 4, and 5) in 93% and simple VPB in 7%. Twenty-one patients (60%) had nonsustained VT consisting of 3 to 46 beats (8 ± 5) with rates from 75 to 210/min. No difference between patients with and those without VT was observed in regard to the presenting symptoms, functional classification, electrocardiographic findings, heart size on chest X-ray, and the hemodynamic measurements including cardiac index, left ventricular end-diastolic pressure, and ejection fraction. Patients with VT were older ($p < 0.05$). Follow-up observation from 4 to 74 months (34 ± 17) showed that 2 patients died suddenly (1 with and 1 without previous VT), a third patient died from intractable congestive heart failure, and the fourth from sepsis. It is concluded that (1) the incidence of ventricular arrhythmias in IDC is high, (2) VT is frequent and tends to occur in the nonsustained form, and (3) there is no correlation between VT and the clinical and hemodynamic findings. VT does not appear to predict prognosis during a relatively short follow-up period in patients with IDC.**

Cardiomyopathy is a disease of the heart muscle caused by a spectrum of known (secondary) or unknown (primary or idiopathic) factors.[1] A variety of schemes for classifying the cardiomyopathy have been proposed. Goodwin's classification into congestive, hypertrophic, and restrictive cardiomyopathy has been widely accepted.[2] More recently, the term *dilated* has been substituted for *congestive* as the preferred terminology, that is, idiopathic dilated cardiomyopathy (IDC).[1,3,4] Several studies have correlated clinical features and hemodynamic findings with prognosis of IDC.[4–14] The design of these studies had several limitations because (1) some studies included patients with secondary cardiomyopathy,[4,6,10–14] (2) in others, the patients did not undergo cardiac catheterization and coronary angiography to confirm the diagnosis,[5,6,10] and (3) the prevalence of cardiac arrhythmias was evaluated only with standard electrocardiographic tracings taken at random intervals.[4,5,9,10,12,13]

Long-term dynamic electrocardiographic (Holter) monitoring has been useful in detecting and evaluating the significance of cardiac arrhythmias in different diseases.[15–22] With this diagnostic tool, many studies have focused on the prognostic significance of VPB and VT in patients with coronary artery disease and hypertrophic cardiomyopathy.[19–22] However, little is known about the prevalence of ventricular arrhythmias evaluated by long-term (≥24 hours) Holter monitoring and their clinical significance in patients with IDC. In the present study, we assess 35 consecutive patients with IDC. All patients had cardiac catheterization, angiography, and 24-hour Holter monitoring. We compared various clinical features and hemodynamic findings in patients with and those without VT and evaluated the prognostic significance of VT in patients with IDC.

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## Methods

**Patient selection:** Of 118 consecutive patients with an initial diagnosis of cardiomyopathy screened between January 1976 and December 1980, 47 fulfilled the selection criteria for IDC. Of them, 35 had long-term ambulatory electrocardiograms taken during admission when the diagnosis was made. These 35 patients, 24 male and 11 female patients aged 22 to 72 years (51 ± 11), are our study population.

Diagnostic criteria of IDC included (1) the presence of 2 or more of the following clinical features[4]: (a) symptoms or signs of left or right heart failure, or both, (b) chest x-ray evidence of cardiomegaly, (c) abnormal electrocardiogram, and (d) history of embolization; (2) the presence of all of the following hemodynamic features[4]: (a) dilated left ventricular chamber with global or >3 segment hypokinesia on a single plane (right anterior oblique) left ventriculogram and an abnormal ejection fraction (<55%), (b) absence of significant coronary artery disease, that is, occlusion of >50% in any 1 of the major coronary arteries or their branches; (3) exclusion of all patients with specific heart muscle disease (infective or metabolic), general systemic disease (connective tissue disorders or infiltrative disease), heredofamilial disorders, and sensitivity or toxic reactions.[1]

**Clinical evaluation:** History and physical examinations in all patients were performed by 2 physicians. Interpretation of the electrocardiogram, chest X-ray, angiogram, and the like was performed by at least 2 observers. Functional status was classified according to the criteria of the New York State Heart Association.[23] All patients had standard posteroanterior and lateral chest X-ray films during initial admission. A cardiothoracic ratio of >0.50 was considered evidence of cardiomegaly on chest X-ray. During admission, 12-lead electrocardiograms were taken with simultaneous 3-channel recordings. The diagnosis of left ventricular hypertrophy was made according to the criteria of Romhilt and Estes.[24] Follow-up information was obtained in all patients by reviewing the patient's clinical records, contacting the primary physician, and contacting the patient or relatives by telephone.

**Cardiac catheterization and angiography:** All 35 patients underwent left and right cardiac catheterization, left ventriculography, and coronary cinearteriography. Resting intracardiac pressures were recorded. The cardiac index was determined by the Fick method. Twenty-four patients had single plane (45° right anterior oblique projection) left ventriculography; the other 11 had biplane projections. Left ventricular ejection fraction was obtained by planimetric volume calculation from either single or biplane left ventriculograms.[25,26] Coronary cineangiograms were taken in multiple projections.

**Dynamic electrocardiographic monitoring (Holter):** All patients underwent monitoring for a minimum of 24-hours during admission. All records were analyzed by a trained technician and reviewed by a cardiologist. For classifying ventricular arrhythmias, a modification of Lown's grading system was used[17]: grade 1, ≤30 uniform VPB in any hour of monitoring; grade 2, >30 uniform VPB in any hour of monitoring; grade 3, multiform VPB; grade 4, couplets; grade 5, R on T, defined as having a prematurity index RR′/QT <1. We defined nonsustained VT as having ≥3 consecutive VPB that lasted <1 minute and were self-terminating without specific therapeutic intervention. Each patient's Holter monitor finding with VT was analyzed to determine the number of episodes of VT per 24 hours, the number of VPB per episode, the rate of VT, and the prematurity index of the initiating beat of each episode. Supraventricular arrhythmias, which were analyzed, included the presence of >30 atrial premature beats in any hour of monitoring and the presence of supraventricular tachycardia defined as having ≥3 consecutive atrial premature beats. The corresponding entries in the patient's diary were received in only 12 patients.

**Statistical analysis:** Patients were divided into 2 groups: the VT group consisting of patients who had VT during Holter monitoring and the non-VT group consisting of patients who did not have VT. The VT and non-VT groups were compared with regard to age, sex, presenting symptoms, functional class, cardiomegaly on chest X-ray, electrocardiographic findings, and hemodynamic measurements by either the Student's *t* test or the chi-square test.

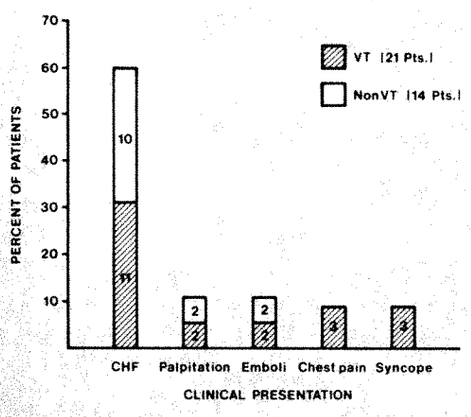



**FIGURE 1.** Clinical presentation of 35 patients with IDC. The numbers inside each bar represent the number of patients with each presenting symptom in the VT (**hatched bars**) and the non-VT (**open bars**) group. Comparison of clinical presentation in the 2 groups was not significantly different.

## Results

**Clinical and electrocardiographic findings:** Twenty-one patients (60%) had nonsustained VT and the remaining 14 patients (40%) had no VT during the initial Holter monitoring. The mean age of the VT group was 55 ± 10 years, which was significantly greater than that of the non-VT group (47 ± 12 years) ($p < 0.05$). There were 16 male and 5 female patients in the VT group and 8 male and 6 female patients in the non-VT group (chi-square = 0.67; p = not significant [NS]).

The presenting symptom was identified for each patient. Congestive heart failure was the most common clinical manifestation, occurring in 21 (60%) of the 35 patients. Three patients presented with cerebrovascular accidents due to systemic emboli and 1 with pulmonary emboli (11%). Three patients were hospitalized for chest pain (9%), 4 for palpitation (11%), and 3 for syncope

**TABLE I New York Heart Association Functional Class at the Time of Diagnosis**

| Functional Class | VT Group | | Non-VT Group | |
|---|---|---|---|---|
| | n | % | n | % |
| I | 2 | 9 | 0 | 0 |
| II | 6 | 29 | 2 | 14 |
| III | 9 | 43 | 10 | 72 |
| IV | 4 | 19 | 2 | 14 |

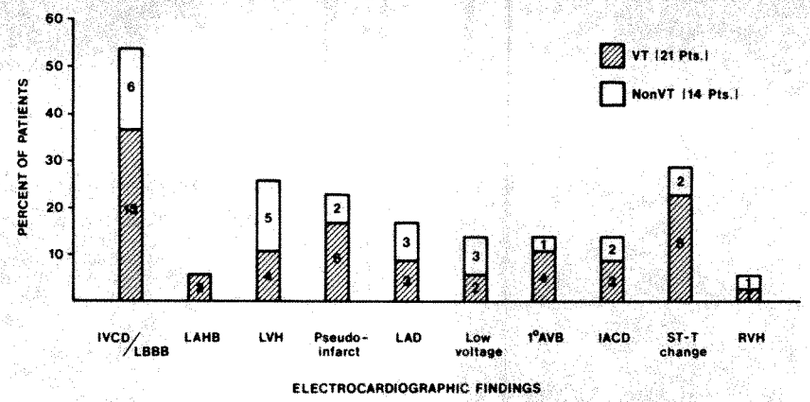



**FIGURE 2.** Electrocardiographic findings in patients with IDC. The numbers inside each bar represent the number of patients with different electrocardiographic findings in the VT and the non-VT group. Left bundle branch block (LBBB) or intraventricular conduction delay (IVCD) was the most common finding (54%). There were no significant differences in electrocardiographic findings in 2 groups. 1° AVB = first degree AV block; IACD = intraarterial conduction defect; LAD = left axis deviation; LAHB = left anterior hemiblock; LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy.

(9%) (Fig. 1). No significant differences in clinical presentation existed between the VT and the non-VT groups (chi-square = 5.44; p = NS). Most patients were New York Heart Association functional class III when the diagnosis of IDC was made. There were no significant differences between the VT and the non-VT group in functional classification (chi-square = 3.46; p = NS) (Table I).

Electrocardiographic abnormalities, present in all 35 patients, included left bundle branch block or intraventricular conduction delay in 19 patients (54%), nonspecific ST-T wave changes in 10 (29%), left ventricular hypertrophy in 9 (26%), and pseudoinfarct Q waves in 9 (23%) (Fig. 2). Other electrocardiographic findings included left axis deviation (17%), low QRS voltage (14%), right ventricular hypertrophy (6%), intraatrial conduction defect (14%), and first degree atrioventricular (AV) block (14%) (Fig. 2). There were no significant differences in electrocardiographic findings between the 2 groups. Cardiomegaly on chest X-ray was noted in 18 (86%) VT patients and 13 (93%) non-VT patients (chi-square = 0.01; p = NS).

**Hemodynamic findings:** The mean cardiac index, which did not differ significantly between the VT and the non-VT groups, was 2.7 ± 0.7 (range 1.6 to 4.0) versus 2.6 ± 0.6 liters/min/m (range 1.7 to 4.0). Similarly, no significant differences between the 2 groups were found regarding left ventricular end-diastolic pressure (17 ± 8 versus 19 ± 11 mm Hg) and left ventricular ejection fraction (33 ± 11 versus 32 ± 7%).

**Dynamic electrocardiographic (Holter) findings:** Table II outlines the Holter monitor findings in 35 patients. Basic sinus rhythm was found in 80% of patients and atrial fibrillation in 20%. Significant atrial premature beats (>30 beats/h) occurred in 15 patients (54%). In 7 patients (25%), 1 to 8 episodes of supraventricular tachycardia developed with a duration of 3 to 40 beats and rates of 105 to 175 beats/min. Frequent VPB (>30 beats/h) were noted in 29 patients (83%), of whom 27 patients (93%) had complex VPB (Lown grades 3, 4, and 5) and 2 (7%) had simple VPB (uniform). The prevalence of ventricular arrhythmias by modified Lown grades in 35 patients is shown in Figure 3.

The prevalence of VPB in patients with and those without VT according to frequency and complexity is shown in Table III. All patients in the VT group had multiform VPB and 90% of them had paired VPB. Thus, the occurrence of multiform and paired VPB was

**TABLE II Holter Monitoring Findings in 35 Patients**

| | n | % |
|---|---|---|
| Atrial fibrillation | 7 | 20 |
| Atrial premature beats (>30/h) | 15 | 54 |
| Supraventricular tachycardia | 7 | 25 |
| Ventricular premature beats (>30/h) | 29 | 83 |
| Simple (uniform) | 2 | 7 |
| Complex (grades 3, 4, and 5) | 27 | 93 |
| VT | 21 | 60 |

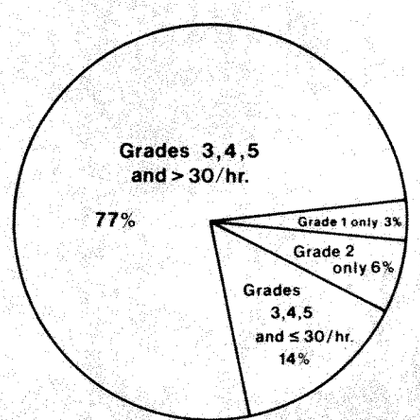



**FIGURE 3.** The prevalence of ventricular arrhythmias by modified Lown's grades in 35 patients with IDC. (See explanation in text.)

**TABLE III Ventricular Arrhythmia Detected During Holter Monitoring in Patients With and Those Without VT**

| | VT Group | | Non-VT Group | | |
|---|---|---|---|---|---|
| | n | % | n | % | p Value |
| No VPB | 0 | | 0 | | |
| VPB ≤30/h | 4 | 19 | 2 | 14 | NS |
| VPB >30/h | 17 | 81 | 12 | 86 | NS |
| Multiform | 21 | 100 | 10 | 71 | <0.05 |
| Couplet | 19 | 90 | 7 | 50 | <0.05 |
| R on T | 7 | 33 | 2 | 14 | NS |

NS = not significant.

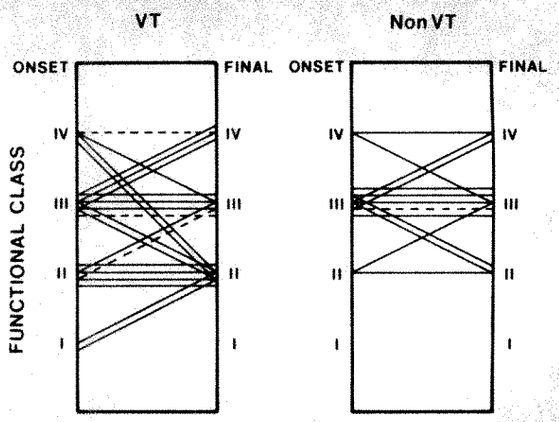



**FIGURE 4.** Change in functional class (New York Heart Association) in patients with IDC. The **dotted lines** indicate the patients who died. **Left,** the VT group; **right,** the non-VT group. No significant differences in the changes in functional classification were noted between the 2 groups.

significantly higher in the VT group (chi-square = 4.25 and 5.24; $p < 0.05$).

Eighty-five episodes of nonsustained VT were recorded in the 21 patients (mean 4.0 episodes/patient; range 1 to 16). No sustained VT was found during monitoring. The duration of VT ranged from 3 to 46 beats (mean ± SD 8 ± 4.7). Forty-six episodes (54%) were 3 beats in duration, 11 episodes (13%) had 4 beats, 7 episodes (8%) had 5 beats, and 21 episodes (25%) had >5 beats. The mean rate of VT was 155 ± 42 beats/min (range 75 to 210) with 58% of episodes at a rate >150 beats/min. Twelve (14%) of the 85 episodes of VT had a prematurity index (RR'/QT) <1.0 for the initiating beat. Only 2 patients recorded complaints of palpitation and dyspnea in the diary that corresponded in real time to the occurrence of VT.

**Follow-up data:** Follow-up data were obtained in all patients, and follow-up ranged from 4 to 74 months (mean ± SD 34 ± 17). Figure 4 shows changes in functional class during the last follow-up observation. Functional status in the 31 surviving patients improved in 8 (26%), deteriorated in 11 (35%), and was unchanged in 12 (39%). The number of patients who improved, were unchanged, or deteriorated in functional class between the 2 groups was not significantly different. A total of 27 patients had repeated 24-hour Holter recordings taken from 1 to 42 months during the follow-up period. Nineteen patients were in the VT group and 8 in the non-VT group. Twelve (44%) of 27 patients had nonsustained VT; 9 had previous VT and 3 patients did not. However, the latter 3 patients had previous complex VPB. The remaining 15 patients had complex ventricular arrhythmias (≥ grade 3). Of these 15 patients, 10 had previous VT and 5 did not. In summary, during follow-up study, 9 patients had VT, 3 had new VT, 10 no longer had VT, and 5 continued to have complex ventricular arrhythmias without VT.

Four patients died during the follow-up period from 4 to 39 months. Two died suddenly, 1 in the VT group and the other in the non-VT group. A third patient died from intractable congestive heart failure and the fourth from sepsis; both were in the VT group. Two of the 4 patients who died had follow-up Holter recordings before death. Both patients showed frequent complex ventricular ectopy without the recurrence of VT.

**Antiarrhythmic drugs:** On entry into the study 5 patients were receiving antiarrhythmic medication, 3 quinidine and 2 procainamide. Four patients were in the VT group and 1 in the non-VT group. At the time of discharge all patients who showed VT on admission and 8 patients in the non-VT group were receiving antiarrhythmic drugs (Table VI). Decision regarding the use of antiarrhythmic drugs was made by the attending physician. During follow-up study, while on antiarrhythmic therapy, 10 patients no longer had VT and 9 continued to show VT on Holter monitoring. Of the 8 patients receiving antiarrhythmic drugs for the treatment of complex ventricular arrhythmias, 3 demonstrated new VT on monitoring and 5 continued to show complex ventricular arrhythmias. All 4 patients who died were receiving antiarrhythmic drugs (Table IV).

**TABLE IV Drug Therapy at Discharge**

| | Digitalis | | Diuretics | | Antiarrhythmics | | Vasodilator | | Coumadin | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % |
| VT (21 patients) | 15 | 71 | 15 | 71 | 21* | 100 | 9 | 43 | 7 | 33 |
| Non-VT (14 patients) | 13 | 93 | 10 | 71 | 8† | 57 | 5 | 36 | 4 | 29 |

* Quinidine 10 patients; procainamide 6; Norpace® 3; quinidine and phenytoin 1; procainamide and phenytoin 1. † Quinidine 5 patients; procainamide 2; Norpace 1.

## Discussion

**Arrhythmias in idiopathic cardiomyopathy:** Our study demonstrates that VPB are frequent in patients with IDC. Frequent VPB (30/hour) occurred in 83% of patients, with a remarkably high percentage (93%) showing complex forms (Lown grades 3, 4, and 5). These findings resemble those in patients with hypertrophic cardiomyopathy.[20-22] McKenna et al[20] reported that 62% of 86 patients with hypertrophic cardiomyopathy had frequent, complex VPB and 74% of 150 patients studied by Savage et al[22] had similar findings. Interestingly, our study demonstrates a considerably higher prevalence of VT than did those of Savage et al[21,22] and McKenna et al[20] in patients with hypertrophic cardiomyopathy. We found that 21 (60%) of 35 patients studied had 1 to 16 episodes (mean 4 episodes/patient) of nonsustained VT during 24 hours of Holter monitoring. Most (86%) VT was initiated by late-coupled ventricular ectopic beats (prematurity index >1.0). This observation is consistent with those of other studies showing that the prematurity index is not an important predictor of subsequent VT.[19] The present study also confirms the previous observation that atrial fibrillation, atrial premature beats, and supraventricular tachycardia were relatively common in patients with IDC.[2,4,5,9]

**Role of clinical findings in VT:** Previous studies showed that several clinical characteristics have prognostic value in patients with IDC. Besides ventricular arrhythmias, Segal et al[5] emphasized that initial heart size, functional class, and presence of atrial fibrillation were indicators of prognosis. A recent study by Fuster et al[4] showed that age and cardiothoracic ratio on chest roentgenography were highly predictive of the clinical course. Nonetheless, the question of whether these clinical characteristics are related to VT has not previously been answered. Our findings indicate that the sex, presenting symptoms, initial functional class, heart size on chest X-ray, and various electrocardiographic findings in patients with VT were no different from those in patients without VT.

**Role of hemodynamic measurements in VT:** Previous reports commented on the high mortality and sudden death associated with reduced cardiac index, elevated left ventricular end-diastolic pressure, and diminished ejection fraction.[2,4,10,11] Our results demonstrate that hemodynamic measurements in patients with VT are no different from those in patients without VT, suggesting that low cardiac index, high left ventricular end-diastolic pressure, or low left ventricular ejection fraction are not determinants of VT in IDC.

**Prognostic value of VT:** Some investigators espouse the predictive value of VT in sudden death in patients with hypertrophic cardiomyopathy.[20,21] Segal and his associates[5] found a 50% mortality rate within 3 years among patients with a diagnosis of IDC who had VT on the electrocardiogram. Follansbee et al[16] demonstrated that patients with congestive cardiomyopathy or congestive heart failure and nonsustained VT detected by ambulatory electrocardiographic monitoring are at high risk for sudden death. In our study of 21 patients with nonsustained VT we had 3 deaths. Only 1 was sudden, whereas the other 2 patients died from intractable congestive heart failure and sepsis, respectively. VT was not demonstrated on subsequent Holter recording during antiarrhythmic therapy in 2 of these 3 patients. Of the 14 patients who did not have VT, 1 died suddenly. No survivor had sustained VT or ventricular fibrillation requiring cardioversion or defibrillation during follow-up study. These findings argue against the role of nonsustained VT as a predictor of prognosis in IDC.

**Limitations of the present study:** The major limitations include (1) the retrospective nature of the study design, (2) the lack of systematic evaluation of antiarrhythmic drug therapy (due to the retrospective nature of the study, where information regarding drug dosage, drug blood levels, and compliance with therapy were usually incomplete, and (3) the relatively small number of patients and a short follow-up period. Although other studies include a larger number of patients, our strict selection criteria limited the number of cases.

**Clinical implications:** This report is the first to investigate the incidence and clinical significance of VT in patients with IDC by long-term ambulatory electrocardiographic recordings. Our study demonstrated no significant differences between patients with and those without nonsustained VT in those clinical characteristics and hemodynamic findings that have been shown to be of prognostic value in IDC. Furthermore, we found no differences in mortality between the VT and the non-VT groups, suggesting that VT is not an independent predictor of prognosis. The relatively low mortality in our study compared with those in other studies is intriguing.[5,16] Antiarrhythmic therapy may have prevented sudden death in some patients in the VT group. However, all 4 patients who died were receiving antiarrhythmic therapy and 2 of them no longer had VT on repeat Holter recording.

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## References

1. **Brandenburg RO, Chazov E, Cerian G, Falase AO, Grosgogeat J, Kawais C, Loogen F, Martin Judez V, Orinius E, Goodwin JF, Olsen EGJ, Oakley CM, Disa Z.** Report of the WHO/ISFC task force on definition and classification of cardiomyopathies. Circulation 1981;64:437-438A.
2. **Goodwin JF.** Congestive and hypertrophic cardiomyopathies. A decade of study. Lancet 1970;1:731-739.
3. **Roberts WC, Ferrans VJ, Buja LM.** Pathologic aspects of the idiopathic cardiomyopathies. Adv Cardiol 1974;13:349-367.
4. **Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL.** The natural history of idiopathic dilated cardiomyopathy. Am J Cardiol 1981; 47:525-531.
5. **Segal JP, Stapleton JF, McClellan JR, Waller BF, Harvey WP.** Idiopathic cardiomyopathy: clinical features, prognosis and therapy. Curr Probl Cardiol 1978;3:1-49.
6. **Oakley CM.** Clinical recognition of the cardiomyopathies. Circ Res 1974;34/35:Suppl II:II-152-II-167.
7. **Goodwin JF.** Prospect and predictions for the cardiomyopathies. Circulation 1974;50:210-219.
8. **Goodwin JF.** Treatment of the cardiomyopathies. Am J Cardiol 1973;32: 341-351.
9. **Stapleton JF, Segal JP, Harvey WP.** The electrocardiogram of myocardiopathy. Prog Cardiovasc Dis 1970;13:217-239.

10. **Hatle L, Orjavik O, Storstein O.** Chronic myocardial disease. I. Clinical picture related to long-term prognosis. Acta Med Scand 1976;199:399–405.
11. **Hatle L, Stabe G, Storstein O.** Chronic myocardial disease. II. Hemodynamic findings related to long-term prognosis. Acta Med Scand 1976;199:407–411.
12. **Shirey EK, Proudfit WL, Hawk WA.** Primary myocardial disease. Correlation with clinical findings, angiographic and biopsy diagnosis. Follow-up of 139 patients. Am Heart J 1980;99:198–207.
13. **Hamby RI, Catangay P, Aplado O, Khan AH.** Primary myocardial disease clinical hemodynamic and angiocardiographic correlates in fifty patients. Am J Cardiol 1970;25:625–634.
14. **Massumi RA, Rios JC, Gooch AS, Nutter D, Derita VT, Datlow DW.** Primary myocardial disease: report of fifty cases and review of the subject. Circulation 1965;31:19–41.
15. **Winkle R.** Ambulatory electrocardiography. Mod Concepts Cardiovasc Dis 1980;49:7–12.
16. **Follansbee WP, Michelson EL, Morganroth J.** Nonsustained ventricular tachycardia in ambulatory patients: characteristics and association with sudden cardiac death. Ann Intern Med 1980;92:741–747.
17. **Lown B, Wolf M.** Approaches to sudden death from coronary heart disease. Circulation 1971;44:130–142.
18. **Ruberman W, Weinblatt E, Goldberg JD, Frank CW, Shapiro S.** Ventricular premature beats and mortality after myocardial infarction. N Engl J Med 1977;297:750–757.
19. **Anderson KP, DeCamilla J, Moss AJ.** Clinical significance of ventricular tachycardia (3 beats or longer) detected during ambulatory monitoring after myocardial infarction. Circulation 1978;57:890–897.
20. **McKenna WJ, England D, Doi YL, Deanfield JE, Oakley C, Goodwin JF.** Arrhythmia in hypertrophic cardiomyopathy. I. Influence on prognosis. Br Heart J 1981;46:168–172.
21. **Maron BJ, Savage DD, Wolfson JK, Epstein SE.** Prognostic significance of 24-hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. Am J Cardiol 1981; 48:252–257.
22. **Savage DD, Seides SF, Maron BJ, Myers DJ, Epstein SE.** Prevalence of arrhythmias during 24-hour electrocardiographic monitoring and exercise testing in patients with obstructive and nonobstructive hypertrophic cardiomyopathy. Circulation 1978;59:866–875.
23. Criteria Committee of the New York Heart Association. Diseases of the Heart and Great Vessels. Nomenclature and Criteria for Diagnosis. 6th ed. Boston: Little, Brown, 1979;112–113.
24. **Romhilt DW, Estes EH.** Point-score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 1968;75:752–758.
25. **Dodge HT, Sandler H, Ballew DW, Lord JD Jr.** The use of biplane angiocardiography for the measurement of left ventricular volume in man. Am Heart J 1960;60:762–776.
26. **Sandler H, Dodge HT.** The use of single plane angiocardiograms for the calculation of left ventricular volume in man. Am Heart J 1968;75:325–334.

# Transesophageal Pacing for Prognostic Evaluation of Preexcitation Syndrome and Assessment of Protective Therapy

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**An esophageal lead was used to perform decremental atrial pacing and elective induction of atrial fibrillation (AF) in 5 patients with the Wolff-Parkinson-White (W-P-W) syndrome before and after amiodarone therapy. In the control state, 1:1 atrioventricular (AV) conduction over the accessory pathway ranged from 220 to 260 ms (mean 232). The shortest R-R interval during AF ranged from 190 to 210 ms (mean 198). The ventricular rate ranged from 175 to 212 beats/min (mean 196). After amiodarone therapy, the shortest cycle length with 1:1 AV conduction increased in all patients, ranging from 290 to 540 ms (mean 370); during AF, no preexcited beat was present in 2 patients, whereas the minimal preexcited R-R interval in the remaining 3 was 290, 240, and 370 ms, respectively. The ventricular response during AF decreased in all patients. Thus, esophageal pacing is a useful method for identifying patients at risk with the W-P-W syndrome and for assessing appropriate management in individual patients. Amiodarone provides protection against life-threatening arrhythmias in these patients.**

The prognosis of preexcitation syndrome due to an accessory AV pathway (W-P-W syndrome) is considered with less optimism than it was in the past, because life-threatening arrhythmias and sudden death have been reported with it.[1-6] The determinant of risk in the preexcitation syndrome is a very short anterograde effective refractory period of the accessory pathway, which can be responsible for a rapid ventricular response when atrial flutter or AF develops.[5,7-10] In fact, previous studies found a correlation between the duration of the anterograde effective refractory period of the accessory pathway and the ventricular response during AF.[11-13] To evaluate the ventricular response during faster atrial rates and to assess protective drug regimen in patients with the W-P-W syndrome at risk, an esophageal lead was used to perform decremental atrial pacing and elective induction of AF.

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## Methods

**Patients:** The study group consisted of 4 male patients and 1 female patient, aged 18 to 38 years (mean 27), selected from 52 consecutive patients with the W-P-W syndrome. One patient had been resuscitated from VF, 1 had a history of tachycardia, and 3 had familial W-P-W syndrome with a history of sudden death in 2 other family members. All patients had previously undergone endocavitary electrode catheter study for electrophysiologic evaluation of the W-P-W syndrome. Four patients had multiple accessory pathways; in addition, enhanced conduction of the AV node was present in 3 and a Mahaim fiber of the fasciculoventricular variety in 1.

**Procedure:** Studies were performed in the postabsorptive, nonsedated state. A bipolar permanent transvenous pacing lead with a 29 mm interelectrode distance (Medtronic Coronary Sinus Permanent Pacing Lead model 6992) was passed through the nares into the distal esophagus with the patient supine. The lead was secured where unipolar atrial electrograms showed the greatest amplitude and the most rapid deflection on the proximal electrode; this electrode was then designated as the cathodal (negative) pacing terminal. The unipolar tracings were filtered at 0.1 to 1 kHz. The pulse duration of the external generator ranged from 7 to 10 ms, and the current strength required for a stable capture ranged from

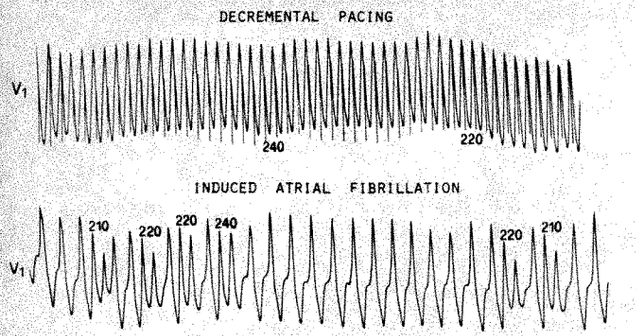



**FIGURE 1.** Transesophageal pacing in a patient with the W-P-W syndrome at risk. Decremental pacing shows 1:1 conduction at a cycle length of 220 ms; during induced AF, the shortest R-R interval measures 210 ms. Numbers are in ms. The tracings are taken from Case 3, Table I.

**TABLE I Transesophageal Pacing in W-P-W Syndrome at Risk Before and During Amiodarone* Treatment**

| Case | 1:1 Conduction Over Accessory Pathway | Induced Atrial Fibrillation: Minimum R-R | Induced Atrial Fibrillation: % Preexcited Beats | Induced Atrial Fibrillation: Ventricular Rate |
|---|---|---|---|---|
| 1 | 230 | 200 | 99 | 212 |
| | 340* | 370* | 65* | 146* |
| 2 | 260 | 190 | 95 | 210 |
| | 310* | 240* | 98* | 180* |
| 3 | 220 | 210 | 100 | 175 |
| | 370* | 290* | 96* | 150* |
| 4 | 230 | 190 | 88 | 195 |
| | 540* | . . .* | 0* | 92* |
| 5 | 220 | 200 | 100 | 190 |
| | 290* | . . .* | 0* | 122* |
| Mean | 232 | 198 | . . . | 196 |
| | 370* | . . . | . . . | 138* |

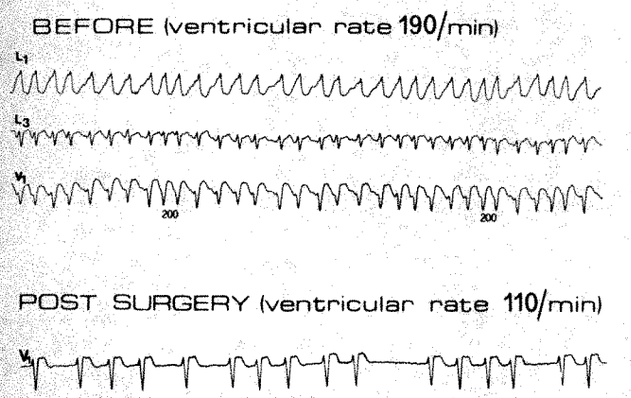



**FIGURE 2.** Case 5. Transesophageal pacing before and after surgery in a patient with the W-P-W syndrome and multiple accessory pathways at risk for sudden death. Note the absence after surgery of preexcited beats with a slow ventricular response during induced AF.

20 to 30 mA. All studies were performed with an intravenous line in place and with resuscitative equipment immediately available. To be certain the ventricle was not paced, pacing was first performed at a slow rate. Decremental pacing was then performed initially at a cycle length just below the sinus cycle length, with progressive reduction in the cycle length until block appeared in the accessory pathway. Finally, AF was induced by pacing at cycle lengths ranging from 60 to 120 ms.

The following variables were defined in the control state and after chronic amiodarone therapy: (1) the shortest cycle length with 1:1 AV conduction over the accessory pathway during decremental atrial pacing; (2) the ventricular response during induced AF as assessed by the minimal R-R interval between preexcited beats, percentage of preexcited beats observed, and the ventricular rate. The first evaluation of drug effect was performed after a 4-week period of treatment with 2,000 mg of amiodarone weekly (administered as 200 mg every 12 hours for 5 consecutive days). Serial esophageal pacing was then

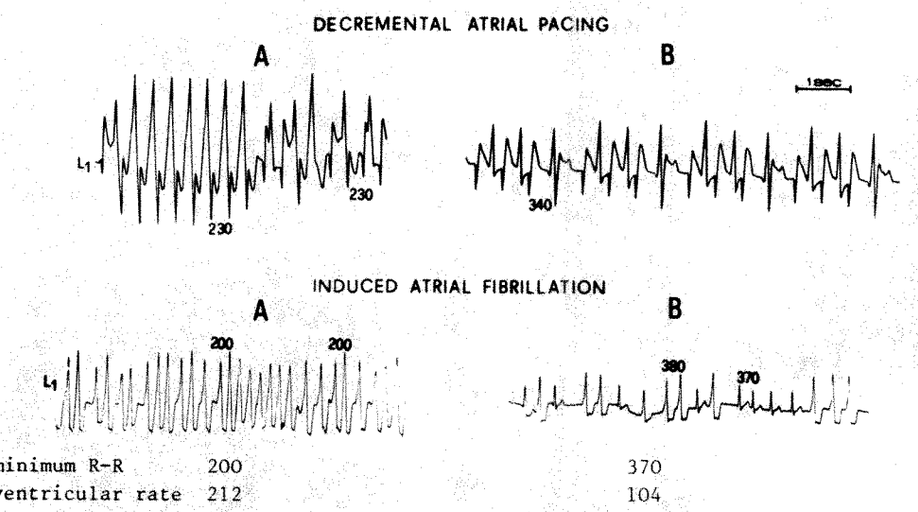



**FIGURE 3.** Case 1. Unsuccessful surgery in the W-P-W syndrome (multiple accessory pathways and enhanced AV node conduction) at risk, documented by transesophageal pacing. The protective drug regimen is assessed using transesophageal pacing. **A**, before amiodarone; **B**, after amiodarone. See text for further details.

performed to check the response to pharmacologic therapy. Figure 1 is an example of the usefulness of the method; in this case, 1:1 AV conduction over the accessory pathway was present at a cycle length of 220 ms; the shortest R-R interval during induced AF was 210 ms.

## Results

Decremental atrial pacing and AF were successfully obtained by esophageal pacing in all patients. During the procedure, all patients experienced discomfort described as a burning chest sensation, but this discomfort was easily tolerated. External direct current shock was not required in any patient, AF terminating at about 10 minutes spontaneously or after intramuscular quinidine administration.

Results are summarized in Table I. In the control state, 1:1 AV conduction over the accessory pathway ranged from 220 to 260 ms (mean 232). The shortest preexcited R-R interval during AF ranged from 190 to 210 ms (mean 198), the ventricular rate ranging from 175 to 212 beats/min (mean 196). During amiodarone therapy, the shortest cycle length with 1:1 AV conduction over the accessory pathway was prolonged in all patients, ranging from 290 to 540 ms (mean 370); during AF, no preexcited beat was present in 2 patients, whereas the minimal preexcited interval in the remaining 3 patients was 370, 240, and 290 ms, respectively. The ventricular response during AF decreased in all patients. No consistent difference in the cycle length required to induce AF or the duration of AF was observed after amiodarone therapy.

Two patients underwent surgical dissection of accessory pathways, and transesophageal pacing permitted repeated assessment of surgical results during

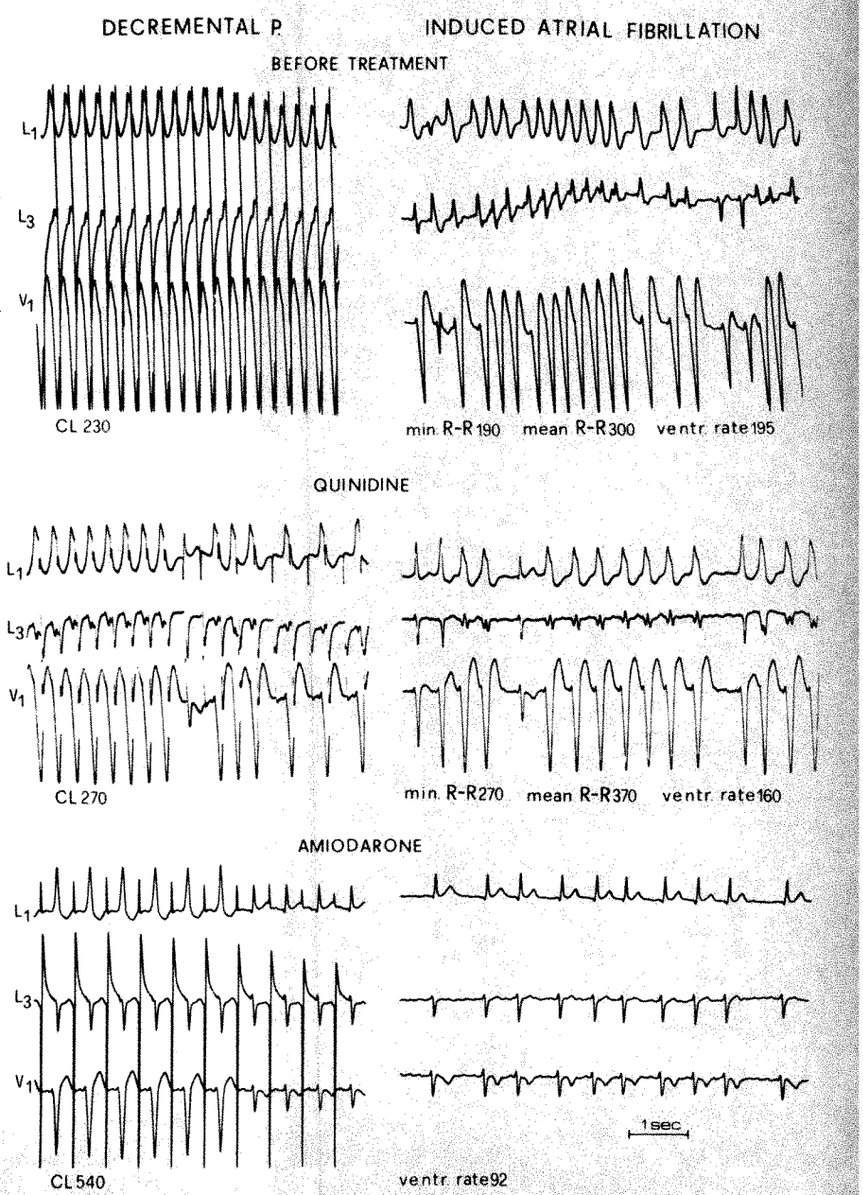



**FIGURE 4.** Case 4. Transesophageal pacing (P.) to assess the pharmacologic regimen in a patient with the W-P-W syndrome at risk. Before treatment, 1:1 conduction at a cycle length (CL) of 230 ms is present; minimal R-R interval of preexcited beats measures 190 ms and ventricular rate is 195 beats/min. Results from quinidine treatment are inconsistent. Amiodarone therapy has a better protective effect on ventricular response during faster atrial rates: block in accessory pathway appears at a cycle length of 540 ms and no preexcited beat is present during AF, the ventricular rate being moderate.

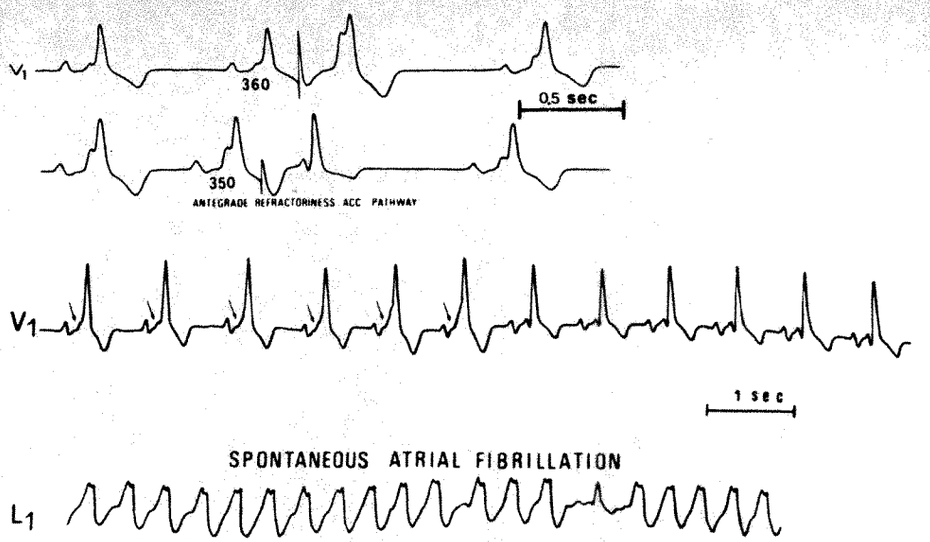



**FIGURE 5.** W-P-W syndrome with a long (350 ms) anterograde effective refractory period of accessory pathway and intermittent preexcitation (**arrows**). A QRS preexcitation morphology is present during AF. Right bundle branch block is evident during sinus rhythm, when preexcitation disappears. (See text for further details.) This illustration is taken from a patient not included in the present study.

long-term follow-up study. In the first patient, the method allowed demonstration of the beneficial effects of the intervention (Fig. 2). Before surgery, induced AF resulted in a minimal preexcited interval of 200 ms, the ventricular response being 190 beats/min; after surgery, no preexcited beat was present during AF, with a ventricular response to 110 beats/min.

In the second patient, a surgical failure was uncovered 2 months later (Fig. 3). In addition to demonstrating preexcitation, decremental pacing resulted in 1:1 AV conduction over the accessory pathways at cycle length of 230 ms; the minimal R-R interval during induced AF was 200 ms with a ventricular response of 212 beats/min. Repeated transesophageal pacing allowed assessment of a protective drug regimen in this patient. Thus, after amiodarone treatment with 2,000 mg weekly for 4 weeks, the Wenckebach phenomenon in AV conduction appeared at a cycle length of 340 ms. During induced AF, the minimal R-R preexcited interval was 370 ms with a moderate ventricular response. A second successful intervention was performed in this patient. In the patients in whom amiodarone therapy was used instead of surgery, the follow-up period was 11 months.

The possibility of using the method repeatedly during chronic drug therapy permitted the comparative evaluation of different antiarrhythmic agents. In 2 patients the effects of quinidine versus amiodarone therapy were evaluated, and amiodarone showed better effectiveness. In the example shown in Figure 4, no consistent modification of the ventricular response to either decremental pacing or induced AF was evident with quinidine therapy; on the contrary, after amiodarone therapy, block in the accessory pathway appeared at a cycle length of 540 ms and the ventricular rate during induced AF was slow, with no preexcited QRS complex.

## Discussion

The use of atrial pacing from the esophagus for diagnosis or therapy is well known,[14,15] but its application has been limited because of either patient discomfort due to high current requirements or the lack of consistent capture. Gallagher and co-workers[16] demonstrated that lower pacing thresholds can be obtained by using a wider pulse duration and a bipolar electrode with a wide interelectrode distance. These investigators pointed out the usefulness of this method as a diagnostic and therapeutic tool for the investigation and treatment of supraventricular tachycardia.[16]

Our study demonstrates that esophageal pacing provides a noninvasive method for identifying patients at risk with the W-P-W syndrome and for assessing appropriate management in individual cases.

A patient with the W-P-W syndrome at risk of sudden death can be identified if an electrocardiographic tracing during atrial flutter/AF is available.[10] In patients not exhibiting this particular tachyarrhythmia, an invasive procedure is required to define the anterograde effective refractory period of the accessory pathway at different cycle lengths and the ventricular response to either decremental atrial pacing or induced AF.[12–14] In addition, because sudden death may be the first manifestation of the W-P-W syndrome,[6,17,18] a similar approach might reasonably be considered in asymptomatic patients. Because an endocavitary study would be impossible in all patients with electrocardiographic evidence of preexcitation, certain criteria have been suggested to noninvasively exclude a short anterograde effective refractory period of the accessory pathway. The findings considered to indicate a relatively long refractory period include (1) intermittent preexcitation,[5] (2) block in the accessory pathway after

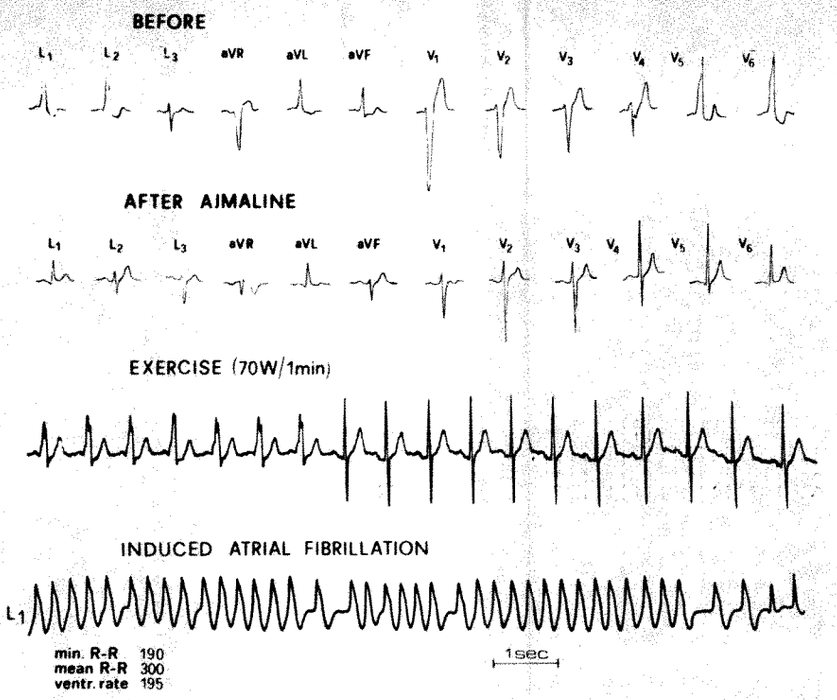



**FIGURE 6.** Case 4. Inability of noninvasive tests to exclude a short anterograde effective refractory period of accessory pathway in the W-P-W syndrome. Both ajmaline administration and exercise testing induce block in accessory pathway, but the ventricular response during AF is rapid with almost all beats preexcited and minimal R-R interval measures 190 ms.

intravenously administered ajmaline,[19] and (3) block in the accessory pathway during exercise testing.[20] All are limited because the assessment takes place during sinus rhythm. In fact, these criteria provide no information on the anterograde effective refractory period of the accessory pathway during fast atrial rates. Because AV bypass tracts in the W-P-W syndrome are usually composed of working myocardium,[21–26] it should not be surprising that in some patients an accessory pathway with a long anterograde effective refractory period during sinus rhythm can increase its conduction capacity when a rapid atrial rhythm develops. Figure 5 shows that despite a long anterograde effective refractory period, that is, 350 ms, of the accessory pathway and a pattern of intermittent W-P-W electrocardiogram during sinus rhythm, maximal preexcitation with a fast ventricular response can occur with the development of AF.

Other noninvasive tests are unable to exclude a very short anterograde effective refractory period of an accessory pathway in some patients. In the patient in Figure 6, although the accessory pathway is blocked both after ajmaline and during exercise, AF induces a rapid ventricular response with preexcited QRS complexes. Thus, the standard electrocardiogram in the W-P-W syndrome, even with exercise and drug testing, lacks sufficient prognostic sensitivity. Atrial pacing, including elective induction of AF, is the most reliable means of evaluating the potential for rapid ventricular response during AF and thus of identifying subjects at risk.

Our study demonstrates that this goal can be achieved using esophageal pacing, thus avoiding several problems that arise from endocavitary studies. In addition, our preliminary study indicates that amiodarone therapy can protect against life-threatening arrhythmias in patients with the W-P-W syndrome at risk.

## References

1. **Okel BB.** The Wolff-Parkinson-White syndrome. Report of a case with fatal arrhythmia and autopsy findings of myocarditis, interatrial lipomatous hypertrophy and prominent right moderator band. Am Heart J 1968;75: 673–678.
2. **Martin-Noel P, Denis B, Grundwald D, Buisson M.** Deux cas mortels de syndrome de Wolff-Parkinson-White. Arch Mal Coeur 1970;63:1647–1656.
3. **Castillo-Fenoy A, Goupil A, Offenstadt G.** Syndrome de Wolff-Parkinson-White et mort subite. Ann Med Interne (Paris) 1973;124:871–875.
4. **Duvernoy WFC.** Sudden death in Wolff-Parkinson-White syndrome. Am J Cardiol 1977;39:472–476.
5. **Wellens HJJ, Bar FW, Farre J, Ross D, Vanagt EJ.** Sudden death in the Wolff-Parkinson-White syndrome. In: Kulbertus HE, Wellens HJJ, eds. Sudden Death. London: Martinus Nijhoff, 1980:392–399.
6. **Critelli G, Gallagher JJ, Sealy WC, Giordano Lanza G, Condorelli M.** Familial sudden death in preexcitation syndrome. Surgical interruption of the anomalous pathways in two brothers. G Ital Cardiol 1981;12:1883–1894.
7. **Kaplan MA, Cohen KL.** Ventricular fibrillation in the Wolff-Parkinson-White syndrome. Am J Cardiol 1969;24:259–264.
8. **Dreifus LS, Haiat R, Watanabe Y, Arriaga J, Reitman NC.** Ventricular fibrillation: a possible mechanism of sudden death in patients with Wolff-Parkinson-White syndrome. Circulation 1971;43:520–527.
9. **Gallagher JJ, Gilbert M, Svenson RH, Sealy WC, Kasell J, Wallace AG.** Wolff-Parkinson-White syndrome: the problem, evaluation and surgical correction. Circulation 1975;51:767–778.
10. **Klein GJ, Bashore TM, Sellers TD, Pritchett ELC, Smith WM, Gallagher JJ.** Ventricular fibrillation in the Wolff-Parkinson-White syndrome. N Engl J Med 1979;301:1080–1085.
11. **Castellanos A Jr, Myerburg RJ, Craparo K, Befeler B, Agha AS.** Factors affecting ventricular rates during atrial flutter and fibrillation in preexcitation (Wolff-Parkinson-White) syndrome. Br Heart J 1973;35:811–816.

12. **Wellens HJJ, Durrer D.** Wolff-Parkinson-White syndrome and atrial fibrillation: relation between refractory period of the accessory pathway and ventricular rate during atrial fibrillation. Am J Cardiol 1974;34:777–782.
13. **Campbell RWF, Smith RA, Gallagher JJ, Pritchett ELC, Wallace AG.** Atrial fibrillation in the preexcitation syndrome. Am J Cardiol 1977;40:514–520.
14. **Stopczyk MJ, Pieniak N, Sadowski Z, Zochowski RT.** Transesophageal atrial pacing as a simple diagnostic and therapeutic procedure. In: Kadefors R, Magnusson RI, Petersen I, eds. The Third International Conference on Medical Physics. Goteborg, Sweden: 1972:40–45.
15. **Santini M, Rocchi M, Masini V.** Study of sinus node recovery time and sinoatrial conduction time in patients with sick sinus syndrome. Chap 8. Sect 1. In: Meere C, ed. Proceedings of VI World Symposium on Cardiac Pacing. Montreal: Pacesymp, 1979.
16. **Gallagher JJ, Smith WM, Kerr CR, Kasell J, Cook L, Reiter M, Sterba R, Harte M.** Esophageal pacing: a diagnostic and therapeutic tool. Circulation 1982;65:336–341.
17. **Coumel Ph, Slama R.** Syndrome de Wolff-Parkinson-White. Rev Prat 1975;25:1821–1839.
18. **Gallagher JJ, Pritchett ELC, Sealy WC, Kasell J, Wallace AG.** The preexcitation syndromes. Prog Cardiovasc Dis 1978;20:285–327.
19. **Wellens HJJ, Bär FW, Gorgels AP, Vanagt EJ.** Use of Ajmaline in patients with the Wolff-Parkinson-White syndrome to discover short refractory period of the accessory pathway. Am J Cardiol 1980;45:130–133.
20. **Levy S, Broustet JP, Clementy J, Guern B, Vircoulon B, Guern P, Bricaud H.** Syndrome de Wolff-Parkinson-White: correlations entre l'exploration electrophysiologique et l'effet de l'épreuve d'effort sur l'aspect electrocardiographique de preexcitation. Arch Mal Coeur 1979;72:634–640.
21. **Lev M, Gibson S, Miller RA.** Ebstein's disease with Wolff-Parkinson-White syndrome. Am Heart J 1955;49:724–741.
22. **Lev M, Kennamer R, Prinzmetal M, De Mesquita QH.** A histopathologic study of the atrioventricular communication in two hearts with the Wolff-Parkinson-White syndrome. Circulation 1961;24:41–50.
23. **Verduyn-Lunel AA.** Significance of annulus fibrosus of heart in relation to A-V conduction and ventricular activation in cases of Wolff-Parkinson-White syndrome. Br Heart J 1972;34:1263–1271.
24. **Rossi L.** A histological survey of preexcitation syndrome and related arrhythmias. G Ital Cardiol 1975;5:816–828.
25. **Becker AE, Anderson RH, Durrer D, Wellens HJJ.** The anatomical substrates of Wolff-Parkinson-White syndrome. A clinicopathologic correlation in seven patients. Circulation 1978;57:870–879.
26. **Klein GJ, Hackel DB, Gallagher JJ.** Anatomic substrates of impaired antegrade conduction over an accessory atrioventricular pathway in the Wolff-Parkinson-White syndrome. Circulation 1980;61:1249–1256.

# Electrophysiologic Studies Before and After Myocardial Revascularization in Patients With Life-Threatening Ventricular Arrhythmias

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**Electrophysiologic studies with programmed cardiac stimulation were performed in a selected group of 17 patients with severe proximal coronary artery disease involving at least 2 major vessels and left ventricular ejection fractions >30% who were undergoing coronary artery bypass graft surgery after prehospital cardiac arrest or ventricular tachycardia (VT) unassociated with acute myocardial infarction. Before surgery and without antiarrhythmic drug therapy, programmed cardiac stimulation induced ventricular fibrillation (VF) in 4 patients, and VT (≥5 beats) in 11 patients. Inducible VT or VF was suppressed by antiarrhythmic drugs in 7 of 13 patients in whom they were tried. Patients underwent coronary artery bypass graft surgery unassociated with perioperative myocardial infarction. When studied again an average of 19 days after surgery, 10 patients had no inducible VT or VF without antiarrhythmic drug therapy; 6 had induced VT. One patient had spontaneous VT. An effective antiarrhythmic regimen that suppressed inducible or spontaneous VT, or both, was defined by serial electrophysiologic studies in 4 patients, whereas 3 patients continued to manifest electrically inducible VT with all antiarrhythmic regimens tested. All but 1 patient, in whom postoperative VT could not be suppressed, are free of arrhythmias after a mean follow-up period of 23 months (range 6 to 53). It is concluded that myocardial revascularization alone may improve the abnormal electrophysiologic findings in certain patients; however, this effect of coronary artery bypass graft surgery is unpredictable, and pre- and postoperative electrophysiologic studies are recommended as part of the evaluation of these patients.**

The role of myocardial ischemia in the genesis of sudden, life-threatening ventricular tachyarrhythmias is a complex and poorly understood topic. Consequently, the role of surgical myocardial revascularization in the management of patients with ventricular arrhythmias resulting from ischemic heart disease has not been well established. Although there have been several reports on this topic,[1–3] no study to date has examined systematically the efficacy of coronary artery bypass graft surgery in suppressing the ventricular arrhythmias that are inducible by programmed ventricular stimulation.[4–6] Although the majority of patients with lethal ventricular arrhythmias have severely depressed left ventricular function,[4,6,7] a selected subgroup of them have, in addition to severe proximal coronary artery disease, left ventricular function not depressed enough to preclude cardiac surgery with myocardial revascularization. We investigated the effect of myocardial revascularization on inducible ventricular arrhythmias by performing programmed cardiac stimulation before and after coronary artery bypass surgery in such a selected group of 17 patients.

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## Methods

The patient population included 11 men and 6 women, ranging in age from 51 to 74 years, who satisfied the following criteria: proximal coronary artery disease with ≥70% reduction in diameter, involving at least 2 of the major coronary arteries (Table I), and left ventricular ejection fraction >30%, calculated from biplane angiography.[8] Thirteen of the 17 patients collapsed unexpectedly and VF was documented at the time of resuscitation. In no patient was the episode of VF associated with the evolution of a new myocardial infarction. The remaining 4 patients had a history of syncope with documented VT. Eight patients had a history of remote myocardial infarction. Only 2 patients had been having stable

**TABLE I Presurgical Cardiac Catheterization and Electrophysiologic Findings**

| Patient | Contrast Left Ventriculogram | LV Ejection Fraction (%) | Coronary Angiography (% Diameter) | Pre-CABG Response to PCS | Pre-CABG Drug Trials | Post-CABG Response to PCS | Post-CABG Drug Trials |
|---|---|---|---|---|---|---|---|
| RO | Anteroapical HK | 63 | LM<br>LAD 100<br>LC 70<br>R 80 | VT | Quinidine;<br>S | NVA | Quinidine,*<br>mexiletine,<br>propranolol;<br>S |
| MB | Normal LV | 76 | LM<br>LAD 80<br>LC 80<br>R 50 | VF | Quinidine,<br>propranolol;<br>S | NVA | . . . |
| AG | Apical AK<br>Anterolateral HK | 42 | LM 60<br>LAD >70<br>LC >95<br>R 100 | VF | Quinidine,<br>procain-<br>amide,<br>mexiletine,<br>propranolol;<br>NS | NVA | . . . |
| JR | Apical AK<br>Anterolateral HK<br>Inferior HK | 35 | LM<br>LAD 50 then<br>100<br>LC 100<br>RCA 70<br>RI 90 | NVA | . . . | NVA | . . . |
| TM | Apical AK<br>Anterolateral HK<br>Inferior HK | 40 | LM<br>LAD 100<br>LC 70<br>R 90 | VT | Propranolol,<br>procain-<br>amide;<br>S | VT | Propranolol,<br>procainamide,<br>mexiletine;<br>S |
| JR | Anterolateral HK<br>Posterobasal AK | 50 | LM<br>LAD 40<br>LC 80<br>R 100 | VF | Quinidine;<br>S | NVA | . . . |
| WK | Normal LV | 73 | LM<br>LAD 90<br>LC 70<br>R 100 | VT | . . . | NVA | . . . |
| MW | Anterolateral HK | 62 | LM 20<br>LAD 80<br>LC 100<br>R 60 | VT | Quinidine,<br>disopyramide,<br>propranolol,<br>mexiletine,<br>procainamide,<br>NS | VT | Quinidine<br>procainamide,<br>propranolol,<br>mexiletine;<br>NS |
| VB | Inferobasal HK | 50 | LM<br>LAD 60<br>LC 90<br>R 100 | VT | Mexiletine;<br>S | NVA | . . . |

* This patient was not tested without drugs after surgery. AK = akinesia; CABG = coronary artery bypass graft; HK = hypokinesia; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; LM = left main coronary artery; LV = left ventricle; NS = nonsuppression

angina pectoris. Two other patients were receiving antiarrhythmic therapy with quinidine at the time of ventricular arrhythmia. None of the other patients were receiving any antiarrhythmic drugs when VF or VT occurred. One patient had already undergone coronary artery bypass graft surgery once, with successful relief of angina, 10 months before prehospital cardiac arrest. The cardiac catheterization and the presurgical electrophysiologic studies were performed 1 to 14 days apart. The electrophysiologic studies were carried out an average of 2.5 weeks after resuscitation from cardiac arrest without any complications. All antiarrhythmic drugs were discontinued under continuous electrocardiographic monitoring at least 48 hours before the initial electrophysiologic study. No patient had received amiodarone before the initial electrophysiologic study. Endocavitary recordings from the high right atrium, the bundle of His, and the right ventricular apex were obtained, and programmed cardiac stimulation was carried out using quadripolar electrode catheters inserted percutaneously by way of femoral or antecubital veins. The protocol for programmed cardiac stimulation included single, double, and triple programmed premature ventricular stimuli applied during sinus rhythm and fixed-rate ventricular pacing, and brief (3 to 5 beat) bursts of rapid ventricular pacing during normal sinus rhythm. VT (≥5 beats) or VF was considered an end point during the stimulation protocol. If no inducible ventricular tachyarrhythmia occurred in response to stimulation from the right ventricular apex, the stimulation protocol was repeated from the right ventricular outflow tract.

Serial drug trials with oral antiarrhythmic drug therapy were conducted in an attempt to suppress the inducible ventricular arrhythmias during the period before the coronary artery bypass graft surgery in all but 2 patients who had inducible ventricular arrhythmias (Table I). One of these 2 patients had a stenosis with 70% reduction in diameter involving the left main coronary artery. Both patients were kept under continuous cardiac monitoring without any antiarrhythmic drug therapy and without serial drug trials until surgery. Coronary artery bypass graft surgery was performed an average of 2.8 months after out-of-hospital cardiac arrest (range 1 to 6 months). Two patients continued to have angina pectoris during the iterim period, but no patient had myocardial infarction during this period. There were no surgical complications and no enzymatic or electrocardiographic evidence of acute myocardial infarction associated with coronary

**TABLE I (Continued)**

| Patient | Contrast Left Ventriculogram | LV Ejection Fraction (%) | Coronary Angiography (% Diameter) | Pre-CABG Response to PCS | Pre-CABG Drug Trials | Post-CAGB Response to PCS | Post-CABG Drug Trials |
|---|---|---|---|---|---|---|---|
| AS | Normal LV | 65 | LM 70<br>LAD 50<br>LC<br>R 70 | VT | . . . | VT | Quinidine, mexiletine, propranolol; S |
| MG | Apical HK<br>Anterolateral HK<br>Inferior HK | 37 | LM<br>LAD diffuse plaques<br>LC 90<br>R 75<br>Severe stenoses in grafts | NVA | . . . | NVA | . . . |
| BC | Apical HK | 63 | LM<br>LAD 80,90<br>LC 80<br>R >95 | VT | Propranolol; S | NVA | . . . |
| JM | Inferior HK<br>Apical HK | 39 | LM<br>LAD 75<br>LC 90<br>R 70 | VT | Quinidine, procainamide, tocainide, mexiletine; NS | VT | Quinidine, mexiletine, disopyramide, amiodarone; NS |
| EV | Anterolateral HK<br>Inferior HK<br>Apical AK<br>Septal AK | 35 | LM<br>LAD 100<br>LC 100<br>R 90 | VF | Quinidine, mexiletine, propranolol; S | NVA | . . . |
| CM | Anterolateral HK<br>Inferior HK<br>Apical AK | 32 | LM<br>LAD 95<br>LC 90<br>R 90 | VT | Quinidine, tocainide, mexiletine, disopyramide; S | NVA | . . . |
| RF | Apical AK<br>Anterolateral HK<br>Inferior HK | 36 | LM<br>LAD 80<br>LC 100<br>R | VT | Quinidine, procainamide, mexiletine, propranolol; NS | VT | Procainamide; S |
| PL | Apical HK<br>Posterobasal AK<br>Inferobasal HK | 44 | LM<br>LAD 50<br>LC 70<br>R 100 | VT | Quinidine, propranolol, disopyramide, procainamide, mexiletine; NS | VT | Quinidine, mexiletine, propranolol, amiodarone; NS |

of inducible VT/VF; NVA = no ventricular arrhythmia, <3 repetitive ventricular responses to PCS; PCS = programmed cardiac stimulation; R = right coronary artery; RI = ramus intermedius; S = suppression of inducible VT/VF; VF = ventricular fibrillation; VT = ventricular tachycardia.

artery bypass graft surgery in any of the 17 patients. Every patient had continuous electrocardiographic monitoring for at least 10 days after surgery. All 17 patients underwent repeat electrophysiologic studies using the same stimulation protocol an average of 19 days (range 12 to 47) after cardiac surgery. The mean interval between the pre- and postoperative electrophysiologic study was 2.5 ± 0.8 months (mean ± standard deviation of the mean). In all but 3 patients this period was <3 months long; in these 3 patients, the periods were 4, 5, and 6 months long. The patients in whom programmed cardiac stimulation induced VT after revascularization surgery underwent serial antiarrhythmic drug tests with programmed cardiac stimulation in an attempt to define a regimen that suppressed inducible ventricular arrhythmia.

## Results

**Electrophysiologic and angiographic findings before coronary artery bypass graft surgery (Table I):** Before aortocoronary saphenous vein bypass graft surgery, 15 of the 17 patients had inducible ventricular arrhythmias in response to programmed cardiac stimulation: inducible VF in 4 (Fig. 1), and inducible VT in 11. In 3 of the 11 patients, the induced VT was sustained, whereas in 8 other patients the induced VT ended spontaneously after 6 to 27 beats. The remaining 2 patients manifested 1 to 3 repetitive ventricular responses with programmed cardiac stimulation from both the right ventricular apex and the right ventricular outflow tract. Programmed double premature ventricular stimuli during normal sinus rhythm did not initiate ventricular arrhythmias in any patient. VT and VF were initiated by double premature ventricular beats delivered during ventricular pacing in 13 patients (Fig. 1) and by bursts of 3 and 4 ventricular stimuli applied during normal sinus rhythm in 2 patients. The average rate of the induced VT was 265 beats/min. Of all the patients, only 1 had angina pectoris or manifested electrocardiographic signs of myocardial ischemia during programmed cardiac pacing.

In 14 of the 17 patients, biplane contrast left ventriculography revealed single or multiple segmental wall motion abnormalities of varying severity. Three patients

had normal left ventricular systolic function by angiographic criteria. No patient had a single, large, discrete, dyskinetic segment or aneurysm that was suitable for resection. The mean left ventricular ejection fraction calculated from biplane angiography[8] was 49 ± 7% (mean ± standard error of the mean) with a range of 32 to 76%. All patients had extensive proximal coronary artery disease, including 2 who had left main coronary artery stenosis of ≥60% reduction in diameter and, in addition, stenoses involving the right coronary artery. In general, there were no distinct patterns of coronary artery disease or left ventricular contraction abnormalities that predicted specific electrophysiologic responses to programmed ventricular stimulation.

Serial antiarrhythmic drug tests were carried out preoperatively in conjunction with programmed cardiac stimulation in 13 of the 15 patients with inducible VT or VF. A total of 39 drug trials (average 3/patient), were carried out without complications. In 8 of these 13 patients, complete suppression of electrically inducible ventricular arrhythmias (defined as a maximum of 3 repetitive ventricular responses during programmed ventricular stimulation) was achieved with the use of either conventional antiarrhythmic drugs or mexiletine. In the remaining 5 patients, programmed ventricular stimulation repeatedly resulted in VT or VF despite therapeutic trials with quinidine, procainamide, disopyramide, propranolol, mexiletine, tocainide, and amiodarone. The only patient who received amiodarone before surgery underwent programmed cardiac stimulation after 2 weeks of therapy with this drug.

**Electrophysiologic findings after coronary artery bypass graft surgery (Table I):** All 17 patients underwent electrophysiologic evaluation with programmed ventricular stimulation an average of 19 days after aortocoronary saphenous vein bypass graft surgery. Patients who were taking digoxin before surgery underwent postoperative electrophysiologic study while taking digoxin and were discharged on this drug therapy. All but 1 of the 17 patients were tested without antiarrhythmic therapy after surgery. The only patient who received amiodarone before surgery had not been

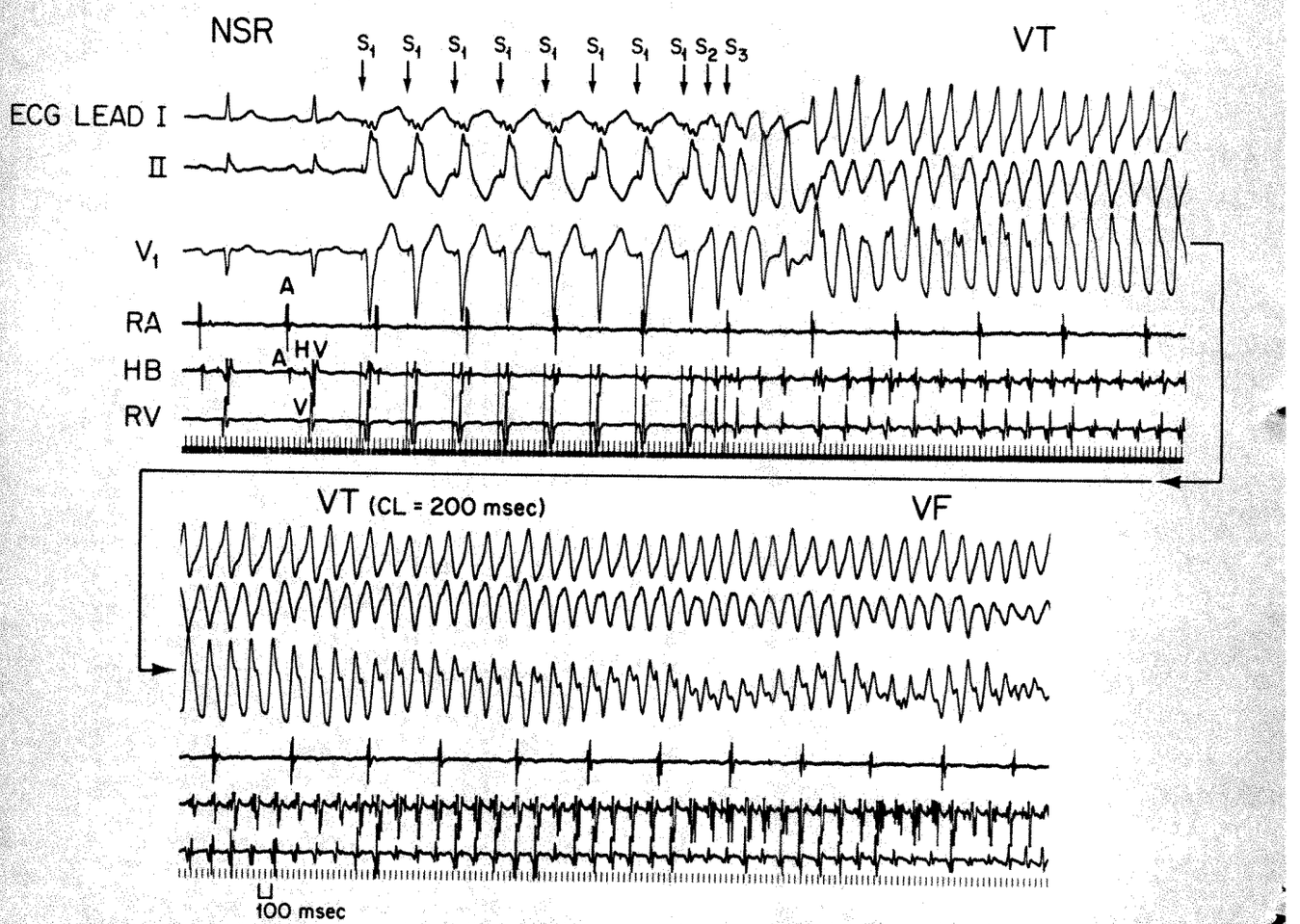



**FIGURE 1.** Response to programmed double premature ventricular depolarizations during ventricular pacing in 1 patient. The continuous tracing shows the initiation of VT with a cycle length (CL) of 200 ms and its gradual transformation into VF. Electrocardiographic (ECG) limb leads I and II and precordial lead $V_1$ are displayed simultaneously with right atrial (RA), His bundle (HB), and right ventricular (RV) electrograms. A = atrial depolarization; H = His electrogram; NSR = normal sinus rhythm; $S_1$, $S_2$, $S_3$ = stimulus artifacts; V = ventricular depolarization.

taking this drug for 35 days at the time of postoperative programmed cardiac stimulation. One patient had recurrent spontaneous VT which was suppressed with quinidine, mexiletine, and propranolol. This patient underwent a postoperative electrophysiologic evaluation while following this antiarrhythmic regimen, was found to have no inducible ventricular arrhythmia in response to programmed ventricular stimulation, and was discharged on this regimen. Ten patients manifested no VT or VF in response to any mode of programmed ventricular stimulation without any antiarrhythmic drug therapy after coronary artery bypass graft surgery. Included in this group of 10 were all 4 patients who had VF in response to programmed stimulation before coronary artery bypass graft surgery. Eight of these 10 patients were discharged without any antiarrhythmic drug therapy. The remaining 2 patients without inducible arrhythmias continued to have spontaneous symptomatic ventricular ectopic activity of a higher degree than before surgery, which was suppressed empirically with quinidine, mexiletine, and propranolol by the attending physicians. These 2 patients underwent repeat electrophysiologic testing while taking these antiarrhythmic drugs and, as observed in the absence of antiarrhythmic drugs, no ventricular arrhythmias could be initiated by programmed ventricular stimulation.

The remaining 6 patients manifested VT in response to programmed cardiac stimulation during postoperative electrophysiologic studies. The ventricular arrhythmias induced by programmed ventricular stimulation in these 6 patients before and after coronary artery bypass graft surgery were similar. Five patients manifested nonsustained (5 to 22 beats) and 1 had sustained VT in response to the same mode of programmed cardiac stimulation as before surgery. The average tachycardia rate was also comparable (265 beats/min before and 246 beats/min after surgery). Serial antiarrhythmic drug trials were carried out in conjunction with programmed cardiac stimulation in these 6 patients. In 3 patients, a drug regimen that prevented electrical induction of VT after coronary artery bypass graft surgery was defined, whereas the other 3 patients had inducible VT with all drug regimens tested. The latter 3 patients were discharged on antiarrhythmic drug regimens that were thought to modify the inducible ventricular arrhythmias favorably by decelerating or abbreviating them.

In summary, 2 patients who manifested no inducible ventricular arrhythmia before surgery also remained free of inducible ventricular arrhythmias after surgery. In 15 patients who had inducible VT or VF before surgery, these arrhythmias became noninducible through myocardial revascularization alone in 8 (53 %), and through surgery and antiarrhythmic drugs in another 4 (27 %); the remaining 3 patients (20 %) continued to have inducible arrhythmias.

**Clinical follow-up:** None of the 17 patients in this series died during a mean follow-up of 23 months (range 6 to 53). Only 1 had recurrent VT. This patient was 1 of 3 in whom inducible VT could not be suppressed completely by antiarrhythmic drugs even after myocardial revascularization. Twenty-four hour ambulatory electrocardiographic recordings obtained after discharge were either normal or showed low-grade ventricular ectopic activity with uniform, nonrepetitive, premature ventricular beats, but no VT. The patients have remained free of angina as well as of signs and symptoms of heart failure. Two patients underwent repeat electrophysiologic studies with programmed cardiac stimulation without any antiarrhythmic drug therapy 6 months after surgery. One of these patients who had no inducible ventricular arrhythmia 2 weeks after surgery also had no inducible arrhythmia 6 months later. The other patient had inducible VT 2 weeks as well as 6 months after surgery.

## Discussion

Recent studies have found that important electrophysiologic abnormalities can be demonstrated by programmed cardiac stimulation in patients with severe coronary artery disease who have been rescuscitated from an episode of prehospital cardiac arrest unassociated with acute myocardial infarction.[4–6] However, no study to date has examined systematically the effects of surgical revascularization on inducible ventricular arrhythmias and only limited data are available on the role of coronary artery bypass graft surgery, specifically in survivors of prehospital cardiac arrest.[1–3,4,6] These data suggest that recurrent VF remains a serious problem even after coronary artery bypass graft surgery.[1,3] Our study shows that inducibility of ventricular arrhythmias, which is an important prognostic factor, can be substantially influenced by surgical myocardial revascularization in a select group of patients.

By selection, our patients had relatively well-preserved left ventricular function and critical proximal coronary artery disease. The mean left ventricular ejection fraction of 49 ± 7% in this group of patients reflects better left ventricular function than the previously reported patients resuscitated from out-of-hospital cardiac arrest.[4,5,7] The stimulation study results seen in this selected group of patients were also different from those previously reported, with a greater incidence of VF and a smaller incidence of sustained VT.[4,5] Although the majority of inducible ventricular arrhythmias are observed in patients with infarcted left ventricles,[4,5,6,9,10] the presence of an angiographically detectable scar was neither necessary nor sufficient for the presence of an inducible ventricular arrhythmia in our patients. For example, VF was induced in a patient with normal left ventricular wall motion and VT in a patient with a single hypokinetic segment. On the other hand, in 2 patients with multiple wall motion abnormalities no VT could be induced by programmed cardiac stimulation. These differences are not likely to be due to differences in stimulation technique, since in patients with only repetitive ventricular responses the entire stimulation protocol was carried out. Thus, there could be a complex and poorly understood interaction of reversible ischemia with chronically fixed anatomic and electrophysiologic abnormalities underlying the genesis

of ventricular arrhythmias in this select group of patients. Despite the absence of subjective or objective criteria for reversible myocardial ischemia in the majority of the patients during the electrophysiologic studies, pacing-induced changes in myocardial perfusion could play a role in the genesis of induced ventricular arrhythmias, because in half of our patients myocardial revascularization alone prevented the induction of ventricular arrhythmias. This phenomenon was true especially in cases of induced VF but was also seen in patients with reproducible VT.

In our study, the comparison between electrophysiologic findings is made on studies performed no more than 3 months apart except for 3 cases; in 2 of these 3 cases, pre- and postoperative findings were the same. It is unlikely that the changes observed in electrophysiologic study results were related to the time intervals between the studies rather than the surgical intervention. More importantly, the reproducibility of the findings observed during the postoperative electrophysiologic studies may be questioned because of several factors, such as plasma catecholamine level, that may differ from baseline values due to recent surgery. This question can be resolved only by repeating the programmed stimulation several weeks or months after surgery—a difficult prospect since it involves invasive studies in asymptomatic patients. The repeat studies were done in only 2 patients in our study group and the results obviously cannot be generalized to the whole group. Nevertheless, in these 2 patients the responses to programmed cardiac stimulation 2 weeks and 6 months after surgery were the same.

Only 2 patients in our study group were receiving antiarrhythmic drugs at the time of their out-of-hospital cardiac arrest or VT. Since antiarrhythmic drugs can be proarrhythmic, their contribution to the mechanism producing ventricular arrhythmias cannot be ruled out. However, both of these patients also had inducible ventricular arrhythmias when studied without any antiarrhythmic drug therapy, thus manifesting at least their potential to have lethal ventricular arrhythmias even in the absence of antiarrhythmic drugs.

In most of the patients with spontaneous complex ventricular ectopic activity, these arrhythmias persist after coronary artery bypass surgery, and the frequency and severity of ventricular ectopic activity may even exceed that observed before surgery.[11-13] Our study showed that surgical myocardial revascularization may influence spontaneous ventricular ectopy and inducible ventricular arrhythmias differentially, thus presenting a therapeutic dilemma for the clinician concerning the use of antiarrhythmic agents. When symptomatic ventricular ectopic activity requires treatment even when VT is no longer inducible, our approach has been to select an antiarrhythmic drug regimen which suppresses electrically inducible ventricular arrhythmias as well as spontaneous ventricular ectopy.

In summary, our study shows that myocardial revascularization has a role in suppressing lethal ventricular arrhythmias, alone, or in conjunction with antiarrhythmic drugs in a selected group of patients even when scarred myocardium is left in situ. During the follow-up period, all patients in whom inducible ventricular arrhythmias were suppressed by surgery alone or in conjunction with antiarrhythmic drugs remained free of VT or VF. However, it is not possible to select these patients from preoperative angiographic data alone. The differences in the outcome of surgery may reflect the nonuniformity of the underlying disease process as well as our lack of understanding of the electrophysiologic mechanisms responsible for VT and VF in this patient population. As long as the efficacy of coronary artery bypass surgery in eliminating susceptibility to life-threatening ventricular arrhythmias remains unpredictable, pre- and postoperative electrophysiologic studies constitute an important part of the evaluation and treatment of patients who are known to be at high risk for sudden cardiac death.

**Acknowledgment:** We thank Ellen DiBiase for assistance in preparing the manuscript.

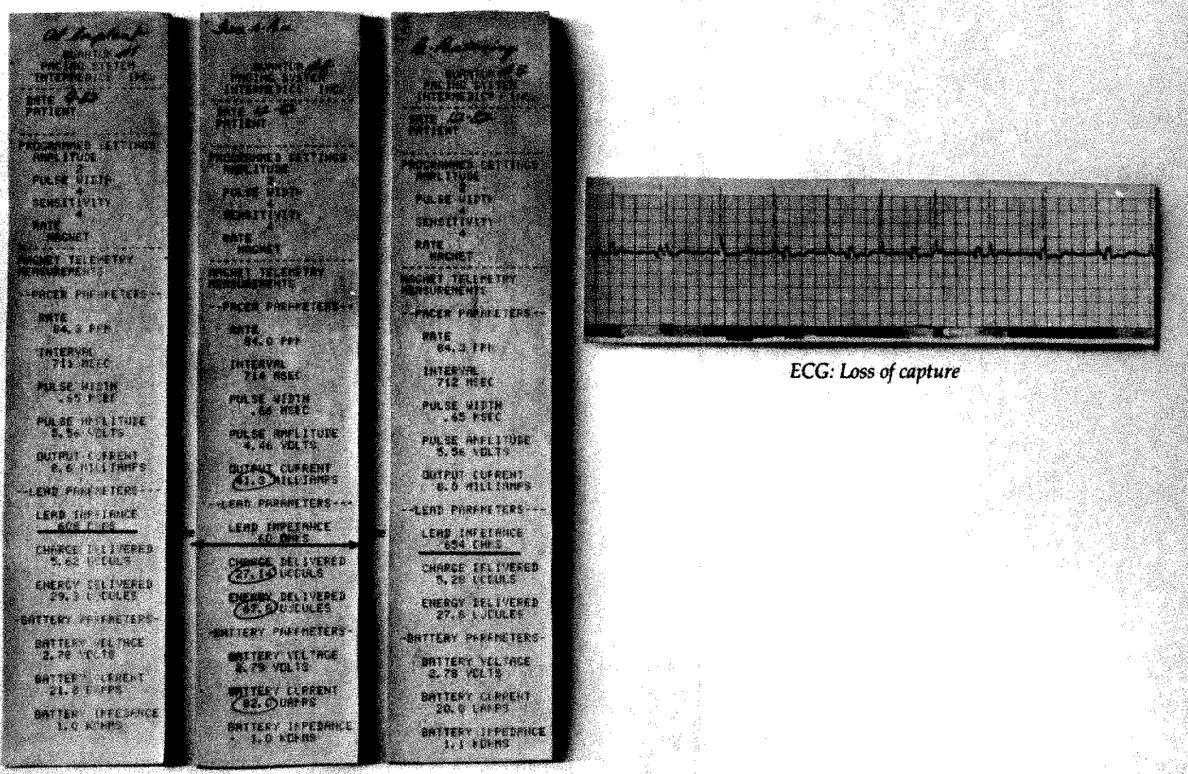
## References

1. **Kaiser GA, Ghahramani A, Bolooki H, Vargas A, Thurer RJ, Williams WH, Myerburg RJ.** Role of coronary artery surgery in patients surviving unexpected cardiac arrest. Surgery 1975;78:749–754.
2. **Bonchek LI, Olinger GN, Keelan MH Jr, Tresch DT, Siegel R.** Management of sudden coronary death. Ann Thorac Surg 1977;24:337–345.
3. **Tresch DD, Grove JR, Keelan M Jr, Siegel R, Bonchek LI, Olinger GN, Brooks HL.** Long-term follow-up of survivors of prehospital sudden coronary death. Circulation 1981;64:Suppl II:II-1–II-6.
4. **Ruskin JN, DiMarco JP, Garan H.** Out-of-hospital cardiac arrest: electrophysiologic observations and selection of long-term antiarrhythmic therapy. N Engl J Med 1980;303:607–613.
5. **Josephson ME, Horowitz LN, Spielman SR, Greenspan AM.** Electrophysiologic and hemodynamic studies in patients resuscitated from cardiac arrest. Am J Cardiol 1980;46:948–955.
6. **Kehoe R, Bauernfeind RA, Wyndham CRC, Meyers S, Talano J, Rosen KM.** Inducible ventricular tachycardia in patients with out-of-hospital ventricular fibrillation (abstr). Am J Cardiol 1980;45:444.
7. **Weaver D, Lorch G, Alvarez H, Cobb L.** Angiographic findings and prognostic indicators in patients resuscitated from sudden cardiac death. Circulation 1976;54:895–900.
8. **Sandler H, Dodge HT.** The use of single plane angiocardiogram for the calculation of left ventricular volume in man. Am Heart J 1968;75:325–334.
9. **Fenoglio JJ Jr, Aibala A, Silva FG, Friedman PL, Wit AL.** Structural basis of ventricular arrhythmias in human myocardial infarction: a hypothesis. Hum Pathol 1976;7:547–563.
10. **Josephson ME, Horowitz LN, Farshidi A, Kastor JA.** Recurrent sustained ventricular tachycardia. Circulation 1978;57:431–440.
11. **Guinn GA, Mathur VS.** Ambulatory, nocturnal and exercise arrhythmias in coronary artery disease: a prospective randomized study to assess the influence of aortocoronary bypass surgery (abstr). Am J Cardiol 1977;39:270.
12. **DeSoyza N, Murphy ML, Bissett JK, Kane JJ, Doherty JE.** Ventricular arrhythmia in chronic stable angina pectoris with surgical or medical treatment. Ann Intern Med 1978;89:10–14.
13. **Leutenegger F, Giger G, Fuhr P, Raeder EA, Burkart F, Schmitt H, Graedel E, Burckhardt D.** Evaluation of aortocoronary venous bypass for prevention of cardiac arrhythmias. Am Heart J 1979;98:15–19.

# #2

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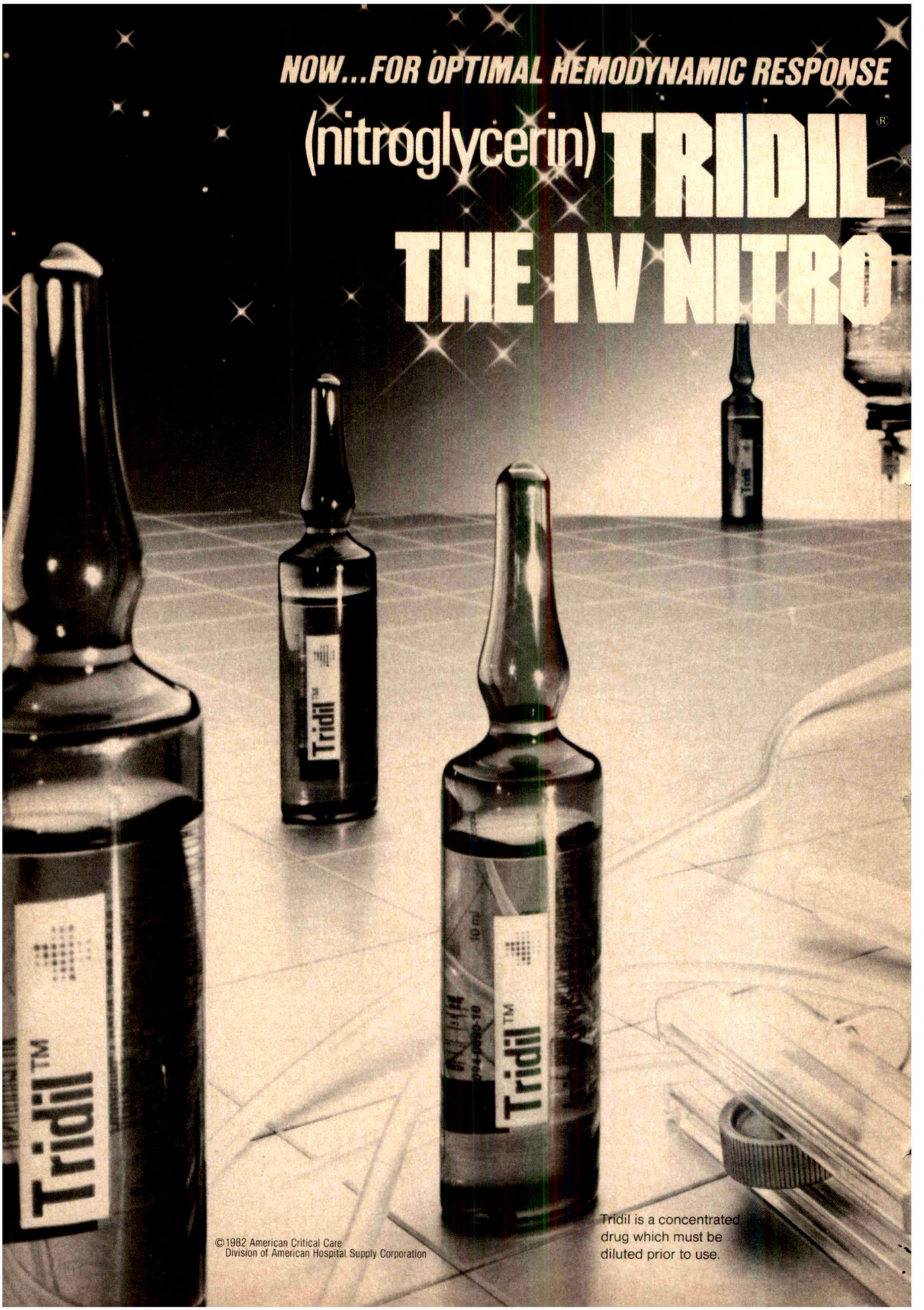
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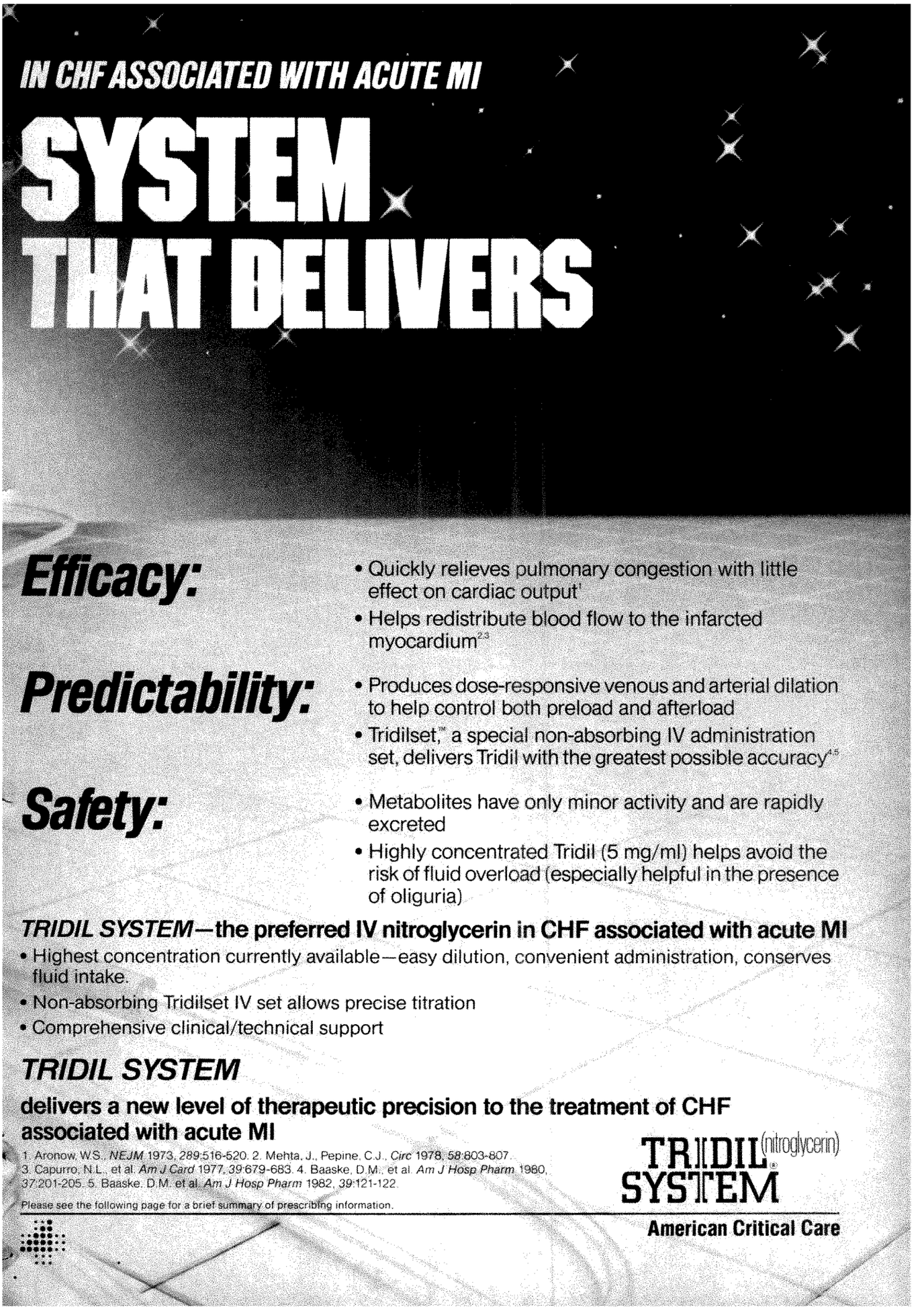
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1. Aronow, W.S., NEJM 1973, 289:516-520. 2. Mehta, J., Pepine, C.J., Circ 1978, 58:803-807. 3. Capurro, N.L., et al. Am J Card 1977, 39:679-683. 4. Baaske, D.M., et al. Am J Hosp Pharm 1980, 37:201-205. 5. Baaske, D.M. et al. Am J Hosp Pharm 1982, 39:121-122.
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TRIDIL (nitroglycerin) SYSTEM
American Critical Care

# TRIDIL® (nitroglycerin)

**Brief Summary of Full Prescribing Information**

NOT FOR DIRECT INTRAVENOUS INJECTION. TRIDIL® MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION (SEE DOSAGE AND ADMINISTRATION SECTION OF FULL PRESCRIBING INFORMATION). THE ADMINISTRATION SET USED FOR INFUSION WILL AFFECT THE AMOUNT OF TRIDIL DELIVERED TO THE PATIENT. (SEE WARNINGS, AND DOSAGE AND ADMINISTRATION SECTIONS.)

**CAUTION**

SEVERAL PREPARATIONS OF NITROGLYCERIN FOR INJECTION ARE AVAILABLE. THEY DIFFER IN CONCENTRATION AND/OR VOLUME PER VIAL. WHEN SWITCHING FROM ONE PRODUCT TO ANOTHER ATTENTION MUST BE PAID TO THE DILUTION AND DOSAGE AND ADMINISTRATION INSTRUCTIONS.

**CONTRAINDICATIONS**

TRIDIL should not be administered to individuals with:

1. A known hypersensitivity to nitroglycerin or a known idiosyncratic reaction to organic nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of TRIDIL in such states could produce severe hypotension or shock.
3. Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage).
4. Constrictive pericarditis and pericardial tamponade.

**WARNINGS**

1. Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of TRIDIL for intravenous infusion should be made only in *glass* parenteral solution bottles.
2. Some filters absorb nitroglycerin; they should be avoided.
3. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by the polyvinylchloride (PVC) tubing of the intravenous administration sets currently in general use. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and the administration set is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest) the loss is neither constant nor self-limiting; consequently no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.

Because of this problem, American Critical Care has developed TRIDILSET,™ an administration set in which loss of TRIDIL is minimal (less than 1%). TRIDILSET (or a similar administration set) is recommended for infusions of TRIDIL.

DOSING INSTRUCTIONS MUST BE FOLLOWED WITH CARE. IT SHOULD BE NOTED THAT WHEN TRIDILSET IS USED, THE CALCULATED DOSE WILL BE DELIVERED TO THE PATIENT BECAUSE THE LOSS OF TRIDIL DUE TO ABSORPTION IN STANDARD PVC TUBING WILL BE KEPT TO A MINIMUM. NOTE THAT THE DOSAGES COMMONLY USED IN PUBLISHED STUDIES UTILIZED GENERAL-USE PVC ADMINISTRATION SETS AND RECOMMENDED DOSES BASED ON THIS EXPERIENCE ARE TOO HIGH WHEN TRIDILSET IS USED.

**PRECAUTIONS**

TRIDIL (nitroglycerin) should be used with caution in patients with severe liver or renal disease.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of TRIDIL. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

**Carcinogenesis, mutagenesis, impairment of fertility**

No long-term studies in animals were performed to evaluate carcinogenic potential of TRIDIL.

**Pregnancy**

Category C. Animal reproduction studies have not been conducted with TRIDIL. It is also not known whether TRIDIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRIDIL should be given to a pregnant woman only if clearly needed.

**Nursing Mothers**

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRIDIL is administered to a nursing woman.

**Pediatric Use**

The safety and effectiveness of TRIDIL in children have not been established.

**ADVERSE REACTIONS**

The most frequent adverse reaction in patients treated with TRIDIL is headache, which occurs in approximately 2% of patients. Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

The following additional adverse reactions have been reported with the oral and/or topical use of nitroglycerin: cutaneous flushing, weakness, and occasionally drug rash or exfoliative dermatitis.

**OVERDOSAGE**

Accidental overdosage of TRIDIL may result in severe hypotension and reflex tachycardia which can be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilizes. Since the duration of the hemodynamic effects following TRIDIL administration is quite short, additional corrective measures are usually not required. However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (e.g., methoxamine or phenylephrine) should be considered.

**DOSAGE AND ADMINISTRATION**

(For complete information, please see Full Prescribing Information)

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Some patients with normal or low left ventricular filling pressures or pulmonary capillary wedge pressure (e.g., angina patients without other complications) may be hypersensitive to the effects of TRIDIL and may respond fully to doses as small as 5 mcg/min. These patients require especially careful titration and monitoring.

There is no fixed optimum dose of TRIDIL. Due to variations in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (e.g., blood pressure and heart rate in all patients, other measurements such as pulmonary capillary wedge pressure, as appropriate), MUST BE PERFORMED to achieve the correct dose. Adequate systemic blood pressure and coronary perfusion pressure must be maintained.

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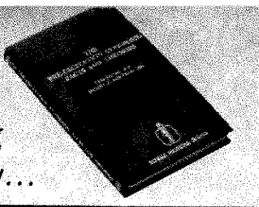
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# THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

**Libi Sherf, MD, FACC**

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

**Henry N. Neufeld, MD, FACC**

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

*"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."*

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*The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals.*

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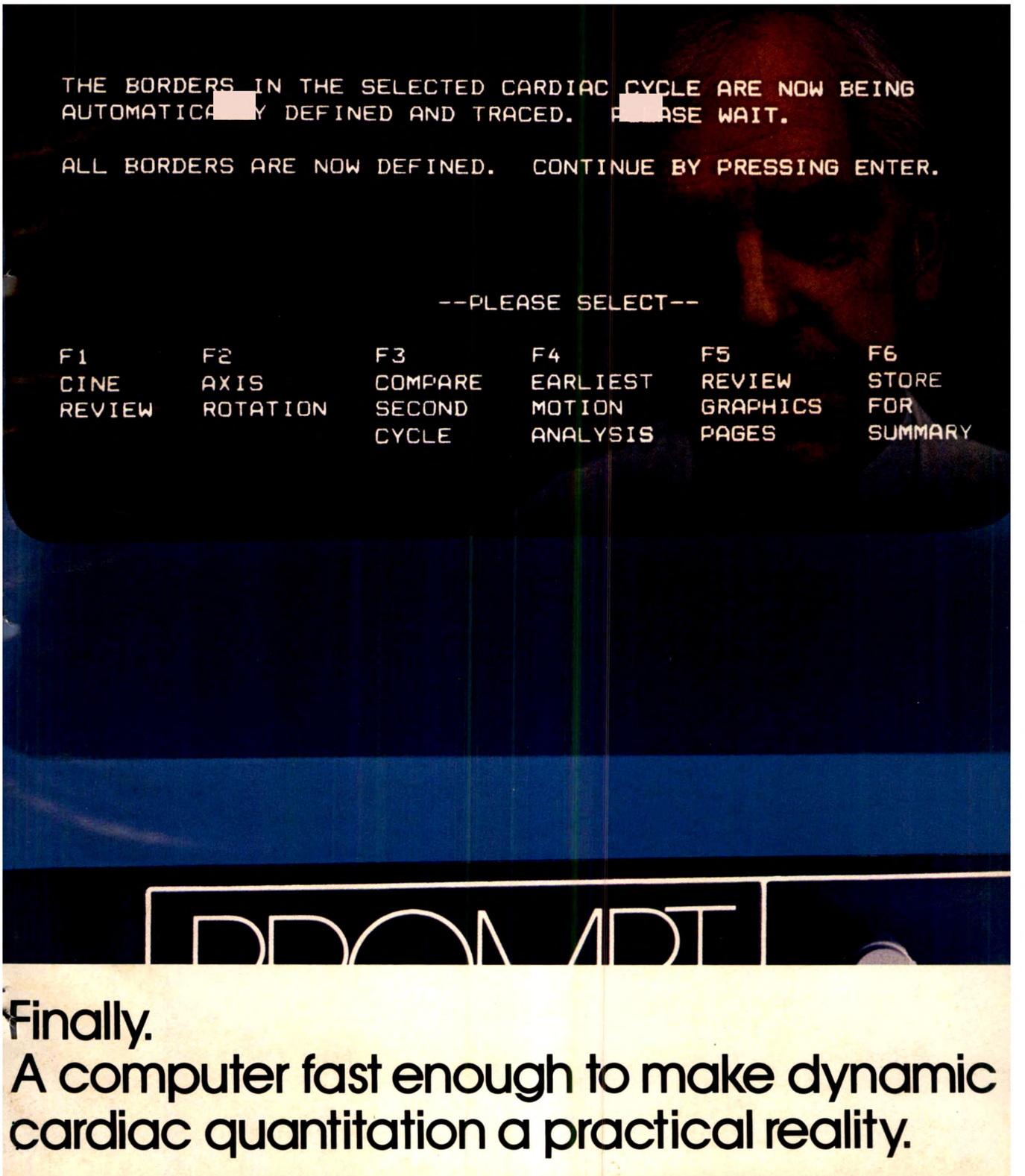
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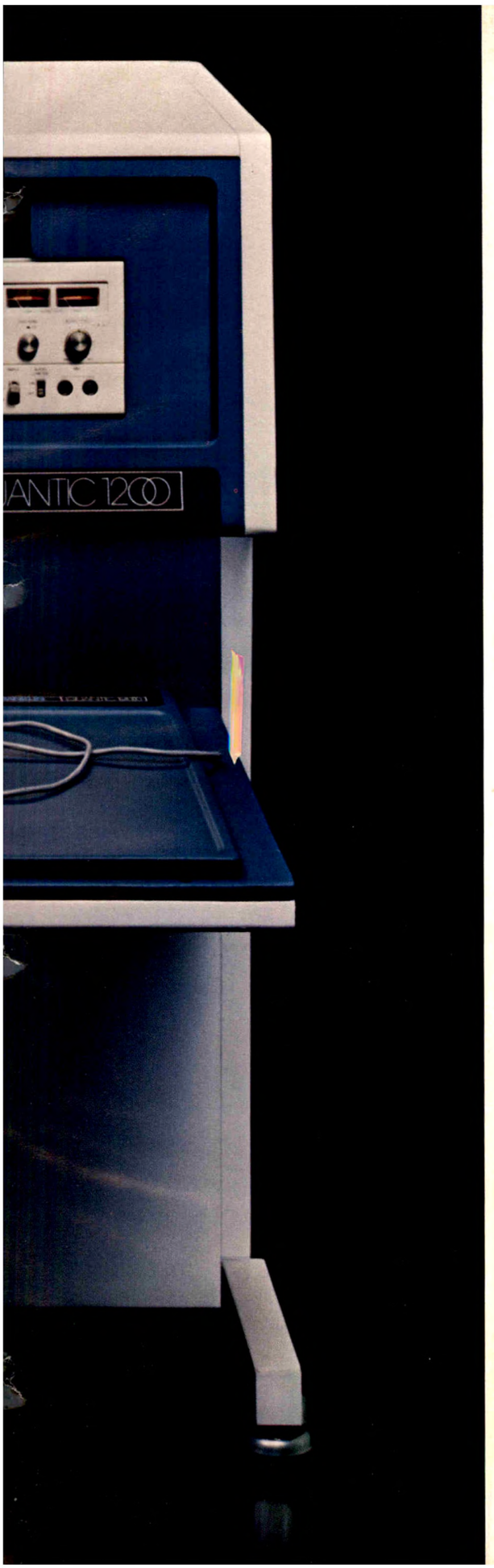
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# Electrophysiologic Mechanism of Exercise-Induced Sustained Ventricular Tachycardia

RUEY J. SUNG, MD, EDWARD N. SHEN, MD, FRED MORADY, MD,
MELVIN M. SCHEINMAN, MD, DAVID HESS, MD, and ELIAS H. BOTVINICK, MD

**To elucidate electrophysiologic mechanism of exercise-induced ventricular tachycardia (VT), electrophysiologic studies were performed in 12 patients in whom sustained VT had developed during treadmill exercise testing. Six patients had arteriosclerotic coronary heart disease, 3 had cardiomyopathy, and 3 had no clinical evidence of organic heart disease. All patients had had documented episodes of sustained VT related to exertion and had experienced dizziness, syncope, or both. In addition, 3 patients had had nonfatal cardiac arrest. Electrophysiologic studies provoked paroxysms of sustained VT identical to those observed during treadmill exercise testing in 10 patients and provoked ventricular flutter/fibrillation in 1. Seven patients had VT suggestive of a reentrant mechanism, as the VT could be readily initiated with programmed ventricular extrastimulation or terminated by ventricular overdrive pacing, or both. Three patients had VT suggestive of catecholamine-sensitive automaticity. The VT could not be initiated with programmed electrical stimulation, but it could be provoked by intravenous isoproterenol infusion; furthermore, the VT could not be terminated with ventricular overdrive pacing, but it could be abolished by discontinuing isoproterenol infusion. Reproduction of VT in these 10 patients allowed serial pharmacologic testing in selecting an effective antiarrhythmic regimen. Thus (1) exercise-induced VT can be caused by either reentry or cathecholamine-sensitive automaticity, and (2) electrophysiologic studies are of use in defining the underlying mechanism of exercise-induced sustained VT.**

In 1927, Bourne[1] suggested the use of exercise in exposing ventricular arrhythmias, particularly in patients with arteriosclerotic coronary heart disease. In 1932 Wilson et al[2] described a form of paroxysmal VT induced by exertion in patients without clinical evidence of organic heart disease. Several clinical investigators[3–11] subsequently demonstrated that exercise stress testing may provoke ventricular arrhythmias in normal subjects as well as in those with cardiac disease. Although changing heart rate, enhanced sympathetic nervous activity, increased catecholamine secretion, and development of myocardial ischemia have been implicated as contributing factors, the mechanism by which exercise-induced ventricular arrhythmias occur remains poorly understood. In the course of evaluating 12 patients in whom sustained VT developed during treadmill exercise testing, we performed electrophysiologic studies to delineate the underlying electrophysiologic mechanism. Our findings suggest that exercise-induced sustained VT can be caused either by reentry or by catecholamine-sensitive automaticity.

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## Methods

**Study patients:** The study population consisted of 12 patients who had sustained VT (lasting >30 seconds or requiring pharmacologic or electrical intervention, or both, because of circulatory collapse) during multistaged graded-treadmill stress testing using the Bruce protocol.[12] We selected these patients because electrophysiologic studies are more likely to reproduce the arrhythmia in patients with sustained than those with nonsustained VT.[13] Nine patients had complete cardiac catheterization and coronary angiography before admission.

**Electrophysiologic study:** Before the study, antiarrhythmic drugs were withheld for over 5 half-lives. The study was performed with patients in a postabsorptive, nonsedated state. With the conventional method,[14] a tetrapolar electrode catheter was introduced from the right femoral vein and, under fluoroscopy, placed in the right atrium across the tricuspid valve to record the His bundle potential. Another tetrapolar electrode catheter was also introduced from the right femoral vein and placed in the high right atrium for programmed atrial stimulation or placed in the right ventricle for programmed right ventricular stimulation. Electrocardio-

graphic leads $V_1$, I, and III were simultaneously displayed with intracardiac electrograms on a multichannel oscilloscope (Electronics for Medicine, VR-12, White Plains, New York), and recordings were made at a paper speed of 50 to 100 mm/s using filter frequency settings of 30 to 500 Hz.

A programmed digital stimulator (Bloom & Associates, Narberth, Pennsylvania) was used to deliver electrical impulses of 2.0 ms duration at approximately twice diastolic threshold. Programmed electrical stimulation consisted of incremental pacing and extrastimulation,[15] and was performed in the right atrium, right ventricle (apex and outflow tract), and, if necessary, in the left ventricle by way of a bipolar electrode catheter placed in the left ventricular apex through the right femoral artery. During programmed ventricular extrastimulation, the ventricle was paced at 2 cycle lengths (usually 500 and 400 ms). If a single ventricular extrastimulus failed to elicit VT, timed double or triple ventricular extrastimuli were delivered until the arrhythmia was provoked or until all extrastimuli failed to evoke ventricular responses.

If programmed electrical stimulation could not initiate VT, isoproterenol was infused intravenously at a rate of 1 to 4 μg/min until the sinus rate was accelerated to a maximum of 150 beats/min. If intravenous infusion of isoproterenol alone did not provoke an onset of VT, programmed electrical stimulation was repeated during isoproterenol infusion.[16]

After initiation of a sustained paroxysm of VT, timed ventricular premature stimuli, short bursts of rapid (overdrive) ventricular pacing, or both, were delivered to terminate the VT.

**Classification of mechanisms of VT:** Mechanisms of VT can be only presumptive during electrophysiologic studies in humans.[17] The 3 major ones are reentry, abnormal automaticity, and triggered activity. VT of a reentrant mechanism is suggested by the ability to initiate the VT with ventricular extrastimulation, or terminate the VT with ventricular extrastimulation or ventricular overdrive pacing. VT of automaticity is caused by rapid automatic discharge related to spontaneous phase 4 depolarization.[18] Its presence is suggested by the fact that it can neither be initiated nor terminated by programmed electrical stimulation.[17] In contrast, triggered activity related to delayed afterdepolarizations[19,20] does not arise spontaneously and is dependent upon previous depolarizations for its initiation. Clinical electrophysiologic studies[21,22] have suggested that this type of VT may be initiated during sinus rhythm or during atrial or ventricular paced rhythm within a critical range of cycle lengths and may be abolished by intravenous infusion of slow channel blockers such as verapamil.

## Results

**Clinical observations:** There were 9 men and 3 women aged 18 to 74 years (mean 49). The clinical data are summarized in Table I. Six patients had arteriosclerotic coronary heart disease (5 had prior myocardial infarction and 2 had ventricular aneurysm), 3 patients had cardiomyopathy (2 dilated and 1 hypertrophic), and the remaining 3 patients were judged to have no clinically recognizable heart disease except for the rhythm disturbance. None had prolongation of the Q-T interval. All 12 patients had a history of recurrent sustained VT that occurred during exertion but not at rest, the duration of which ranged from 3 months to 5 years. The physical activities that precipitated onset of VT included walking, jogging, house cleaning, and playing golf or tennis. All of them had had palpitations, dizziness, syncope, or a combination of these. Three patients (Cases 2, 8, and 11) also had had nonfatal cardiac arrest, presumably due to degeneration of VT to ventricular fibrillation.

Before electrophysiologic studies, we analyzed the onset of sustained VT induced during treadmill exercise testing: 1 patient had VT during stage II, 2 patients during stage III, 4 patients during stage IV, and 1 patient during stage V of the Bruce protocol; in the remaining 4 patients VT developed during the recovery period after exercise. None of the 12 patients had chest pain or exhibited ischemic S-T segment depression before the onset of VT. Three patients (Cases 1, 4, and 12) received intravenous lidocaine and 2 patients (Cases 2 and 8) required direct-current countershock because of hemodynamic deterioration.

The rates of VT ranged from 150 to 210 beats/min. Seven patients had VT of a right and 5 patients of a left bundle branch block pattern.

**Electrophysiologic studies:** Except for 2 patients (Cases 6 and 12), we were able to provoke paroxysms of sustained VT with a QRS morphology identical to that induced with treadmill exercise testing. Based on the mode of initiation and termination of the arrhythmia, we classified the 12 patients into 3 groups:

1. *Induction of VT suggestive of reentry.* In 7 patients (Cases 1, 2, 4, 8, 9, 10, and 11), the mechanism of VT was considered due to reentry as the tachycardia

**TABLE I Clinical Observations**

| Case | Age (yr) & Sex | Type of Cardiac Disease | Duration of Symptomatic VT (mo) | Stage of TET (VT Induction) | VT | |
|---|---|---|---|---|---|---|
| | | | | | Rate (beats/min) | QRS Morphology BBB Pattern |
| 1 | 74F | Coronary (HMI) | 6 | II | 180 | Right |
| 2 | 70M | Coronary (HMI) | 12 | III | 200 | Right |
| 3 | 18M | 0 | 24 | IV | 200 | Left |
| 4 | 56M | Cardiomyopathy | 60 | RP | 210 | Right |
| 5 | 52M | 0 | 18 | RP | 150 | Left |
| 6 | 41M | Cardiomyopathy | 3 | IV | 160 | Left |
| 7 | 28F | Cardiomyopathy | 12 | IV | 160 | Left |
| 8 | 58M | Coronary (HMI) | 24 | IV | 190 | Right |
| 9 | 32M | 0 | 12 | V | 180 | Left |
| 10 | 47M | Coronary (HMI) | 6 | RP | 200 | Right |
| 11 | 39F | Coronary (HMI) | 36 | III | 160 | Right |
| 12 | 61M | Coronary | 6 | RP | 170 | Right |

BBB = bundle branch block; HMI = healed myocardial infarction; RP = recovery period; TET = treadmill exercise testing; VT = ventricular tachycardia.

could be initiated by programmed ventricular extrastimulation—6 patients from the right ventricle (2 patients with single ventricular extrastimuli, 1 patient with double ventricular extrastimuli, and 3 patients with triple ventricular extrastimuli) and 1 patient from the left ventricle with double ventricular extrastimuli. One example to illustrate provocation of the same tachycardia with exercise and with ventricular extrastimulation is shown in Figures 1 to 3. The VT so induced could be terminated by ventricular overdrive pacing in 4 patients and by direct-current countershock because of circulatory collapse in 3 patients (Cases 2, 4, and 11).

*2. Induction of VT suggestive of catecholamine-sensitive automaticity.* In 3 patients (Cases 3, 5, and 7), the mechanism of VT was judged due to automaticity because the tachycardia could not be initiated with programmed electrical stimulation. In each instance, VT was provoked by isoproterenol infusion at a dose of 2 to 4 μg/min. Furthermore, VT could not be terminated with timed ventricular extrastimuli or ventricular overdrive pacing; however, it could be abolished by dis-

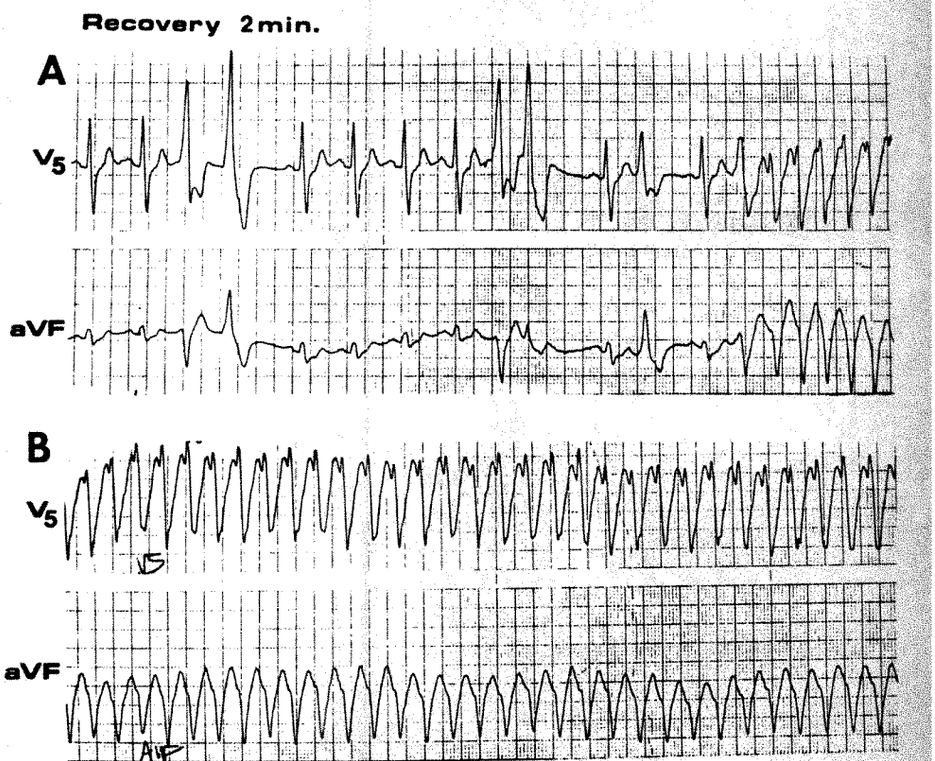



**FIGURE 1.** Onset of sustained VT during the recovery period after a treadmill exercise testing in a 47-year-old man with arteriosclerotic heart disease. The treadmill test was negative for myocardial ischemia up to a heart rate of 160 beats/min. Tracings A and B are continuous and electrocardiographic leads $V_5$ and aVF were simultaneously recorded. Multiform ventricular extrasystoles appear at 2 minutes into the recovery period and are followed by an onset of sustained VT at a rate of 200 beats/min.

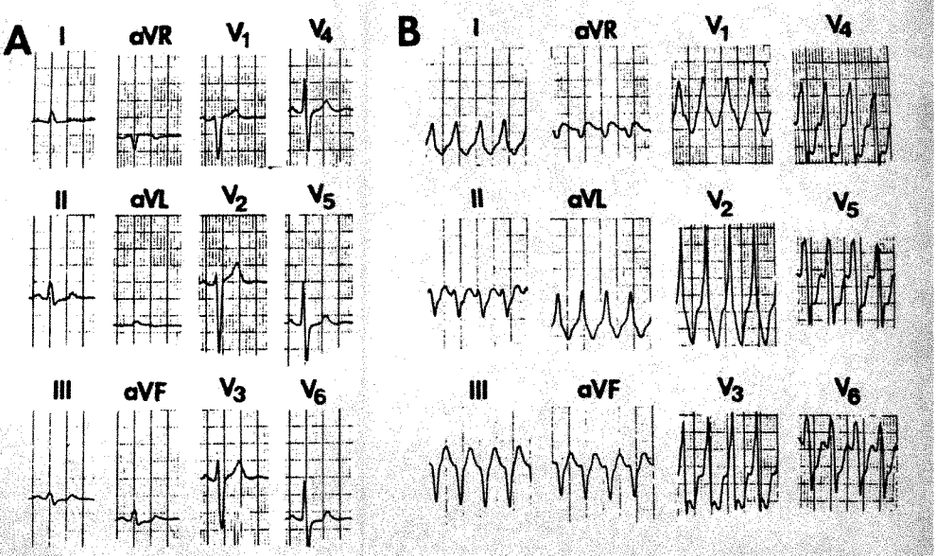



**FIGURE 2.** Same patient as in Figure 1. Comparison between 12-lead electrocardiogram taken during normal sinus rhythm (**A**) and that taken during exercise-induced VT (**B**) as demonstrated in Figure 1. Note that the VT has a positive QRS deflection in leads $V_1$ and I, and a negative QRS deflection in lead III.

continuing isoproterenol infusion. One example to illustrate provocation of the same tachycardia with exercise and with isoproterenol infusion is shown in Figures 4 to 6.

*3. Failure to reproduce VT.* In 2 patients (Cases 6 and 12) exercise-induced VT could not be reproduced during electrophysiologic studies. In 1 (Case 12), programmed right ventricular stimulation provoked ventricular flutter-fibrillation necessitating direct-current countershock. The mechanism of exercise-induced VT could not be classified in this patient. In the remaining patient (Case 6), programmed electrical stimulation and isoproterenol infusion failed to induce ventricular arrhythmia. The mechanism of exercise-induced VT was presumed to be due to automaticity.

**Pharmacologic testing and subsequent follow-up:** In 3 of the 7 patients with VT suggestive of reentry, propranolol was first administered intravenously (0.15 to 0.20 mg/kg) and failed to suppress the inducibility of the arrhythmia. Subsequently, 2 of these 3 patients responded to intravenous infusion of procainamide (15 to 20 mg/kg). In the remaining 4 patients, 2 responded to intravenous infusion of procainamide and 2 did not. Overall, 4 patients (Cases 1, 9, 10, and 11) responded to intravenous infusion of procainmide and were treated with oral procainamide (2 to 6 g/day). The 3 patients (Cases 2, 4, and 8) who did not respond to intravenous procainamide were subsequently treated with oral amiodarone (400 to 600 mg/day) since the arrhythmia was refractory to other antiarrhythmic drugs. In a follow-up period of 5 months to 2 years (mean 14 ± 3 months), 3 patients (Cases 1, 9, and 10) required readjustment of medications because of recurrence of symptoms, but all were clinically improved.

In the 3 patients with VT suggestive of catecholamine-sensitive automaticity, intravenous infusion of propranolol (0.15 to 0.20 mg/kg) prevented acceleration of the sinus rate beyond 100 beats/min and suppressed inducibility of VT during isoproterenol infusion in all 3 patients. They were subsequently treated with oral nadolol (120 to 320 mg/day). During a follow-up period of 6 to 15 months (mean 8 ± 2), 1 patient (Case 5) required addition of oral procainamide (2 g/day) to control exertion-induced palpitations and the remaining 2 patients remained free of symptoms.

Amiodarone was given to the 2 patients in whom electrophysiologic studies failed to reproduce the arrhythmia because of a history of failure to respond to conventional drugs. These 2 patients did well without recurrence of symptoms during a follow-up period of 4 and 7 months, respectively.

## Discussion

Observations made in the present study indicate that electrophysiologic studies can reproduce exercise-induced sustained VT in 10 of the 12 patients, and that the occurrence of exercise-induced sustained VT can be caused either by reentry or by catecholamine-sensitive automaticity.

**Mechanism of exercise-induced ventricular arrhythmias:** Several clinical studies[4,5,7,8] have demonstrated that ventricular arrhythmias may be heralded by ischemic S-T segment depression or angina pectoris, particularly in patients with arteriosclerotic coronary heart disease. Development of ischemic S-T segment depression, angina pectoris, or both usually diminishes the duration of exercise and thereby decreases the degree of myocardial stress preventing provocation of ventricular arrhythmias. Several investigators[6-8] have noted that exercise-induced ventricular arrhythmias often occur in the absence of ischemic S-T segment depression or angina pectoris. It is postulated that enhanced sympathetic nervous activity or increased secretion of catecholamines may alter electrophysiologic properties of the ventricular myocardium or the subendocardial Purkinje network, thereby enhancing automaticity or favoring the occurrence of reentry, or both.[23] Although myocardial ischemia cannot be completely excluded without perfusion scintigraphy, the results of our study confirmed that either reentry or catecholamine-sensitive automaticity may cause exercise-induced sustained VT.

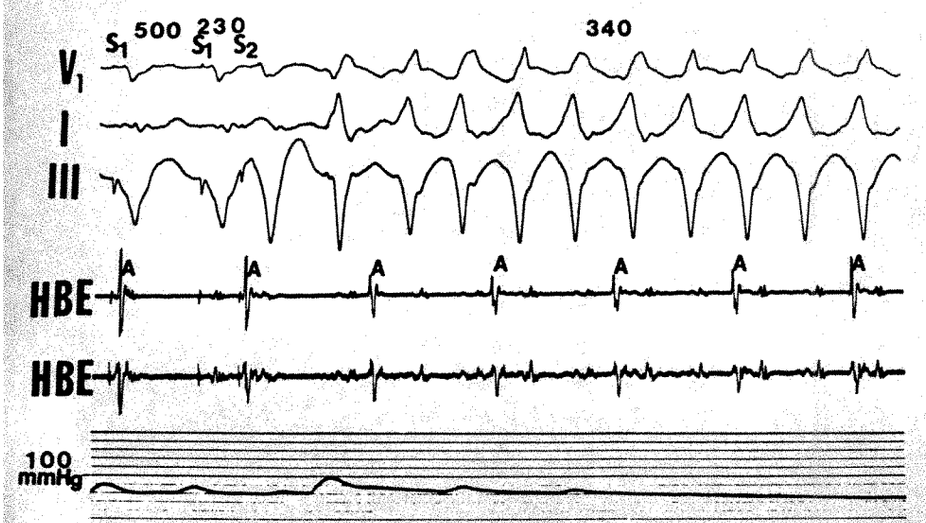



**FIGURE 3.** Same patient as in Figures 1 and 2. Initiation of sustained VT with programmed right ventricular extrastimulation. Electrocardiographic leads $V_1$, I, and III are simultaneously recorded with the His bundle electrographic lead (HBE). Right femoral arterial pressure is recorded at the **bottom**. During right ventricular pacing at a cycle length ($S_1$–$S_1$) of 500 ms, a ventricular premature beat ($S_2$) with a premature coupling interval ($S_1$–$S_2$) of 230 ms initiates an onset of VT with a cycle length of 340 ms. Note that the QRS morphology of the VT is identical to that induced during treadmill exercise testing (Fig. 2). The VT could be terminated by overdrive suppression (not shown). A = atrial electrogram.

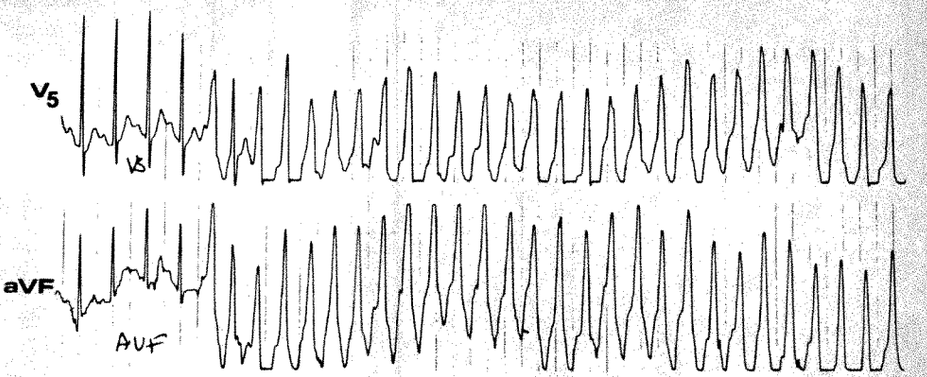



**FIGURE 4.** Onset of sustained VT at 1.1 minute into stage IV of a treadmill exercise testing in an 18-year-old man without clinical evidence of organic heart disease. The sinus rate is accelerated to 150 beats/min before the onset of VT at a rate of 190 beats/min. Electrocardiographic leads $V_5$ and aVF are simultaneously recorded.

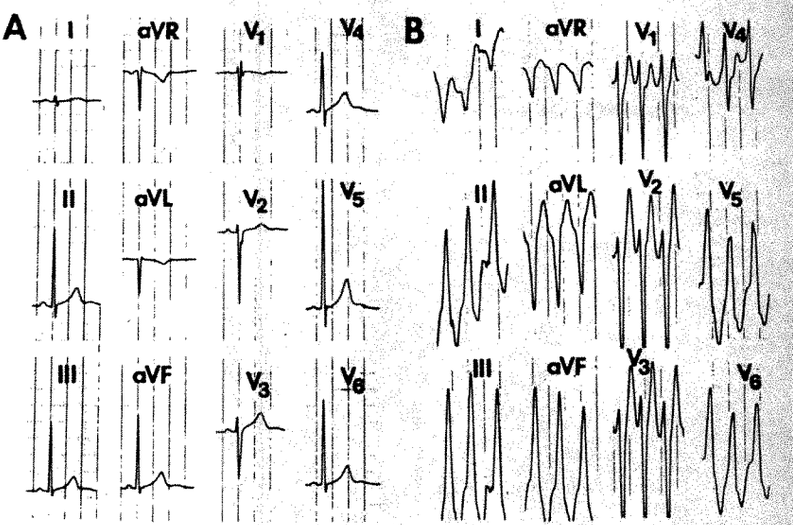



**FIGURE 5.** Same patient as in Figure 4. Comparison between 12-lead electrocardiogram taken during sinus rhythm (**A**) and that taken during exercise-induced VT (**B**) as demonstrated in Figure 4. Note that the VT has a predominantly negative QRS deflection in leads $V_1$ and I, and a positive QRS deflection in lead III.

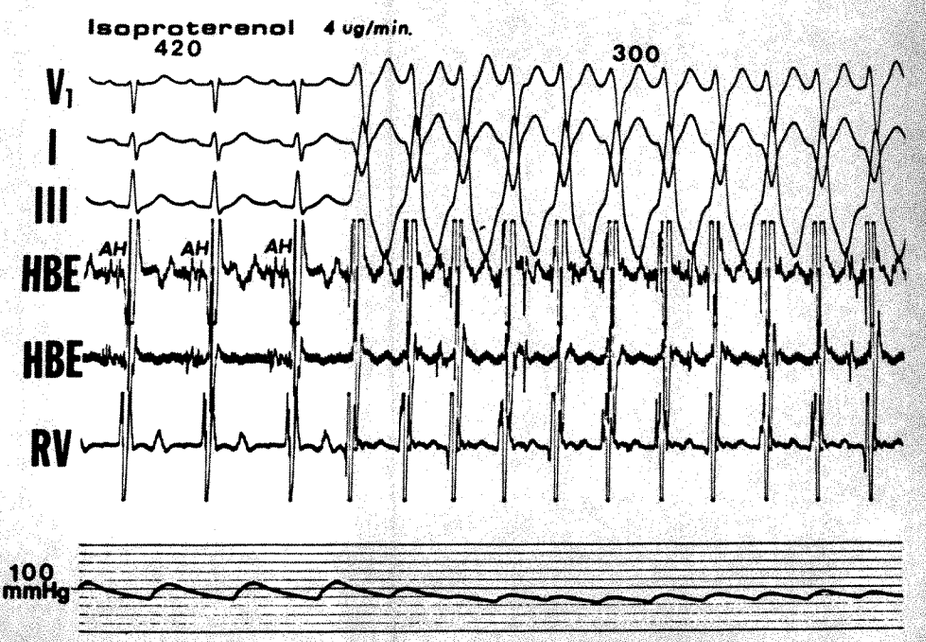



**FIGURE 6.** Same patient as in Figures 4 and 5. After failure of programmed electrical stimulation to induce arrhythmia, isoproterenol infusion at 4 $\mu$g/min accelerates the sinus rate (cycle length 420 ms) and provokes an onset of sustained VT with a cycle length of 300 ms. Electrocardiographic leads $V_1$, I, and III, His bundle electrographic lead (HBE), and right ventricular electrogram (RV) are simultaneously recorded. Right femoral arterial pressure is recorded at the bottom. A = atrial electrogram; H = His bundle electrogram. Note that the QRS morphology of the VT is identical to that induced during treadmill exercise testing (see Fig. 5).

Triggered activity related to delayed afterdepolarizations has been raised as a possible mechanism of exercise-induced VT.[24] Based on our recent study,[22] we believe that VT caused by such a mechanism has certain electrophysiologic characteristics: (1) its onset depends on a critical range of cycle lengths; therefore, it may or may not require exercise to induce the arrhythmia; (2) it can be initiated during sinus, atrial, or ventricular paced rhythm within the critical range of cycle lengths; (3) it is more easily triggered with pacing the atrium or ventricle for several beats than with single extrastimuli; (4) the interval between the first beat of tachycardia and the last sinus or paced beat (QRS complex) gradually decreases as the sinus or paced cycle length progressively shortens; and (5) its initiation can be prevented by intravenous infusion of slow channel blockers such as verapamil. In the evaluation of patients with exercise-induced VT, the possibility of having triggered activity as the underlying mechanism should also be considered.

**Treatment of exercise-induced ventricular arrhythmias:** In patients with exercise-induced ventricular arrhythmias related to myocardial ischemia, treatment should be directed toward prevention of the development of myocardial ischemia. This includes the use of nitrates, beta-adrenergic blocking agents, and slow channel blockers in the presence or absence of coronary artery spasm as a contributing factor.[25] In this situation, aortocoronary bypass grafting may be expected to be useful in abolishing the arrhythmia.[26,27]

In patients with exercise-induced ventricular arrhythmias not related to myocardial ischemia, the treatment should, however, be directed toward controlling the underlying mechanism. In this series, beta-adrenergic blockade with intravenous propranolol failed to suppress inducibility of VT suggestive of a reentrant mechanism (3 patients), but was effective in preventing induction of VT suggestive of catecholamine-sensitive automaticity (also 3 patients). Overall, amiodarone appeared to be an effective antiarrhythmic agent for cases that are refractory to or intolerant of conventional drugs (5 patients). We realize that the number in each group of patients is small, and further studies are necessary to define the long-term efficacy of various antiarrhythmic agents in the treatment of exercise-induced VT.

Myocardial revascularization is not expected to be useful in abolishing ventricular arrhythmias not related to ischemia.[28] Nevertheless, it should be pointed out that VT caused by reentry or automaticity may be corrected by surgical removal of the reentrant pathways or the automatic focus.[29]

**Clinical implications:** Observations made in the present study have the following important clinical implications: (1) Exercise-induced ventricular arrhythmias may or may not be related to myocardial ischemia, and electrophysiologic mechanisms responsible for these arrhythmias vary among patients. Reentry, automaticity, and triggered activity all need to be considered. Understanding of the underlying pathophysiology allows a more rational approach to the treatment. (2) In patients with exercise-induced sustained VT, electrophysiologic studies may be useful in reproducing the arrhythmia, thereby allowing serial pharmacologic testing for selecting a proper antiarrhythmic regimen.

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## References

1. **Bourne G.** An attempt at the clinical classification of premature ventricular beats. Q J Med 1927;20:219–243.
2. **Wilson FN, Wishart SW, Macleod AG, Barker PS.** A clinical type of paroxysmal tachycardia of ventricular origin in which paroxysms are induced by exertion. Am Heart J 1932;8:155–169.
3. **Mann RH, Burchell HB.** Premature ventricular contractions and exercise. Proc Staff Meet Mayo Clinic 1952;27:383–389.
4. **Gooch AS, McConnell D.** Analysis of transient arrhythmias and conduction disturbances occurring during submaximal treadmill exercise. Prog Cardiovasc Dis 1970;13:293–307.
5. **Andrews MT, Lee GB, Campion BC.** Cardiac dysrhythmias associated with exercise stress testing. Am J Cardiol 1972;30:763–767.
6. **McHenry PL, Fish C, Jordan JW, Corya BR.** Cardiac arrhythmias observed during maximal treadmill exercise testing in clinically normal men. Am J Cardiol 1972;29:331–336.
7. **Goldschlager N, Cake D, Cohn K.** Exercise-induced ventricular arrhythmias in patients with coronary artery disease: their relation to angiographic findings. Am J Cardiol 1973;31:434–440.
8. **Jelinek MV, Lown B.** Exercise stress testing for exposure of cardiac arrhythmia. Prog Cardiovasc Dis 1974;16:497–522.
9. **Faris JV, McHenry PL, Jordan JW, Morris SN.** Prevalence and reproducibility of exercise-induced ventricular arrhythmias during maximal exercise testing in normal men. Am J Cardiol 1976;37:617–622.
10. **Mokotoff DM, Quinones MA, Miller RR.** Exercise-induced ventricular tachycardia. Clinical features, relation to chronic ventricular ectopy, and prognosis. Chest 1980;77:1–16.
11. **Codini MA, Sommerfeldt L, Eybel CE, Messer JV.** Clinical significance and characteristics of exercise-induced ventricular tachycardia. Cathet Cardiovasc Diagn 1981;7:227–234.
12. **Doan AE, Peterson DR, Blackmon JR, Bruce RA.** Myocardial ischemia after maximal exercise in healthy men. A method for detecting potential coronary disease. Am Heart J 1965;69:11–20.
13. **Denes P, Wu D, Dhingra RC, Amat-y-Leon F, Wyndham C, Mautner R, Rosen KM.** Electrophysiological studies in patients with chronic recurrent ventricular tachycardia. Circulation 1976;54:229–236.
14. **Scherlag BJ, Lau SH, Helfant RH, Berkowitz WD, Stein E, Damato AN.** Catheter technique for recording His bundle activity in man. Circulation 1969;39:13–19.
15. **Sung RJ, Castellanos A, Mallon SM, Bloom MG, Gelband H, Myerburg RJ.** Mode of initiation of reciprocating tachycardia during programmed ventricular stimulation in the Wolff-Parkinson-White syndrome: with reference to various patterns of ventriculoatrial conduction. Am J Cardiol 1977;40:24–31.
16. **Reddy CP, Gettes LS.** Use of isoproterenol as an aid to electrical induction of chronic recurrent ventricular tachycardia. Am J Cardiol 1979;44:705–713.
17. **Wellens HJJ.** Value and limitations of programmed electrical stimulation of the heart in the study and treatment of tachycardias. Circulation 1978;57:845–853.
18. **Hoffman BF, Rosen MR.** Cellular mechanisms for cardiac arrhythmias. Circ Res 1981;49:1–14.
19. **Wit AL, Cranefield PF.** Triggered activity in cardiac muscle fibers of the simian mitral valve. Circ Res 1976;38:85–98.
20. **Rosen MR, Feder RF.** Does triggered activity have a role in the genesis of cardiac arrhythmias? Ann Intern Med 1981;94:794–801.
21. **Zipes DP, Foster PR, Troup PJ, Pedersen DH.** Atrial induction of ventricular tachycardia: reentry versus triggered automaticity. Am J Cardiol 1979;44:1–8.
22. **Sung RJ, Shen EN, Shapiro W, Morady F, Davis J.** Effects of verapamil on ventricular tachycardia of various mechanisms—with special reference to triggered activity in man (abstr). Clin Res 1982;30:224A.
23. **Han J, Moe GK.** Nonuniform recovery of excitability of ventricular muscle. Circ Res 1964;14:44–60.
24. **Wu D, Kou H, Hung J.** Exercise-triggered paroxysmal ventricular tachycardia. A repetitive rhythmic activity possibly related to afterdepolarization. Ann Intern Med 1981;95:410–414.
25. **Brodsky SJ, Cutler SS, Weiner DA, McCabe CH, Ryan TJ, Klein MD.** Treatment of stable angina of effort with verapamil: a double-blind, placebo-controlled randomized crossover study. Circulation 1982;66:569–579.
26. **Bryson AL, Parisi AF, Schechter E, Wolfson S.** Life-threatening ventricular arrhythmias induced by exercise. Cessation after coronary bypass surgery. Am J Cardiol 1973;32:995–999.
27. **Cline RE, Armstrong RG, Stanford W.** Successful myocardial revascularization after ventricular fibrillation induced by treadmill exercise. J. Thorac Cardiovasc Surg 1973;65:802–805.
28. **Lehrman KL, Tilkian AG, Hultgren HN, Fowles RE.** Effect of coronary arterial bypass surgery on exercise-induced ventricular arrhythmias. Long-term follow-up of a prospective randomized study. Am J Cardiol 1979;44:1056–1061.
29. **Josephson ME, Harken AH, Horowitz LN.** Endocardial excision: a new surgical technique for the treatment of recurrent ventricular tachycardia. Circulation 1979;60:1430–1439.

# Programmed Electrical Stimulation of the Heart in Coronary Artery Disease

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**The induction of ventricular arrhythmia in patients with a history of malignant ventricular arrhythmia by programmed electrical stimulation (PES) is associated with a poor prognosis. However, the incidence and significance of inducible arrhythmia in patients with stable coronary artery disease (CAD) who do not have a history of serious arrhythmia are unknown. We studied 32 such patients (31 men, mean age 55 years) with PES at the time of cardiac catheterization. Fourteen patients (Group I) manifested ≥3 extraventricular responses when challenged with 1 to 3 propagated right ventricular extrastimuli during ventricular pacing. Twelve (86%) of these 14 had evidence of left ventricular dysfunction (LVD), defined by a global ejection fraction of <50% or regional wall motion abnormalities. The remaining 18 patients (Group II) manifested ≤2 responses to extrastimulation. Only 4 (22%) of these 18 had LVD. Proximal 3-vessel CAD was more frequent in Group I patients (10 of 14, 71%) than in Group II (7 of 18, 39%). Only 5 patients (4 from Group I and 1 from Group II) demonstrated complex arrhythmia during exercise testing or ambulatory monitoring. The induction of extraventricular responses during PES may serve as an independent marker of electrical instability in the coronary population and is a much more common finding in those with LVD.**

Identifying the patient at risk for sudden cardiac death is one of the key problems in contemporary cardiology.[1-3] Patients with CAD have been found to be uniquely susceptible to sudden death, but current methods to distinguish those at highest risk are neither specific nor sensitive.[4,5] One approach is based on the ventricular premature beat (VPB) hypothesis[6] and uses exercise testing and ambulatory monitoring to expose advanced grades of ventricular premature depolarizations.[7,8] Since about 40% of patients with ischemic heart disease have advanced grades of VPBs on monitoring and exercise testing, it is necessary to select from this subgroup the much smaller group of patients who are susceptible to sudden death. This more precise identification of high-risk patients will require additional techniques.

PES has been increasingly useful in the study and treatment of recurrent ventricular arrhythmia. Heretofore, this method has been largely limited to the selection of a therapeutic regimen in symptomatic patients.[9,10] Whether PES can be applied to a group of patients with CAD who are at risk of sudden death in order to determine the degree of susceptibility has not been systematically explored.

The objective of the present study was to evaluate the response of patients with stable angina pectoris to programmed electrical stimulation. We were most interested in establishing whether a relation exists between the number of responses to PES and markers of severity of CAD such as the left ventricular ejection fraction, regional wall motion abnormalities, and extent of atherosclerotic lesions determined by angiography. In addition, we compared the response to extrastimulation with the amount of arrhythmia which could be exposed by exercise testing and ambulatory monitoring.

## Methods

Consenting patients with a history of stable angina pectoris who underwent diagnostic cardiac catheterization at the West Roxbury Veterans Administration Medical Center were included in the study. Informed consent was obtained in all cases using a form previously approved by the Human Studies Committee at the West Roxbury Veterans Administration Medical Center. Patients were excluded if there was (1) a history of a myocardial infarction in the previous 3-month period, (2) a suspicion of significant valvular heart disease, (3) unstable angina pectoris defined as angina at rest accompanied by S-T segment changes, or (4) a history of unexplained

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syncope or known ventricular tachycardia or fibrillation. All medication was withdrawn with the exception of digitalis, beta-adrenergic blocking agents, and nitrate derivatives. Five half-lives of the medication withdrawn were allowed to elapse before any testing was performed.

**Exercise testing and ambulatory monitoring:** Before catheterization all patients underwent exercise treadmill testing according to the protocol of Bruce and Doan.[11] Each patient exercised to fatigue but the test was prematurely terminated for severe angina pectoris, claudication, ventricular tachycardia, S-T segment elevation, or hypotension. Heart rate and blood pressure were continuously monitored along with rhythm, before, during, and after the exercise period.

Ambulatory monitoring was carried out within 48 hours of catheterization using a portable cassette system. A 24-hour period was chosen since it provided the highest yield of arrhythmia within the time constraints of the patient's hospitalization and represented 1 complete diurnal sleep-wake cycle. The recording system allowed simultaneous recording of 2 electrocardiographic leads ($V_1$ and $V_5$). An audiovisual scanning technique was used to review tape records. The accuracy of the interpretation was assessed by a physician who personally reviewed direct printouts of each grade of VPB.

For purposes of quantification, VPBs exposed by either monitoring or exercise testing were graded according to the Lown grading system, wherein Grade 0 = no VPBs; Grade 1 = <30 VPBs/h; Grade 2 = >30 VPBs/h; Grade 3 = multiform VPBs; Grade 4A = ventricular couplets; Grade 4B = ventricular salvos (≥3); and Grade 5 = early cycle (R on T) VPBs.[6]

**Cardiac catheterization:** Patients were taken to the cardiac catheterization laboratory in the postabsorptive state, after having received 5 to 10 mg of oral diazepam. A maximum of 10 ml of 1% xylocaine was used as the local anesthetic for introduction of the catheters using an antecubital or femoral approach. Right heart catheterization was first carried out and included determinations of right heart chamber pressures, pulmonary capillary wedge pressures, and oxygen saturation. A left heart catheterization was then performed which included left ventricular angiography and coronary arteriography. At the conclusion of the left heart study, all catheters were withdrawn. In patients found to have a lesion of the left main coronary artery of >75% and in those who had severe angina pectoris during the catheterization, the procedure was ended. A total of 12 patients were thus disqualified. In the remainder of the patients, electrophysiologic studies were carried out after a waiting period of at least 30 minutes.

**Electrophysiology study:** A quadripolar catheter (interelectrode distance of 1.0 cm) was introduced directly into the cephalic vein or into the femoral vein, using the venous introducer which was employed during the right heart catheterization. This pacing catheter was passed directly into the apex of the right ventricle. An intraventricular electrogram was recorded from the proximal 2 poles of the quadripolar unit, together with standard electrocardiographic leads I, II, and $V_1$. Signals were recorded on an Electronics-for-Medicine multichannel recorder (VR-12) at a paper speed of 25 to 50 mm/s using a frequency range of 30 to 500 Hz. The distal 2 poles of the quadripolar catheter were used for pacing and programmed stimulation. A Lown design cardiac stimulator was used, capable of delivering test stimuli of 2 ms duration with a square wave contour. The unit included a constant current operational power supply with a 2% accuracy, and a timing accuracy of ±3 ms. This unit included a ventricular demand pacemaker adjusted to deliver rectangular pulses of 2 ms duration. Each patient was paced at a rate which was 10 beats/min greater than the intrinsic heart rate. Pacing current used was the lowest amount necessary to achieve consistent ventricular capture.

The mid-diastolic threshold was determined by setting the first extrastimulus ($S_2$) approximately 400 ms after the pacing artifact ($S_1$), beyond the inscription of the T wave on the intracavitary electrocardiogram. $S_2$ was delivered after 8 consecutive ventricular paced beats. After the delivery of the extrastimulus, the output of the pacemaker was interrupted for 3 seconds to allow for a clear observation of the stimulus responses. The current of $S_2$ was set at 0.2 mA and increased in 0.2 mA steps until an extrasystole ($V_2$) was provoked. That current defined the mid-diastolic threshold.

The protocol used for the extrastimulation testing is displayed in Figure 1. The extrastimulus ($S_2$) was initially set at twice the mid-diastolic threshold, 400 ms after the pacing artifact. $S_2$ was then delivered progressively earlier in the cardiac cycle, scanning in 10 ms steps, until the effective refractory period was reached. If no extra responses were observed, $S_2$ was reset to thrice mid-diastolic threshold and scanning toward the refractory period was repeated. If $S_2$ failed to elicit extraventricular responses, it was set at a point 10 ms outside the effective refractory period at an intensity equal to twice mid-diastolic threshold. A second extrastimulus ($S_3$) was then added 400 ms after $S_2$, at twice and thrice its mid-diastolic threshold, and scanning in 10 ms increments toward $S_2$ was carried out for each stimulus intensity. Again, if no repetitive forms were elicited, a third stimulus ($S_4$) was similarly introduced. The end point of testing was the introduction of 3 extrastimuli, the third delivered at thrice the mid-diastolic threshold, or the provocation of ≥3 extraventricular responses to any test sequence. All stimulation sequences which provoked extraventricular responses were repeated unless sustained ventricular arrhythmia was induced. A response was considered present only if it was observed in 2 of 3 stimulation sequences. His bundle recordings were not obtained. However, electrocardiograms were scrutinized and

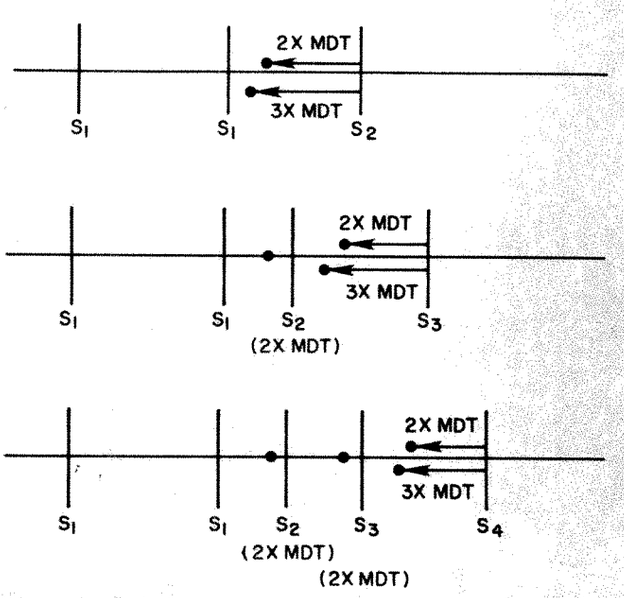



**FIGURE 1.** Protocol used for extrastimulation testing. **Closed circles,** effective refractory period; **arrows,** scanning in 10 ms decrements toward refractory period. MDT = mid-diastolic threshold.

**TABLE I Clinical Characteristics of the Study Population**

| | Group I | Group II |
|---|---|---|
| Number | 14 | 18 |
| Mean age (yr) | 58 ± 10 | 53 ± 7 |
| Angina severity* | | |
| Class I–II | 4 | 8 |
| Class III | 5 | 5 |
| Class IV | 5 | 5 |
| Prior myocardial infarction | 10 | 3† |
| Anterior | 4 | 1 |
| Inferior | 5 | 2 |
| Posterior | 1 | 0 |
| Congestive heart failure | 7 | 4 |
| Medications | | |
| Digitalis | 7 | 5 |
| Beta blockers | 9 | 15 |
| Nitrates | 13 | 16 |

* New York Heart Association classification.
† $p < 0.01$.

an assessment made of whether the responses elicited were due to bundle branch reentry or intraventricular reentry. Criteria for bundle branch reentry were those used by Greene et al[12] and included delay between the ventricular premature stimulus and the extra beat and a QRS morphology similar to the paced complex.

**Analysis of data:** Results of exercise testing, ambulatory monitoring, and cardiac catheterization were analyzed by 2 cardiologists who were blinded to the results of electrophysiologic testing. In addition to quantification of ventricular arrhythmia, each exercise test was scrutinized for evidence of ischemic electrocardiographic response, exercise duration, and indexes of exercise effort, including peak heart rate achieved and functional aerobic impairment. Catheterization results included the number of coronary vessels involved with atherosclerotic lesions, together with an assessment of the proximity and severity of each lesion. A lesion was considered significant if >75% of luminal diameter was obstructed. Ejection fraction was determined using single plane left ventricular angiography in a right anterior oblique projection. Systolic and diastolic volumes were calculated utilizing standard area-length equations.[13] Cineangiograms were likewise scrutinized for evidence of regional wall motion abnormalities using the area method. Segmental ejection fractions were determined for each of 5 major regions of the ventricle. The ejection fraction of each region was calculated as the difference between the diastolic and systolic regional areas divided by the diastolic regional area. A segmental ejection fraction was deemed abnormal if it fell below the 97% confidence interval defined by a group of 17 normal patients.[14] All values given in text represent mean ± standard error of the mean.

Statistical analysis of the data was performed using an unpaired Student's $t$ test wherein differences were considered significant when $p < 0.05$.

## Results

**Clinical characteristics:** A total of 32 patients participated in the study. There were 31 men and 1 woman; the mean age was 55 years. Patients were divided into 2 groups based on their response to programmed electrical stimulation. Group 1 consisted of 14 patients with ≥3 extraventricular responses to up to 3 ventricular stimuli. There were 18 patients in Group II who had 0 to 2 extra responses to 3 stimuli. Table I is a summary of the clinical information for each group. The mean age, angina severity, and medications used were not significantly different. There was a slightly greater number of patients in Group II receiving beta-adrenergic blocking agents (p = not significant [NS]), but the mean daily dose of propranolol taken was similar (120 ± 10 versus 150 ± 8 mg; p = NS). There was a higher incidence of prior myocardial infarction in Group I patients and more frequent congestive failure.

**TABLE II Results of Exercise Testing and Ambulatory Monitoring**

| | Group I | Group II |
|---|---|---|
| Number | 14 | 18 |
| Mean exercise duration (min) | 5.5 ± 0.9 | 6.3 ± 1.4 |
| Mean peak heart rate (% of maximum predicted) | 110 ± 12 (63%) | 108 ± 14 (60%) |
| Number with S-T segment depression >1 mm | 11 | 14 |
| **Maximal Grade of Arrhythmia by Exercise Testing** | | |
| Grade | | |
| 0–1 | 10 | 17 |
| 2 | 2 | 1 |
| 3 | 0 | 0 |
| 4A | 2 | 0 |
| 4B | 0 | 0 |
| **Maximal Grade of Arrhythmia by 24-Hour Ambulatory Monitoring** | | |
| Grade | | |
| 0–1 | 9 | 15 |
| 2 | 3 | 2 |
| 3 | 2 | 1 |
| 4A | 0 | 0 |
| 4B | 0 | 0 |

The results of exercise testing and ambulatory monitoring are shown in Table II. There was no statistically significant difference between the 2 groups in exercise duration or peak heart rate response. The incidence of S-T segment depression of >1 mm was comparable. Five patients manifested Lown Grade 3 or 4 arrhythmia during either exercise testing or ambulatory monitoring.

**Electrophysiologic testing:** There was no significant difference between the 2 groups in either the mean cycle length used during ventricular pacing (750 ± 15 ms versus 800 ± 12 ms) or in mid-diastolic threshold for $S_2$ (0.8 ± 0.1 versus 0.9 ± 0.2 mA). The threshold current for ventricular pacing ($S_1$) was <2 mA in all cases. The results of electrophysiologic testing are presented in Figure 2. Five patients in Group II manifested no extra responses, 8 had 1 extra response, and 5 had 2 responses. Of these 18 Group II patients, 14 had a global ejection fraction of >50%, including only 1 who displayed an abnormality of wall motion on left ventricular angiography. Eleven of the 14 patients in Group I were shown to have an ejection fraction of <50% ($p < 0.01$ compared with Group II). One of the 3 patients with a global ejection fraction of >50% had inferior wall hypokinesia.

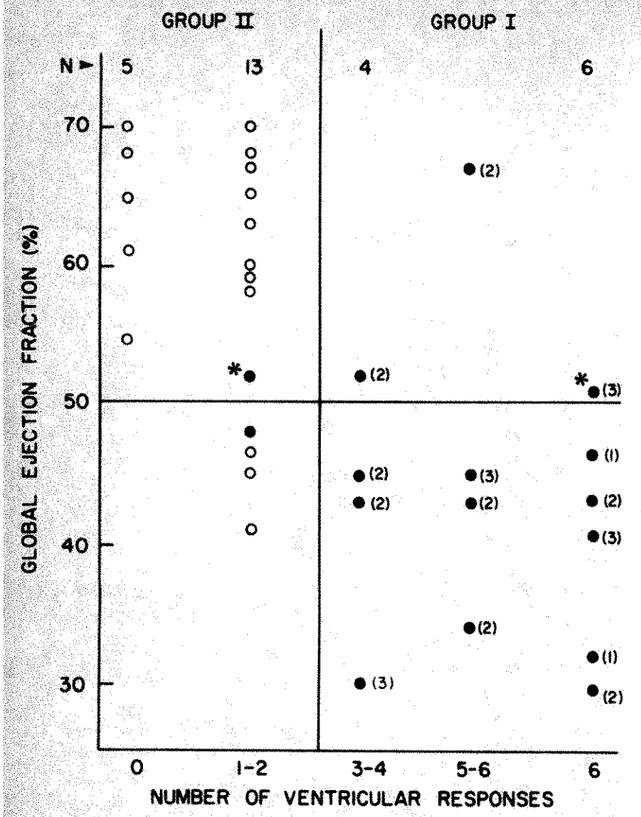



**FIGURE 2.** Number of extraventricular responses provoked during electrophysiologic testing correlated with global ejection fraction. **Parentheses** indicate the number of stimuli used in each Group I patient. **Asterisks** denote the presence of regional wall motion abnormalities in patients with global ejection fraction >50%. **Open and closed circles** denote whether responses resemble bundle branch or intraventricular reentry, respectively.

The number of extrastimuli required to elicit ≥3 responses in Group I patients is shown in parentheses in Figure 2. Although 2 of the patients had >6 responses induced with but 1 stimulus, there was no apparent correlation between severity of ventricular dysfunction and ease of provocation of extra responses. There was also no relation between the severity of dysfunction and the number of responses elicited. More than 6 responses were observed in 6 patients who had global ejection fractions from 28 to 52%. One patient in the series had unexpected ventricular tachycardia which accelerated and required immediate cardioversion. The remainder of the episodes of ventricular tachycardia were self-limited or broken by deep cough. Also shown in Figure 2 is a designation of whether responses resembled bundle branch or intraventricular reentry. Eleven of the 13 patients with 1 or 2 responses manifested bundle branch reentry while all multiple responses of ≥3 appeared to represent intraventricular reentry.

**Cardiac catheterization:** Fourteen of the 18 Group II patients had no regional wall motion abnormalities, in contrast to Group I patients, of whom only 2 had a normal wall motion pattern shown on angiography (Table III). Eight Group I patients with wall motion abnormalities manifested hypokinesia of the anterior and apical segments. The remaining 3 patients had a pattern of diffuse hypokinesia. Akinetic or dyskinetic regions were observed in 3 patients, all of whom were in Group I (one with 4 responses and 2 with >6 responses). There was also a lower left ventricular end-diastolic pressure and end-diastolic volume in Group II patients compared with Group I.

**TABLE III Cardiac Catheterization Data**

| | Group I | Group II |
|---|---|---|
| Number | 14 | 18 |
| End-diastolic volume (ml/M²) | 86 ± 10 | 72 ± 8* |
| End-diastolic pressure (mm Hg) | 15 ± 3 | 10 ± 2* |
| Number of regions with wall motion abnormalities | | |
| 0 | 2 | 14† |
| 1 | 3 | 2 |
| 2 | 4 | 1 |
| 3 | 2 | 1 |
| 4 | 3 | 0 |
| Number of vessels with severe (>75%) proximal stenosis | | |
| 1 | 2 | 6 |
| 2 | 2 | 5 |
| 3 | 10 | 7 |

* $p < 0.05$.
† $p < 0.001$.

The results of coronary arteriography are also displayed in Table III. There was a slightly higher frequency of severe (>75% stenosis) 3-vessel coronary disease in the inducible Group I patients and a greater incidence of 1- or 2-vessel disease in the noninducible Group II patients, but the differences were not statistically significant. There was also no significant difference in the state of collaterals vessels and quality of distal vasculature between the 2 groups.

## Discussion

Techniques routinely used to define coronary anatomy and left ventricular function permit only general conclusions regarding the patient's propensity to die suddenly. Furthermore, methods commonly employed to expose ventricular premature depolarizations, such as exercise testing and ambulatory monitoring, serve well as general screening methods but cannot be used, in many cases, for a precise assessment of risk. PES of the ventricle appears to be capable of uncovering the electrophysiologic lesion that predates the development of ventricular fibrillation. The bulk of experience with this technique, however, has focused on those patients who have had symptomatic arrhythmia and it has been used for the selection of an effective therapeutic regimen. There have been few previous studies which have specifically examined the application of these methods to a high-risk population, free of symptomatic arrhythmia.[15-18] Greene et al[15] studied patients with a recent myocardial infarction and found that the elicitation of repetitive responses was predictive of future cardiac death. Hamer et al[16] also found a higher incidence of sudden death after myocardial infarction in patients who manifested ≥5 extra responses to pro-

grammed stimulation. In a population of patients with heart disease of several types, Gomes et al[17] found that repetitive responses, even those caused by local reentry, were not a reliable predictor of sudden death. Naccarelli et al[18] also found a low predictive accuracy of repetitive responses in a mixed population.

The purpose of the present study was to apply ventricular stimulation techniques in a group of patients, all having stable coronary disease, in order to define the incidence of inducible arrhythmia in this particular population. We found that nearly 40% of the patients studied manifested ≥3 extraventricular responses to 1 to 3 stimuli. This incidence of inducibility is similar to that obtained in patients studied after myocardial infarction[15–16] but greater than that observed in other studies of patients free of symptomatic ventricular arrhythmia.[19,20] The differences in yield are difficult to interpret given the diversity in testing protocols and end points. For example, we used a regimen of cardiac testing which consisted of 1 to 3 ventricular stimuli delivered during ventricular pacing. This type of protocol consistently provokes the greatest number of extra responses in patients with a history of ventricular tachycardia, when compared with other regimens which employ single ventricular stimuli delivered during atrial drive or sinus rhythm.[21,22] In any case, the similar rates of inducibility in our study and previous postinfarction studies suggest that a myocardial infarction renders the heart more susceptible to extrastimulation. The fact that there was no correlation between extent of LVD, defined by global ejection fraction, and the number of responses provoked suggests that the presence rather than the extent of infarct renders the ventricle unstable. This general association between presence of LVD and electrical instability is in agreement with a previous study by Josephson et al[23] who showed a higher rate of inducibility in patients who suffered a cardiac arrest and had evidence of LVD compared with those victims with normal left ventricular function.[23]

We were unable to demonstrate a relation between the extent of CAD and the inducibility of arrhythmia, although there was a trend toward a greater frequency of single-vessel disease in noninducible patients and 3-vessel involvement in those who were inducible. Therefore, the extent of CAD may not influence the susceptibility of the ventricle to electrical stimulation. Studies of larger numbers of patients with varying amounts of atherosclerotic disease will be required to answer this question.

The ability to induce ventricular arrhythmia by programmed stimulation did not correlate with detection of complex ventricular ectopic activity by exercise testing or ambulatory monitoring. In fact, only 5 of the 32 patients manifested either Grade 3 or 4 arrhythmia by either method. It is clear that the disclosure of complex ventricular arrhythmia indicates an increased risk of sudden cardiac death.[24] However, as with any screening measure, absence of ventricular arrhythmia in any individual patient may not obviate that risk and more sensitive, albeit invasive, techniques may be indicated. Programmed stimulation does appear to provide a more sensitive measure of electrical stability in a population of patients with stable CAD. Its specificity and predictive accuracy have yet to be determined.

**Limitations of the study:** Our study was conducted after left ventricular angiography and coronary arteriography. It is conceivable that radiographic contrast material rendered the ventricle more susceptible to electrical stimulation. This is unlikely since electrical testing was performed after a 30-minute respite when electrocardiogram, blood pressure, and heart rate had returned to baseline values.

Patients were studied while continuing cardioactive medication, including digitalis, nitrates, and propranolol. This constitutes a problem since these drugs, in particular beta-blocking agents, may alter inducibility by reducing myocardial ischemia or by a primary antiarrhythmic effect. There was no statistically significant difference between inducible and noninducible groups in the number of patients receiving these drugs nor in the dose used. Furthermore, there was no intergroup difference in exercise duration, peak rate achieved during exercise, number of patients with S-T segment depression, or grade of arrhythmia provoked with exercise or detected by ambulatory monitoring. The similarities in clinical data in inducible and noninducible patients suggest that the results were not significantly influenced by continuation of cardiac drugs.

The electrophysiologic mechanism of the responses elicited in our patients was not fully elucidated. We chose not to employ His bundle recordings, since to do so would have added to the complexity and length of the procedure. His recordings are of obvious importance in differentiating reentry within the His-Purkinje system (macroreentry), a response observed in some normal subjects, from reentry within the ventricle (microreentry), which is felt to be a precursor of sustained arrhythmia.[25,26] The end point of testing in our study was the elicitation of ≥3 ventricular responses. This end point was chosen because reentry within the His-Purkinje system is rarely if ever sustained for >2 beats.[27] Greene et al[12] have pointed out that microreentry is frequently the mechanism of 1 and 2 beat responses in patients with a history of serious arrhythmia. In fact, all responses which persisted for ≥3 beats appear to represent intraventricular reentry using the less precise method of assessing mechanism by timing of the response and QRS morphology.

Finally, no long-term information is available from this study since nearly all of the patients eventually underwent coronary artery bypass surgery. Revascularization procedures have been found to have variable effects on the inducibility of ventricular arrhythmia.[28] Therefore, conclusions regarding the specificity and predictive accuracy of PES in a stable coronary population will await studies which provide more comprehensive follow-up information in patients who do not undergo coronary surgery, or who are studied after revascularization procedures.

**Conclusion:** This study suggests that techniques of PES may be safely applied in patients with CAD. As a group, patients with LVD tended to have more inducible arrhythmia than those with normal ventricles. However, there was a wide spectrum of inducible ar-

rhythmias within the group of patients with ventricular dysfunction; thus the response of any individual patient could not be predicted by routine markers of CAD severity, such as extent of atherosclerotic lesions. Furthermore, most of the inducible patients did not manifest high-grade ventricular ectopy during exercise testing or ambulatory monitoring. The significance of provocable arrhythmia in asymptomatic coronary patients is presently unknown and will only be determined in a long-term study of their outcome. However, if characterization of the response to PES proves to be a marker of the risk of sudden death, these techniques should be integrated into the invasive evaluation of the patient with CAD.

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## References

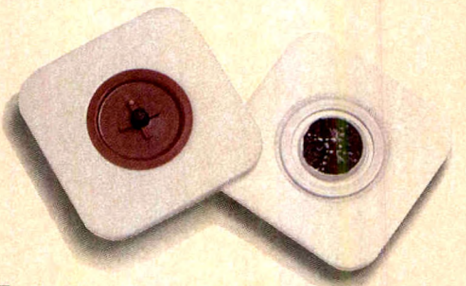
1. **Bigger J, Heller C, Wenger T, Weld F.** Risk stratification after acute myocardial infarction. Am J Cardiol 1978;42:202–210.
2. **Vismara L, Vera Z, Foerster J, Amsterdam E, Mason D.** Identification of sudden death risk factors in acute and chronic coronary artery disease. Am J Cardiol 1977;39:821–828.
3. **Lown B.** Sudden cardiac death: the major challenge confronting contemporary cardiology. Am J Cardiol 1979;43:313–328.
4. **Kannel W, Doyle J, McNamara P, Quickenton P, Gordon T.** Precursors of sudden cardiac death. Factors related to incidence of sudden death. Circulation 1975;51:606–613.
5. **Kuller L, Lilienfeld A, Fisher R.** An epidemiologic study of sudden and unexpected deaths due to atherosclerotic heart disease. Circulation 1966;34:1056–1068.
6. **Lown B, Wolf M.** Approaches to sudden death from coronary heart disease. Circulation 1971;44:130–142.
7. **Ryan M, Lown B, Horn H.** Comparison of ventricular ectopic activity during 24 hour monitoring and exercise testing in patients with coronary heart disease. N Engl J Med 1975;292:224–229.
8. **Lown B, Calvert A, Armington R, Ryan M.** Monitoring for serious arrhythmias and high risk of sudden death. Circulation 1975;52:Suppl III:III-189–III-198.
9. **Mason J, Winkle R.** Electrode-catheter arrhythmia induction in the selection and assessment of antiarrhythmic drug therapy in recurrent ventricular tachycardia. Circulation 1978;58:971–985.
10. **Horowitz L, Josephson M, Farshidi A, Spielman S, Michelson E, Greenspan A.** Recurrent sustained ventricular tachycardia. Role of electrophysiologic study in selection of antiarrhythmic regimens. Circulation 1978;58:986–997.
11. **Doan A, Peterson D, Blackman J, Bruce R.** Myocardial ischemia after maximal exercise in healthy men: a method for detecting potential coronary disease: Am Heart J 1965;69:11–21.
12. **Greene H, Reid P, Schaeffer A.** Mechanism of the repetitive ventricular response in man. Am J Cardiol 1980;45:227–235.
13. **Kennedy J, Trenholme S, Kasser I.** Left ventricular volume and mass from single plane cineangiocardiogram. A comparison of anteroposterior and right anterior oblique methods. Am Heart J 1970;80:343–352.
14. **Gelbert H, Brundage B, Glantz S, Parmley W.** Quantitative left ventricular wall motion analysis: a comparison of area, chord and radial methods. Circulation 1979;59:991–1000.
15. **Greene H, Reid P, Schaeffer A.** The repetitive ventricular response in man: a predictor of sudden death. New Engl J Med 1978;299:729–734.
16. **Hamer A, Vohra J, Hunt D, Sloman G.** Prediction of sudden death by electrophysiologic studies in high risk patients surviving acute myocardial infarction. Am J Cardiol 1982;50:223–229.
17. **Gomes J, Kang P, Khan R, Kelen G, El-Sherif N.** Repetitive ventricular response. Its incidence, inducibility, reproducibility, mechanism, and significance. Br Heart J 1981;46:159–167.
18. **Naccarelli G, Prystowsky E, Jackman W, Heger J, Rinkenberger R, Zipes D.** Repetitive ventricular response: prevalence and prognostic significance. Br Heart J 1981;46:152–158.
19. **Fisher J, Ostrow E, Mehra R.** Clinical correlation of ventricular vulnerability to electrophysiologic stress. In: Proceedings of the Sixth World Symposium on Cardiac Pacing. Montreal: LaPlante Langevin, 1979.
20. **VandePol C, Farshidi A, Spielman S, Greenspan A, Horowitz L, Josephson M.** Incidence and clinical significance of induced ventricular tachycardia. Am J Cardiol 1980;45:725–731.
21. **Mason J.** Repetitive beating after single ventricular extrastimuli. Incidence and prognostic significance in patients with recurrent ventricular tachycardia. Am J Cardiol 1980;45:1126–1131.
22. **Ruskin J, DiMarco J, Garan H.** Repetitive responses to single ventricular extrastimuli in patients with serious ventricular arrhythmias. Incidence and clinical significance. Circulation 1981;63:767–772.
23. **Josephson M, Horowitz L, Spielman S, Greenspan A.** Electrophysiologic and hemodynamic studies in patients resuscitated from cardiac arrest. Am J Cardiol 1980;46:948–955.
24. **Ruberman W, Weinblatt E, Goldberg J, Frank C, Shapiro S, Chaudhary B.** Ventricular premature complexes in prognosis of angina. Circulation 1980;61:1172–1178.
25. **Akhtar M, Damato A, Batsford W, Ruskin J, Ogunkelu B, Vargas G.** Demonstration of reentry with the His-Purkinje system in man. Circulation 1974;50:1150–1162.
26. **Akhtar M, Gilbert C, Wolff G, Schmidt D.** Reentry within the His-Purkinje system. Elucidation of reentrant circuit utilizing right bundle branch and His bundle recordings. Circulation 1978;58:295–304.
27. **Foster J, Simpson R.** Initiation of ventricular tachycardia by reentry within the bundle branches. Am J Cardiol 1980;45:895–900.
28. **Garan H, Ruskin J, DiMarco J.** Electrophysiologic studies before and after aortocoronary bypass in patients with out-of-hospital ventricular fibrillation (abstr). Am J Cardiol 1981;47:497.

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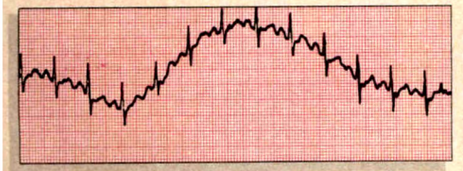



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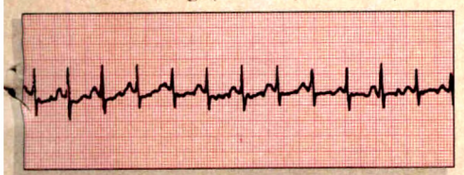
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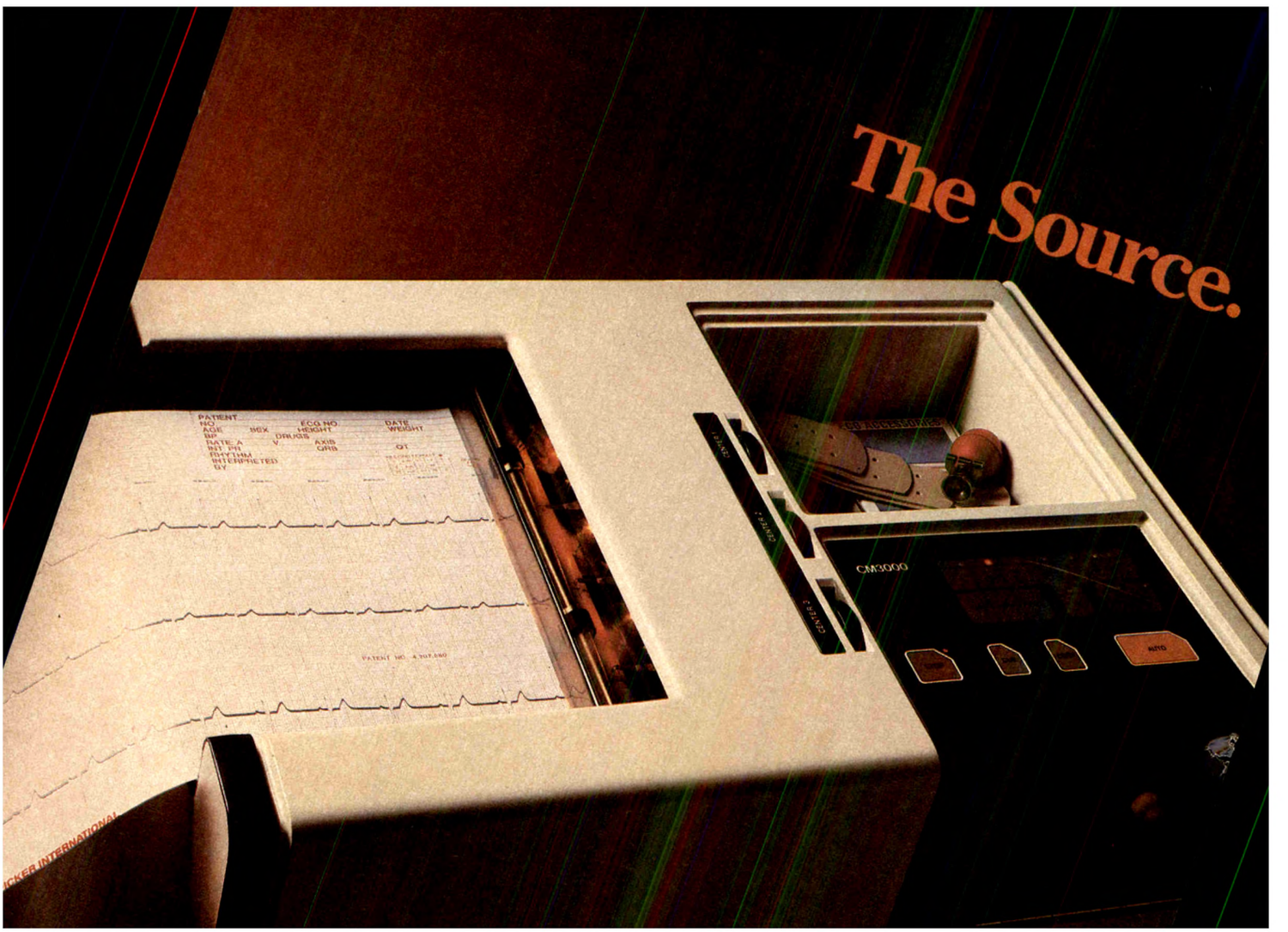
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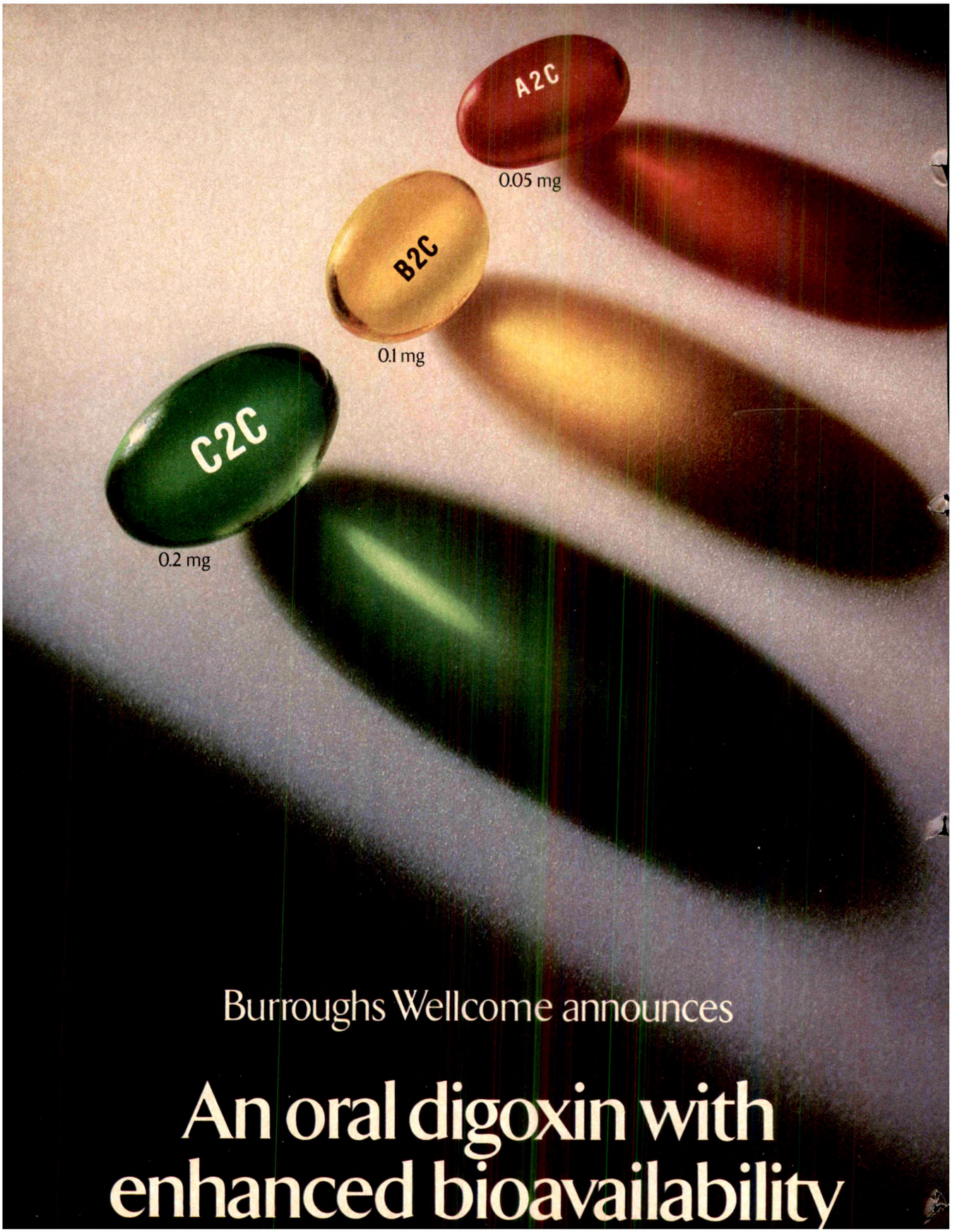
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Due to the more complete absorption of digoxin from Lanoxicaps, recommended oral doses are 80% of those for tablets, elixir, and IM injection.

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Colors of Lanoxicaps are distinctive, for less confusion or misidentification by patients. Please see next page for brief summary of prescribing information.

# new LANOXICAPS®
## (digoxin solution in capsules)

50 μg (0.05 mg) I.D. Imprint A2C (red)
100 μg (0.1 mg) I.D. Imprint B2C (yellow)
200 μg (0.2 mg) I.D. Imprint C2C (green)

LANOXICAPS® shown magnified four times actual size.




**Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

# new LANOXICAPS®
## (digoxin solution in capsules)

**LANOXICAPS®** brand DIGOXIN SOLUTION IN CAPSULES 50 μg (0.05 mg), 100 μg (0.10 mg), and 200 μg (0.20 mg)
*Brief Summary of Prescribing Information*

**INDICATIONS AND USAGE**
**Heart Failure:** The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma).

Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

**CONTRAINDICATIONS**
Digitalis glycosides are contraindicated in ventricular fibrillation.

Any untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin, as is hypersensitivity to digoxin itself. Allergy to digoxin, though rare, does occur. It may not extend to all preparations, and another digitalis glycoside may be tried with caution.

**WARNINGS**
The use of digoxin or other digitalis glycosides is unwarranted in the treatment of obesity.

Digoxin in soft capsules should be administered in divided daily doses to minimize any potential adverse reactions. Where compliance is considered a problem, single daily dosing may be appropriate.

Anorexia, nausea, vomiting, and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section in complete prescribing information).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary. Careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity. Note: Digitalis glycosides are an important cause of accidental poisoning in children.

**PRECAUTIONS**
**General:** Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section in complete prescribing information). More time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range," because potassium depletion sensitizes the myocardium to digoxin. Hypokalemia may result from diuretic, amphotericin B, or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see *Treatment of arrhythmias produced by overdosage*, in OVERDOSAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypocalcemia can nullify the effects of digoxin in man; digoxin may be ineffective until serum calcium is restored to normal.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine causes a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the quinidine dose. Because of the considerable variability of this interaction, digoxin dosage should be carefully individualized.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (eg, hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e., sick sinus syndrome), digoxin may worsen sinus bradycardia or sinoatrial block.

In patients with Wolff-Parkinson-White syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

**Drug Interactions:** Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias. *Quinidine* causes a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. *Antacids, kaolin-pectin, sulfasalazine, neomycin,* and *cholestyramine* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Thyroid* administration to a digitalized hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias, because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although *propranolol* and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

**ADVERSE REACTIONS**
The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5% to 20%, with 15% to 20% being considered serious (1% to 4% of patients receiving digoxin). Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

**Adults:**
*Cardiac*—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease. Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm, and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage.

Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances.

*Gastrointestinal*—Anorexia, nausea, vomiting, and, less commonly, diarrhea are common early symptoms of overdosage. Uncontrolled heart failure may also produce such symptoms.

*CNS*—Visual disturbances (blurred or yellow vision), headache, weakness, apathy, and psychosis can occur.

*Other*—Gynecomastia is occasionally observed.

**Infants and Children:**
Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea, and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular

arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

**OVERDOSAGE** Treatment of arrhythmias produced by overdosage

**Adults:**

Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe.

Potassium salts are commonly used, particularly if hypokalemia is present. Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in infants and children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 ml) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol, and phenytoin, although use of the latter must be considered experimental. In advanced heart block, temporary ventricular pacing may be beneficial.

**Infants and Children:**

See Adults section (immediately above) for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium.

If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

**DOSAGE AND ADMINISTRATION**

*Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions.* Diminished renal function is the most important factor requiring modification of recommended doses.

Due to the more complete absorption of digoxin from soft capsules, recommended oral doses are only 80% of those for tablets, elixir, and IM injection.

Because the significance of the higher peak serum concentrations associated with once-daily capsules is not established, divided daily dosing is presently recommended for:

1. infants and children under 10 years of age;
2. patients requiring a daily dose of 300 μg (0.3 mg) or greater;
3. patients with a previous history of digitalis toxicity;
4. patients considered likely to become toxic;
5. patients in whom compliance is not a problem.

Where compliance is considered a problem, once-daily dosing may be appropriate.

**Adults:**

*Adults: rapid digitalization with a loading dose*—Peak body digoxin stores of 8 to 12 μg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Larger stores (10 to 15 μg/kg) are often required for adequate control of ventricular rate in patients with atrial flutter or fibrillation. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 μg/kg [see PRECAUTIONS section]).

The loading dose should be based on the projected peak body stores and administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6- to 8-hour intervals, *with careful assessment of clinical response before each additional dose.*

If the patient's clinical response necessitates a change from the calculated dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

**Dosage for Previously Undigitalized Patients:**

In previously undigitalized patients, a single initial Lanoxicaps dose of 400 to 600 μg (0.4 to 0.6 mg) usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Additional doses of 100 to 300 μg (0.1 to 0.3 mg) may be given cautiously at 6- to 8-hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Lanoxicaps that a 70-kg patient requires to achieve 8 to 15 μg/kg peak body stores is 600 to 1000 μg (0.6 to 1.0 mg).

*Adults: gradual digitalization with a maintenance dose*—The following table provides average Lanoxicaps daily maintenance dose requirements for patients with heart failure based upon lean body weight and renal function:

Usual Lanoxicaps Daily Maintenance Dose Requirements (μg) for Estimated Peak Body Stores of 10 μg/kg

| Corrected Ccr (ml/min per 70 kg) | Lean body weight (kg/lbs) 50/110 | 60/132 | 70/154 | 80/176 | 90/198 | 100/220 | Number of days before steady-state achieved |
|---|---|---|---|---|---|---|---|
| 0 | 50 | 100 | 100 | 100 | 150 | 150 | 22 |
| 10 | 100 | 100 | 100 | 150 | 150 | 150 | 19 |
| 20 | 100 | 100 | 150 | 150 | 150 | 200 | 16 |
| 30 | 100 | 150 | 150 | 150 | 200 | 200 | 14 |
| 40 | 100 | 150 | 150 | 200 | 200 | 250 | 13 |
| 50 | 150 | 150 | 200 | 200 | 250 | 250 | 12 |
| 60 | 150 | 150 | 200 | 200 | 250 | 300 | 11 |
| 70 | 150 | 200 | 200 | 250 | 250 | 300 | 10 |
| 80 | 150 | 200 | 200 | 250 | 300 | 300 | 9 |
| 90 | 150 | 200 | 250 | 250 | 300 | 350 | 8 |
| 100 | 200 | 200 | 250 | 300 | 300 | 350 | 7 |

*Example*—Based on the above table, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 ml/min should be given 200 μg (0.2 mg) of Lanoxicaps per day, usually taken as a 100 μg (0.1 mg) capsule after the morning and evening meals. Steady-state serum concentrations should not be anticipated before 11 days.

**Digitalizing Dose for Children:**

Usual Digitalizing and Maintenance Dosages for Lanoxicaps in Children With Normal *Renal Function Based on Lean Body Weight*

| Age | Digitalizing* Dose (μg/kg) | *Daily*† Maintenance Dose (μg/kg) |
|---|---|---|
| 2-5 Years | 25-35 | 25%-35% of the oral or IV loading dose‡ |
| 5-10 Years | 15-30 | |
| Over 10 Years | | |

*IV digitalizing doses are the same as Lanoxicaps digitalizing doses.

†Divided daily dosing is recommended for children under 10 years of age.

‡Projected or actual digitalizing dose providing desired clinical response.

More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided above can be used in calculating this dose for patients with normal renal function. In children with renal disease, digoxin dosing must be carefully titrated based upon desired clinical response.

Long-term use of digoxin is indicated in many children who have been digitalized for acute heart failure, unless the cause is transient. Children with severe congenital heart disease, even after surgery, may require digoxin for prolonged periods.

*It cannot be overemphasized that both the adult and pediatric dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.*

**HOW SUPPLIED**

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 50 μg (0.05 mg): bottles of 100. Imprint A2C (red)

LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 100 μg (0.10 mg)†: bottles of 100. Imprint B2C (yellow)

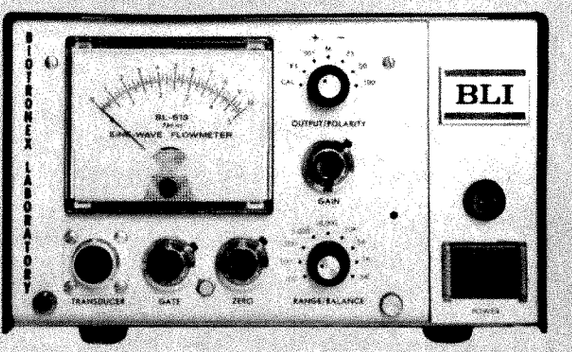
LANOXICAPS (DIGOXIN SOLUTION IN CAPSULES), 200 μg (0.20 mg)†: bottles of 100. Imprint C2C (green)

†U.S. Patent No. 4088750

Wellcome / **Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

# BLI Sine-Wave Blood Flowmeter

## BL-613 with ELECTRONIC ZERO




## Biotronex Laboratory, Inc.

4225 Howard Avenue, Kensington, Md. 20795, Phone: 301-942-1800



**Royal Postgraduate Medical School**
(University of London)

## European and American Cardiology at the Hammersmith

**Presentation and discussion of advances 1983**

**6–10, June 1983**

The salient feature of the course will be the panel and general discussion of selected topics, presented as mini-symposia, introduced by reviews and presentation of new findings.

| **Mini-symposia on:** | **Chairmen:** |
|---|---|
| Hypertrophic Cardiomyopathy: The Hammersmith Approach | J. Goodwin |
| Controversial Management of Hypertension | C. Dollery |
| Prognosis of IHD with and without Surgery | T. Killip |
| New Diagnostic Approach to Patients with IHD | A. Maseri |
| Coronary Spasm: Mechanisms | D. Harrison |
| "Crescendo" Angina: Ca Antagonists, B-blockers, Nitrates of Surgery | D. Julian |
| Acute Myocardial Infarction: Fibrinolysis, B-blockers, Antiarrhythmic Drugs | P. Hugenholtz |
| Plan for Treatment in the First Year after MI | P. Sleight |
| When and How to Treat Dyslipidaemias | M. Oliver |
| Valvular Replacement: Which Valve to Choose | E. Braunwald |
| Endocarditis: Management and Prophylaxis | C. Oakley |
| Nuclear Cardiology: Position Tomography and Ventricular Function | A. Selwyn |
| Sino-atrial and AV Block | D. Krikler |
| The Surgery of Arrhythmias | H. Bentall |
| When to Operate Mildly Symptomatic Valvular Patients | E. Sonnenblick |
| Nuclear Magnetic Resonance for Cardiac Studies | R. Steiner |

*The course will include practical demonstration of routine and research techniques developed or in use at the Hammersmith Hospital for cardiovascular investigations.*

Course organisers: PROFESSOR A. MASERI, PROFESSOR J. F. GOODWIN

**Further details:** School Office, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London, W12 OHS
Tel: 01-743 2030 ext 351

**Fees:** *Before 31 March 1983:* £120 ($200) for home and EEC students
£240 ($400) for overseas students

*After 31 March 1983:* £180 ($300) for home and EEC students
£300 ($500) for overseas students

**ELIGIBLE FOR AMERICAN HEART ASSOCIATION CATEGORY 1 CREDITS**

# Juxtaductal Aortic Coarctation

## Analysis of 84 Patients Studied Hemodynamically, Angiographically, And Morphologically After Age 1 Year

D. LUKE GLANCY, MD, ANDREW G. MORROW, MD, ALLAN L. SIMON, MD, and WILLIAM C. ROBERTS, MD

**Although many studies of juxtaductal coarctation of the aorta have been reported, none has correlated clinical, hemodynamic, angiographic, anatomic, and operative findings. Of 84 patients (62 male and 22 female; age range, 1 to 49 years [mean 17]), all had murmurs; 76 had absent, diminished, or delayed femoral pulsations; 50 had cuff systolic blood pressures in the arm >140 mm Hg, and 30 had diastolic pressures >90 mm Hg. The average pressure gradients (mm Hg) by direct measurements above and below the coarctation in 35 patients were peak systolic, 45; mean, 17; and diastolic, 5. Rib notching, visible in chest roentgenograms in 43 patients, correlated directly with age and inversely with the diameter of the coarctation. Moderate or marked cardiomegaly by radiograph was present in only 1 of 48 patients with isolated coarctation and in 17 of 36 with associated cardiovascular malformations. Electrocardiograms were abnormal in more than two thirds of patients with associated anomalies, but were normal in more than three fourths of those with isolated coarctation. In 70 excised, serially sectioned coarctations the aortic lumens were completely occluded in 4 patients, up to 0.5 mm in internal diameter in 22 patients, from 0.6 to 2 mm in 26 patients, from 2.1 to 5 mm in 14, and >5 mm in 4, and correlated directly with lumens measured angiographically. The most significant anatomic factor causing the coarctation was invagination of the media from the posterior aortic wall, but intimal proliferation (jet lesion) at and immediately distal to the invagination contributed to the narrowing. Three (each with associated anomalies) of 70 patients died early after coarctation repair. Systolic or diastolic blood pressures decreased early postoperatively in 58 (87%) of 67 surviving patients, and both pressures decreased in 42 (63%). Late postoperatively (mean follow-up, 4.7 years), the systolic blood pressure remained elevated in 25% of patients.**

Many reports have described 1 or more features of patients with juxtaductal aortic coarctation, but none has correlated clinical, hemodynamic, angiographic, operative, and detailed anatomic studies in a large number of patients. This report summarizes such observations in 84 patients over age 1 year at the time of study.

### Methods

**Patients:** The diagnosis of aortic coarctation was confirmed by examination of the resected coarctation specimen in 69 patients, by operative examination without resection in 2, by necropsy in 6, and by aortography in 7. The age and sex distributions of the 84 patients are shown in Figure 1. Additional congenital cardiovascular anomalies occurred in 36 patients (43%) (Table I).

Electrocardiograms and chest rogentgenograms were obtained in all 84 patients and aortograms in 52. Direct arterial pressures were measured above and below the aortic coarctation in 35. In 72 operatively excised or necropsy aortic coarctations, the specimens were serially sectioned longitudinally at 6 to 10 $\mu$m intervals. Every 10th section was stained with hematoxylin and eosin, and an occasional section from each patient was stained by the Verhoeff-van Gieson method for elastic fibers.

### Results

**Morphologic features:** In 71 of 72 specimens, the coarctation was juxtaductal: The aortic lumen was narrowed by elastic tissue which invaginated from the posterior wall of the aorta toward the aortic attachment of the ligamentum arteriosum or ductus arteriosus (Fig. 2 to 4). The elastic media of the invaginated aorta was

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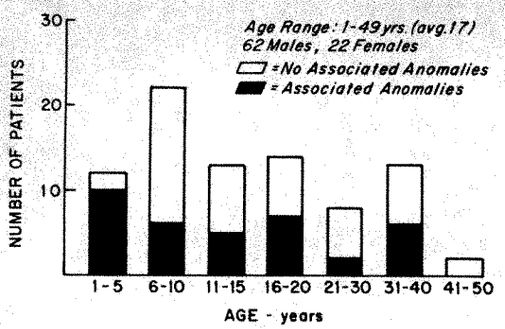



**FIGURE 1.** Ages of the 84 patients with juxtaductal aortic coarctation.

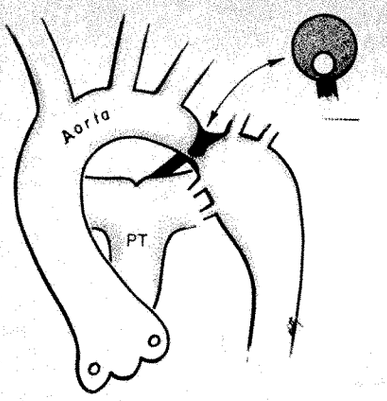



**FIGURE 2.** Diagram of isthmic (juxtaductal) aortic coarctation. The narrowing is caused by invagination of the elastic tissue media of the posterior wall of aorta toward the aortic attachment of the ligament or duct. Fibrous tissue, the result of turbulent blood flow, frequently accumulates on the intima distal to the invaginated aortic wall. Most blood reaching the aorta distal to the coarctation does so through dilated collateral arteries, including large intercostal arteries. **Inset:** a drawing of a cross section of the aorta at the level of the coarctation. PT = pulmonary trunk.

usually thicker on its distal than on its proximal side, and the media of the first several centimeters of aorta distal to the coarctation was usually thicker than that of the aorta just proximal to the narrowing. Near the free margin of the invagination the elastic fibers lost their parallel arrangement. A triangular wedge of fibrous tissue filled the adventitial side of the invagination so that the external aortic narrowing was usually slight compared with the aortic luminal narrowing. The invagination produced an eccentrically located aortic lumen. The *ligamentum or ductus* attached to the anterior wall of the aorta and was directed toward the elastic tissue invaginated from the opposite wall. Small spaces filled with acid mucopolysaccharide often separated elastic fibers of the aortic media. On the anterior aortic wall, opposite the coarctation, these spaces were more prominent proximal to the coarctation.

*Intimal "jet" lesions* formed at the free margins and on the distal side of the coarctation and frequently caused further narrowing of the aortic lumen. Intimal plaques containing atheromatous material were less common than jet lesions in resected specimens and were more often proximal to the coarctation. A tubular narrowing (7 cm long) rather than a distinct invagination of the aorta occurred in 1 patient.

*The relation of the ductus or ligamentum to the coarctation* was determined from serial sections in 63 of the 72 specimens. Maximal aortic narrowing was within 4 mm of the ductus or ligamentum in each: In 41 (65%), it was distal; in 11 (17.5%), it was directly opposite; and in 11 (17.5%), it was proximal to the ductus or ligamentum.

In 52 of 70 serially sectioned coarctations, the luminal diameter was ≤2.0 mm: totally occluded in 4 (6%) (by intimal fibrous tissue); ≤0.5 mm in 22 (31%); 0.6 to 2.0 mm in 26 (37%); 2.1 to 5.0 mm in 14 (20%), and >5.0 mm in 4 (6%).

Of 11 patients in whom it was examined at necropsy or at operation, the aortic valve was bicuspid in 7, tricuspid in 3 (including 1 that was mildly regurgitant and associated with discrete subaortic stenosis) and uni-

**TABLE I Associated Congenital Cardiovascular Anomalies in 84 Patients Aged >1 Year With Juxtaductal Aortic Coarctation**

| Anomaly | Number |
|---|---|
| Aortic valve dysfunction<br>Aortic stenosis (n = 9)<br>Aortic regurgitation (n = 5) | 14 |
| Mitral regurgitation | 6 |
| Patent ductus arteriosus | 5 |
| Ventricular septal defect | 4 |
| Discrete subaortic stenosis | 1 |
| Complete atrioventricular canal | 1 |
| Patent ductus arteriosus + ventricular septal defect | 1 |
| Patent ductus arteriosus + ventricular septal defect + mitral stenosis | 1 |
| Patent ductus arteriosus + scimitar syndrome | 1 |
| Ventricular septal defect + aortic stenosis | 1 |
| Mitral regurgitation + aortic regurgitation + Marfan's syndrome | 1 |
| Total | 36 (43%) |

**TABLE II Symptoms in Aortic Coarctation**

| | Associated Anomalies | |
|---|---|---|
| | Absent (48) (%) | Present (36) (%) |
| Headache | 19 | 17 |
| Epistaxis | 15 | 25 |
| Dizziness | 13 | 17 |
| Fatigue | 23 | 33 |
| Dyspnea | 31 | 61 |
| Chest pain | 21 | 14 |
| Leg discomfort on exertion | 50 | 25 |
| Frequent respiratory infections | 13 | 28 |
| Overt congestive cardiac failure | 0 | 42 |
| Digitalis therapy | 2 | 42 |
| Asymptomatic | 19 | 6 |
| Diagnosis made on routine examination | 65 | 28 |

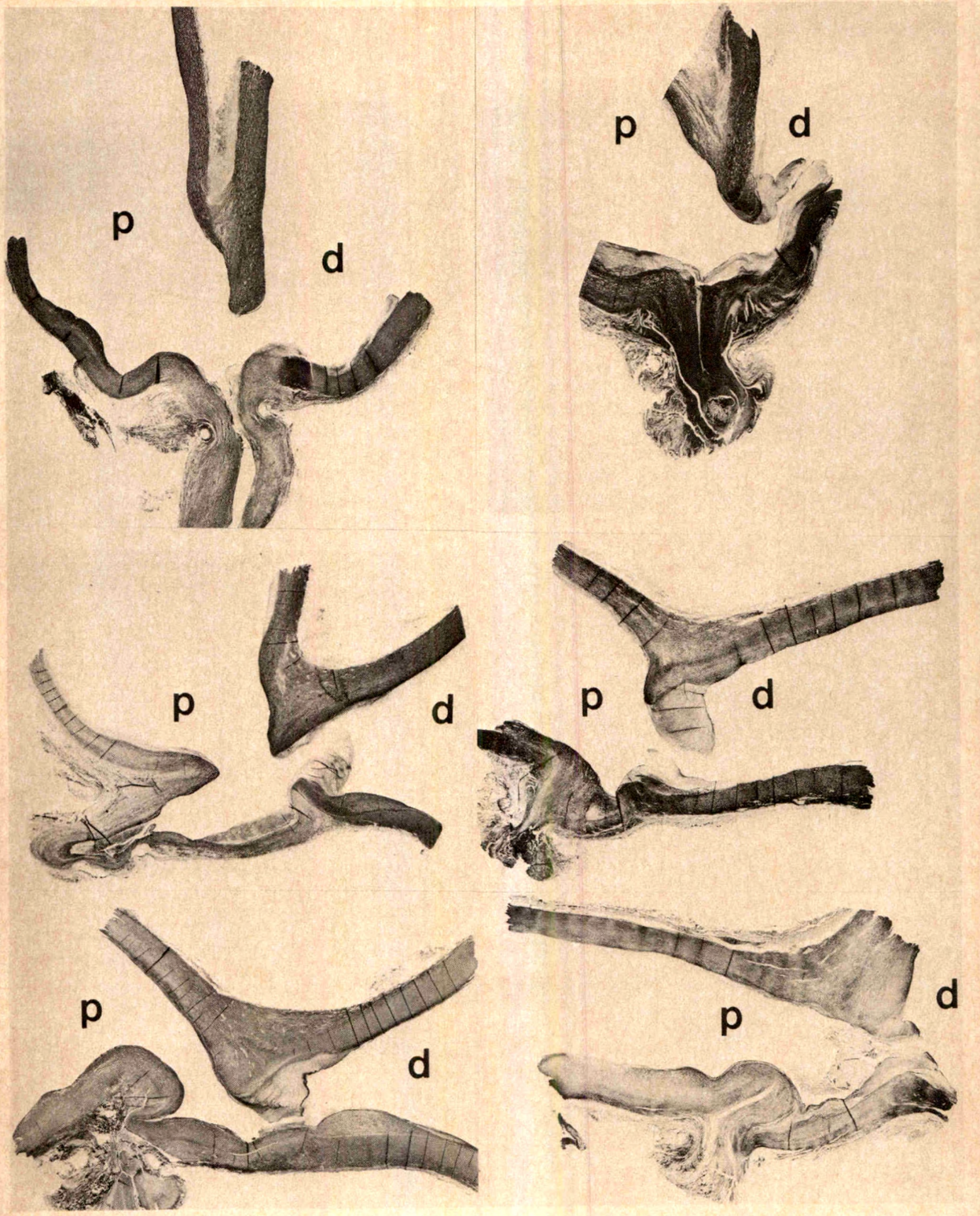



**FIGURE 3.** Histologic sections of 6 aortic coarctations from patients aged 3 to 35 years without associated malformations. Proximal (p) aortic lumen is to the **left;** distal (d) lumen is to the **right;** and the ligamentum arteriosum is **below.** In each specimen, the invaginated media (darkly staining) of the posterior wall of the aorta points toward the ligamentum arteriosum. Thickened intima (lightly staining) just distal to the invaginated V often produces additional aortic obstruction distal to the ligament. The largest luminal diameter (1.1 mm) is in the upper left specimen; the other lumens are narrowed to $\leq$0.5 mm. Each section has been cut longitudinally, stained by the Verhoeff-van Gieson method, and magnified 5 to 6.5 times (reduced 6%).

commissural in 1 (severely stenotic). Of the bicuspid valves, 3 were functionally normal; 2 were calcified and stenotic; 2 were incompetent (1 secondary to active Histoplasma capsulatum endocarditis and the other associated with the Marfan syndrome).

**Preoperative clinical features:** Table II lists the frequencies of various symptoms in the patients with and without associated cardiovascular anomalies. Leg discomfort occurred twice as often in patients without as in those with associated anomalies. More patients in the latter group had mild coarctation, which often was discovered during evaluation for other congenital cardiovascular anomalies. One or more episodes of overt congestive cardiac failure occurred in 15 patients with and in none without associated anomalies. Chest pain was typical of angina pectoris in only 4 patients, but 2 of them had aortic stenosis, and a third had discrete subaortic stenosis. The fourth patient, who had no other congenital anomalies, died from an acute myocardial infarct at age 37 years (1 year after resection of the aortic coarctation), and at necropsy the right coronary artery was completely occluded by atherosclerotic plaque. Three patients with isolated aortic coarctation had syncope, including 1 who had only a single episode during pregnancy. In addition, 1 patient with associated valvular aortic stenosis had syncope, and another had presyncopal episodes with exertion. Although 1 or more symptoms were present in most patients with aortic coarctation, these were seldom limiting when the anomaly was isolated.

*Diagnosis* in 65% of patients with isolated coarctation was made on routine physical examination or chest roentgenography. However, in only 2 of 22 adults did the initial discovery of a murmur or of systemic hypertension lead directly to operative treatment. In 17 other patients, delays of 10 to 33 years occurred between the initial discovery of a murmur or systemic hypertension, or both, and the patient's referral for operation, and in all 17 referral was at least 10 years after operative treatment was available. The remaining 3 adults were first discovered to have aortic coarctation at necropsy, but the diameter at the coarctation was ≥4 mm in each.

All 84 patients had systolic murmurs (Table III) (Fig. 5). Of the 48 with isolated coarctation, the murmur's intensity was grade 1/6 in 5 (10.5%); grade 2/6 or 3/6 in 38 (79%); and grade 4/6 in 5 (10.5%). Systolic murmurs most often were of maximal intensity at the upper left sternal edge and often were easily heard over the entire precordium, neck, and infra- and supraclavicular areas, between the scapulae and over axillary collateral vessels. The murmurs usually began after the first heart sound, were crescendo-decrescendo in character, and at times extended beyond the sound of aortic valve closure,

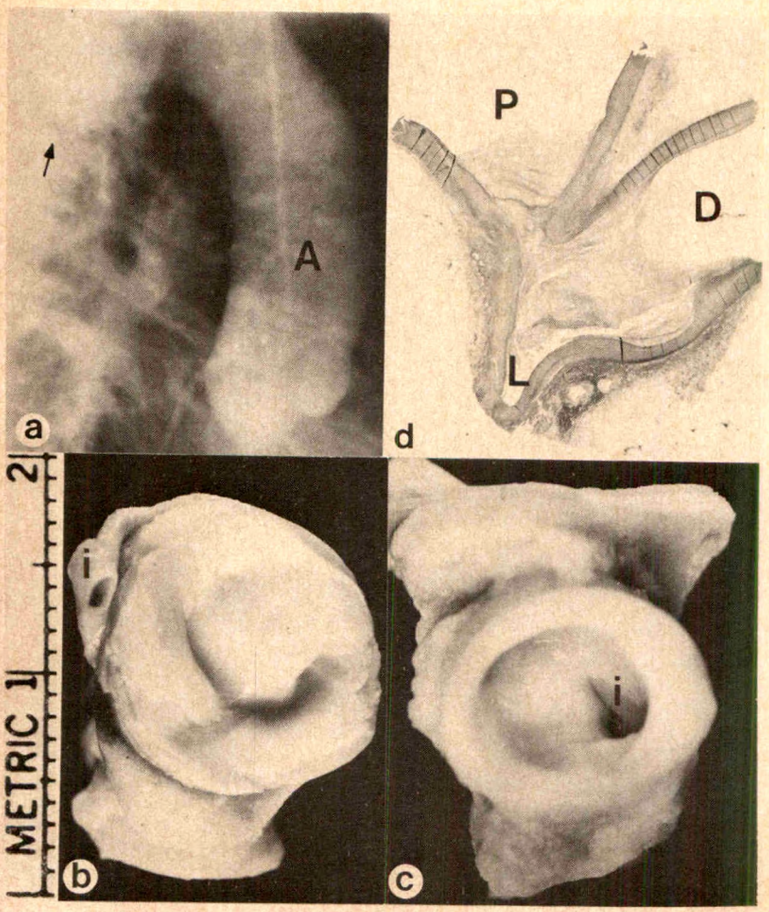



**FIGURE 4.** Coarctation with acquired complete occlusion of the aorta in a 27-year-old man. **a**, lateral film made 2.2 seconds after the injection of contrast material into the ascending aorta (A). No contrast is present beyond the coarctation (**arrow**). **b** and **c**, resected aortic coarctation viewed from its proximal (**b**) and distal (**c**) sides. The aorta is completely occluded. Dilated intercostal arteries (i) can be seen on the adventitial surface of aorta (**b**) and entering the distal aorta (**c**). **d**, longitudinal histologic section (Verhoeff-van Gieson stain; magnification ×6, reduced 25%). The invaginated posterior wall of the darkly stained aortic media narrows the aortic lumen to <1.0 mm. Final closure of the aortic lumen is the result of intimal fibrous tissue. D = distal aorta; L = ligamentum arteriosum; P = proximal aorta.

**TABLE III Physical Findings in Aortic Coarctation**

| | Associated Anomalies | |
|---|---|---|
| | Absent (48) | Present (36) |
| Systolic murmur | 100% | 100% |
| Diastolic or continuous murmur | 27% | 67% |
| Palpable thrill | 21% | 58% |
| Systolic ejection click | 29% | 33% |
| Absent, diminished or delayed femoral pulse | 94% | 86% |
| Palpable collateral pulsations | 35% | 39% |
| Prominent arterial pulses in the neck | 46% | 22% |
| Retinal arterial narrowing | 44% | 18% |
| Systolic blood pressure (mm Hg) | | |
| Range | 110–227 | 108–215 |
| Average | 156 | 145 |
| >140 mm Hg | 69% | 47% |
| Diastolic blood pressure (mm Hg) | | |
| Range | 62–123 | 30–115 |
| Average | 91 | 80 |
| >90 mm Hg | 44% | 25% |
| Height <11th percentile* | 3/20 | 8/16 |
| Weight <11th percentile* | 2/20 | 10/16 |

* Children under 13 years of age.

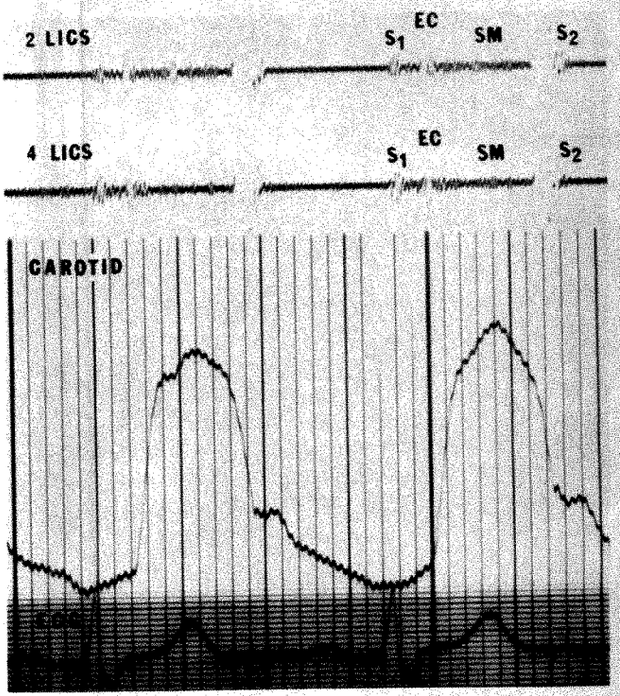



**FIGURE 5.** Phonocardiogram recorded in second (2 LICS) and fourth (4 LICS) left intercostal spaces, carotid pulse tracing, and electrocardiogram (ECG) in a patient with aortic coarctation. An ejection click (EC) follows the first heart sound ($S_1$) and occurs simultaneously with the beginning of the upstroke of the carotid pulse. SM = systolic murmur; $S_2$ = second heart sound.

especially over collateral arteries. Occasionally, apical diastolic rumbles were heard. In the other 36 patients, the associated anomalies modified the auscultatory findings.

Femoral arterial pulsations were absent, diminished or delayed in 76 patients (Fig. 6). In 5 of the 8 patients with normal femoral pulses on clinical examination, the coarctation specimen was serially sectioned: 4 had lumens ≥4 mm in diameter; the lumen in 1 was 0.2 mm in diameter but a large patent ductus inserted distal to the coarctation; and in the other 3 patients, hemodynamic and angiographic studies indicated that the obstruction was mild. Simultaneous arm and leg blood pressures were measured by cuff in 5 of these 8 patients, and in 3 the pressure was slightly lower in the leg. In 6 additional patients, femoral arterial pulsations were full but were decreased or delayed compared with brachial or radial pulsations. Palpable collateral pulsations occurred in over one third of the patients.

Systolic blood pressures in the arm were >140 mm Hg in 33 (69%) of the 48 patients without and in 17 (47%) of the 36 patients with associated anomalies (Table III), and diastolic arm pressures were >90 mm Hg in 21 (44%) of those without and in 9 (25%) of those with associated anomalies. Most patients had pressures that were greater than the pressures in 97.5% of the general population of the same age (Fig. 7). Systolic pressure was above this level in 67 (80%) of the 84 patients with coarctation and in 63 (90%) of the 70 patients undergoing operative repair. In most patients whose systolic pressures were within 2 standard deviations of the mean for the general population, the aortic coarctation was mild. Narrowing and tortuosity of retinal arteries were often seen; retinal hemorrhages, exudates, and papilledema were absent.

*The heights and weights* of the children <13 years of age had a normal distribution, in those with isolated coarctation, but were below the 11th percentile in >50% of those with associated malformations.

*The electrocardiograms* of most patients with isolated coarctation were normal, and those of most patients with associated anomalies were abnormal (Table IV). Increased QRS voltage was the most common ab-

**TABLE IV Electrocardiographic Findings in Aortic Coarctation**

| Associated Anomalies | Cases (n) | QRS Axis | | RVN ± LVH | R $V_5$ or $V_6$ >25 mm | S $V_1$ + R $V_5$ or $V_6$ >40 mm | LVH With Strain | Rhythm or Conduction Disturbance |
|---|---|---|---|---|---|---|---|---|
| | | >110° | < −30° | | | | | |
| 0 | 48 | 0 | 0 | 0 | 5 | 9 | 1 | 1 |
| + | 36 | 2 | 3 | 9 | 15/27* | 16/27* | 5/27* | 12† |

* Excludes the 9 patients with right (RVH) or combined right and left (LVH) ventricular hypertrophy.
† Prolonged (>0.20 second) P-R interval in 7 patients; sinus bradycardia plus atrioventricular dissociation in 1; junctional rhythm in 1; wandering supraventricular pacemaker in 1; and complete right bundle branch block and left anterior hemiblock in 2.

normality in patients with isolated coarctation; the increase was usually slight and no patient with isolated coarctation had R waves ≥30 mm in lead $V_5$ or $V_6$. In contrast, R waves of ≥30 mm occurred in 13 of 27 patients (excluding the 9 with right or combined ventricular hypertrophy) with associated anomalies.

*Chest roentgenography* performed in the 4 standard projections revealed the aortic coarctation in 66% of patients without and in 53% of those with associated anomalies (Table V). It was seen either directly, the so-called figure-of-3 sign, or indirectly by the deformity it produced in the barium-filled esophagus. The frequency of visible rib notching correlated directly with age, and inversely with the diameters of the coarctations measured in the resected specimens. Dilated, tortuous internal mammary arteries were identified in lateral chest roentgenograms in 7 patients. The ascending aorta appeared normal in 51 patients, slightly dilated in 31 patients, and moderately dilated in 2. The intrathoracic portions of the brachiocephalic arteries were normal in 45 patients, slightly dilated in 29 patients, moderately dilated in 9, and markedly dilated in 1 patient, in whom aneurysms of the aortic arch, left subclavian artery, and descending thoracic aorta were present. From the impression it produced on the barium-filled esophagus, the aorta just distal to the coarctation was normal in 34 patients, slightly dilated in 41, moderately dilated in 8 patients, and markedly dilated in 1.

*Increased pulmonary vascular markings* were noted in 9 patients, 8 of whom had left-to-right shunts, and findings of pulmonary venous hypertension were present in 4 patients, each of whom had congenital mitral regurgitation.

*Overall heart size* was normal in 30 (63%) of 48 patients with isolated aortic coarctation and was moderately enlarged in only 1 patient. In contrast, overall heart size was normal in only 2 (6%) of 36 patients with associated anomalies and almost half of the 36 had moderate or marked cardiomegaly. Seven patients (6 with isolated coarctation and 1 with associated con-

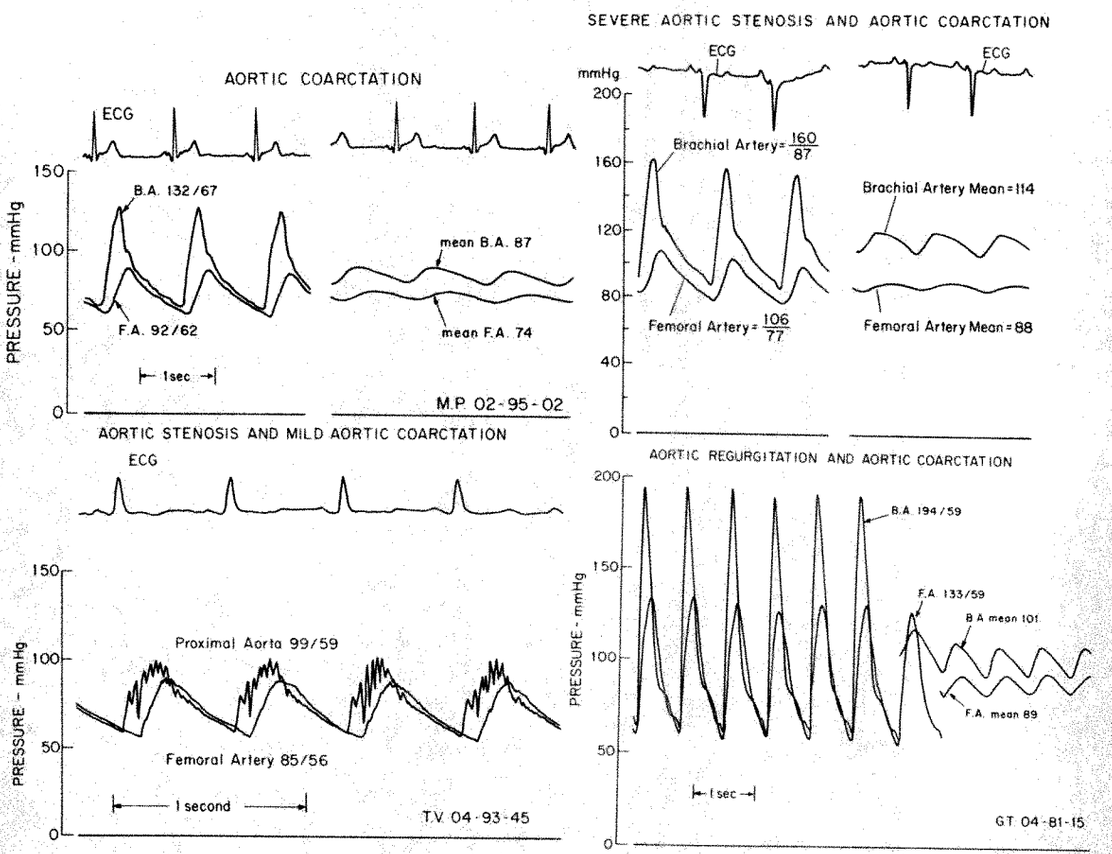



**FIGURE 6.** Pressure tracings above and below aortic coarctation. Electrocardiogram (ECG) and direct brachial arterial (BA) or aortic and femoral arterial (FA) phasic and mean pressure tracings. **Upper left,** in a 32-year-old man with isolated aortic coarctation. The peak FA pulse is 40 mm Hg lower than and occurs 0.09 second later than the peak of the BA pulse. The mean and diastolic pressures differ by only 13 and 5 mm Hg, respectively. **Upper right,** in a 38-year-old man. The peak FA pulse is 54 mm Hg lower than and occurs 0.10 second later than the peak BA pulse. The wide BA pulse pressure and the absence of an anacrotic shoulder do not suggest aortic stenosis, but a 145 mm Hg peak systolic pressure gradient was measured across the aortic valve, which was congenitally bicuspid and heavily calcified. **Lower left,** in a 5-year-old boy with moderately severe aortic valve stenosis and mild aortic coarctation. The small difference between the pulse pressure above and that below the coarctation could not be detected by palpation, but the systolic blood pressure measured by cuff was 8 mm Hg higher in the arm than the leg. **Lower right,** in a 19-year-old man with aortic regurgitation. The FA pulse was brisk and the pulse pressure wide, despite narrowing of the internal diameter of the aorta to <5 mm. Only when compared with the BA pulse is the FA pulse noted to be damped and its peak to occur 0.13 second after the peak of the BA pulse.

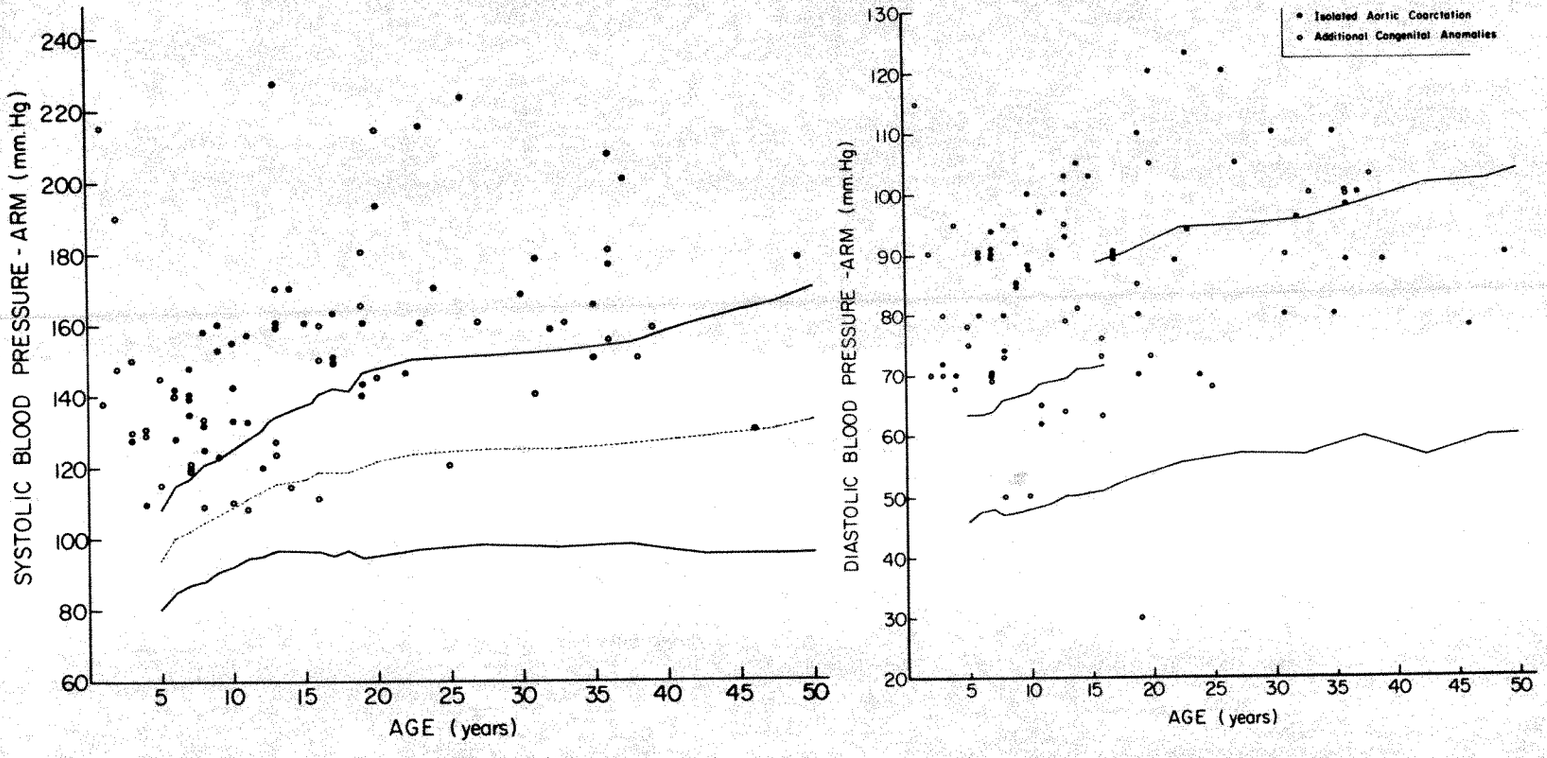



**FIGURE 7.** Systolic and diastolic blood pressures, taken in an arm by cuff, in the 48 patients with isolated aortic coarctation and in the 36 with associated congenital cardiovascular anomalies. The **dotted line (left)** is the mean systolic pressure of the general population. The **solid lines** include the pressures of 95% of the general population. A difference among reference studies[46–48] in technique of recording diastolic pressure accounts for the gap in the **upper line (right)**. Of the 84 patients, 67 (80%), including 63 (90%) of the 70 who subsequently underwent operative repair, had systolic pressures that were greater than the pressures in 97.5% of the general population of comparable age.

**TABLE V Roentgenographic Findings in Aortic Coarctation**

| | Associated Anomalies | |
|---|---|---|
| | Absent (48) | Present (36) |
| Coarctation seen on barium swallow | 66% | 53% |
| Rib notching | 65% | 33% |
| Aortic lumen completely closed | 2/2 | 2/2 |
| Diameter of aortic lumen <0.5 mm | 13/15 | 5/7 |
| Diameter of aortic lumen 0.6 to 2.0 mm | 8/15 | 4/11 |
| Diameter of aortic lumen >2.0 mm | 4/12 | 0/6 |
| Heart size | | |
| Normal | 63% | 6% |
| Slightly enlarged | 35% | 47% |
| Moderately or markedly enlarged | 2% | 47% |

**TABLE VI Hemodynamic Findings in Aortic Coarctation**

| | Associated Anomalies | |
|---|---|---|
| | Absent (12) | Present (23) |
| Gradient Across Coarctation (mm Hg) | | |
| Peak systolic | | |
| Range | 39–100 | 13–90 |
| Average | 55 | 41 |
| Mean | | |
| Range | 13–36 | 5–34 |
| Average | 21 | 16 |
| End-diastolic | | |
| Range | 1–11 | 0–15 |
| Average | 6 | 5 |
| Brachial artery–femoral artery Pulse lag (second) | (9 patients) | (12 patients) |
| Range | 0.09–0.20 | 0.06–0.15 |
| Average | 0.14 | 0.09 |

genital mitral regurgitation) with normal overall heart size had slight enlargement of individual cardiac chambers—the left ventricle in 5 and the left atrium in 2. Thus, 24 of the 84 patients had entirely normal cardiac silhouettes, and 23 of the 24 patients had isolated coarctation.

**Angiographic findings (Fig. 8 to 11):** *Dilatation of the descending aorta immediately distal to the coarctation* was the rule. In 45 patients, poststenotic dilatation was quantified angiographically by determining the ratio of the diameter of the aorta just distal to the coarctation to the diameter of the aorta at the level of the diaphragm: In 2 patients the ratio was 1:1; in 28 patients, 1.0 to 1.5:1; in 14 patients, 1.5 to 1.8:1; and in 1 patient, >1.8:1. Saccular aortic aneurysm distal to the coarctation occurred in 4 patients. Its cause was infective aortitis in 1 patient (Fig. 11). In another the aneurysm developed just distal to a stenotic anastomotic site for coarctation resection 6 years earlier. One patient had multiple saccular aneurysms both proximal and distal to a mild coarctation. In the fourth patient the aneurysm arose just distal to the coarctation. In all patients the aneurysms were resected along with the aortic coarctation. The intercostal arteries frequently were dilated, at times to aneurysmal proportions. In 1 patient the right subclavian artery originated just proximal to the coarctation and reached the right arm by passing behind the esophagus.

*The anatomic relation of the aortic coarctation to the origin of the left subclavian artery* was visualized on angiography in 47 patients: In 15 the coarctation was <1 cm; in 24 patients, 1.0 to 2.9 cm; and in 8 patients, 3.0 to 5.0 cm distal to the caudal margin of the origin of the left subclavian artery. The length of the narrowed aortic segment seen on angiography was <5 mm in 39 patients, 5 mm in 2 patients, and 8 mm in 1.

In 32 patients, both coarctation specimens and aortograms were available for correlative examinations. There was a direct correlation between the internal diameters of the coarctations measured angiographi-

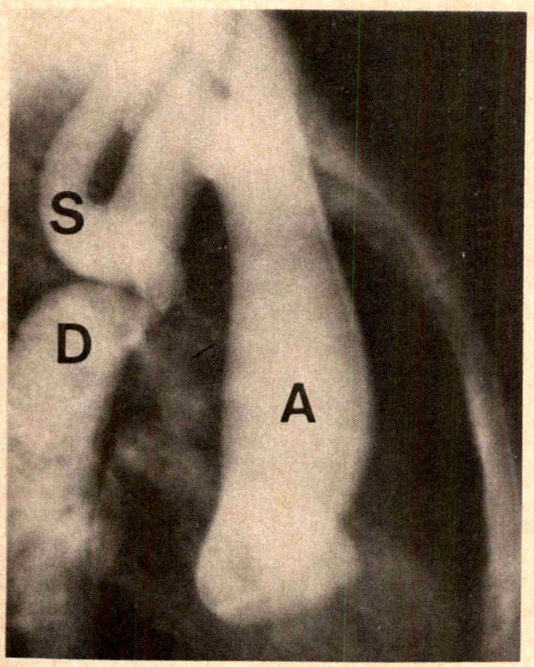



**FIGURE 8.** Lateral aortogram in a 35-year-old woman showing invagination of the posterior wall of aorta just distal to the origin of the left subclavian (S) artery, poststenotic dilation (D) of the descending aorta, and mild dilation of the ascending aorta (A). The patient also had mitral regurgitation.

**TABLE VII Operations for Aortic Coarctation (71 Patients)**

| | |
|---|---|
| Procedure | |
| Resection with direct anastomosis | 61 |
| Resection with graft | 8 |
| Anastomosis left subclavian artery to aorta | 1 |
| Not resected | 1 |
| Complications | |
| Mortality | 3 (4%) |
| Reoperation for bleeding | 6 (8%) |
| Reoperation for coarctation | 2 (3%) |
| Paradoxical hypertension postoperatively | 41 (58%) |
| Recurrent laryngeal nerve palsy | 8 (11%) |

| Systemic Arterial Pressures Postoperatively | | | |
|---|---|---|---|
| | Preoperative | Discharge | Follow-Up |
| Systolic >140 | 47/67 (70%) | 11/67 (16%) | 10/56 (18%) |
| Diastolic >90 | 29/67 (43%) | 7/67 (10%) | 3/56 (5%) |

cally and those measured anatomically, but the diameters measured angiographically (range 0 to 8 mm, average 3.5) tended to be larger than the diameters measured anatomically (range 0 to 4.1 mm, average 1.3). This discrepancy resulted from measuring the angiographic diameters when the aortas were distended by systemic arterial pressure and magnified approximately 25%.

*In 43 patients the magnitude of the collateral arterial circulation* was estimated angiographically: In 5 patients it was normal and in 38 it was increased: 1+ in 10, 2+ in 10, 3+ in 12, and 4+/4+ in 6. The magnitude of the collateral circulation was inversely proportional to the luminal diameters measured in 35 resected coarctations: In 17 patients with 0 to 2+ collateral arteries the average luminal diameter was 2.5 mm, and in 18 patients with 3+ or 4+ collateral arteries the average diameter was 0.7 mm.

**Hemodynamic findings:** *Direct arterial pressure measurements above and below the coarctation*, recorded in 35 patients, showed peak systolic pressure gradients averaging 55 mm Hg in the 12 patients with isolated coarctation and 41 mm Hg in the 23 with associated anomalies (Table VI, Fig. 6). The peak gradient was >60 mm Hg in only 6 (17%) of the 35 patients. The mean gradient averaged 21 mm Hg in the patients without and 16 mm Hg in those with associated anomalies, and was >30 mm Hg in 4 patients. The end-diastolic gradient average 6 mm Hg in patients without and 5 mm Hg in those with associated anomalies; it was >10 mm Hg in 3 patients and was absent in 4 patients.

An inverse correlation was found between the *luminal diameters of the resected aortic coarctations and the preoperative mean gradients* across them. With a luminal diameter of <1.5 mm, however, a progressively smaller lumen was not associated with a higher gradient, suggesting that with this degree of obstruction most of the blood reaches the distal aorta by collaterals vessels. Generally, the gradient across the coarctation and the systemic blood pressure increased with each successive decade through the third. No further increase in the average gradient or blood pressure occurred in patients >30 years of age, but 6 of these 15 patients had mild coarctation with aortic luminal diameters of >4 mm.

Simultaneous brachial and femoral arterial pressures were recorded in 21 patients, and the delay from the peak of the brachial pulse to the peak of the femoral brachial pulse averaged 0.14 second in 9 patients with isolated aortic coarctation and 0.09 second in 12 patients with associated anomalies.

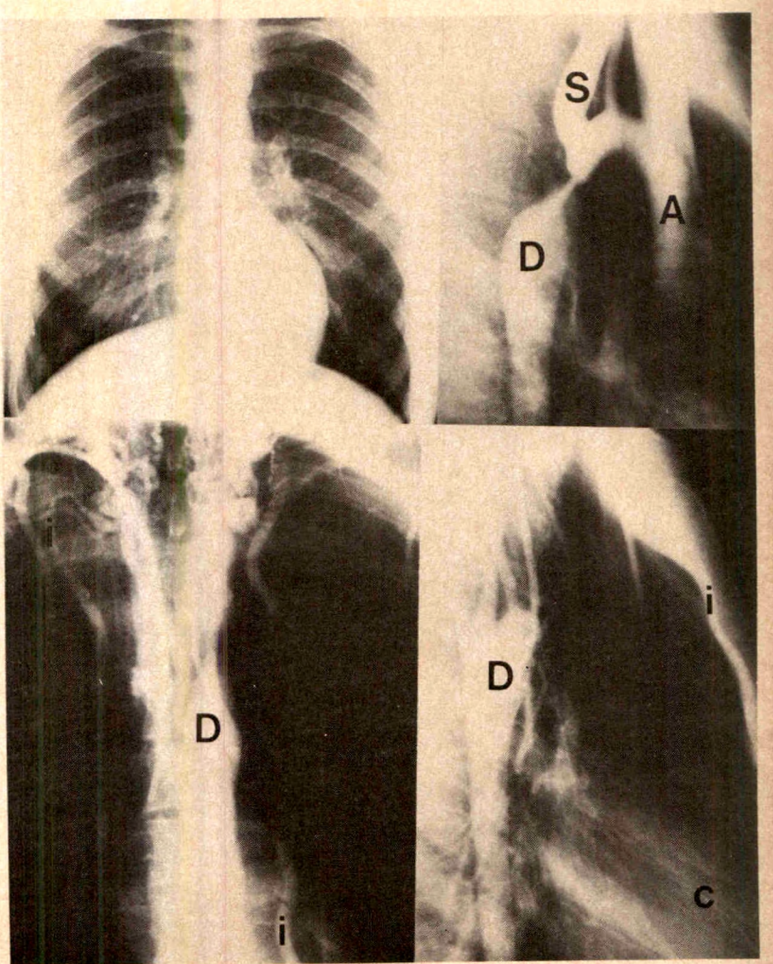



**FIGURE 9.** Posteroanterior chest roentgenogram (**upper left**) and aortograms in a 21-year-old man with aortic coarctation and no other cardiac malformations. The chest roentgenogram shows a figure-of-3 sign, notching of the fifth rib on the right and the fifth and sixth ribs on the left, mild left ventricular enlargement, and no dilatation of ascending aorta. The lateral film (**upper right**), obtained during injection of contrast material into ascending aorta (A), shows a jet of contrast entering the dilated descending aorta (D). The left vertebral artery has a separate origin from the aortic arch just proximal to the origin of the left subclavian artery (S). The anteroposterior (**lower left**) and lateral (**lower right**) films were taken after the ascending aorta had emptied of contrast medium and show the descending aorta (D) being filled by numerous dilated collateral arteries. The markedly dilated superior intercostal arteries enter the descending aorta just below the coarctation. Dilated internal mammary arteries (i) give origin to intercostal arteries (c).

**Operations, complications, and results:** Operation for aortic coarctation was performed in 71 patients (Table VII). In 61, the narrowed segment was resected and the distal aorta anastomosed directly to the proximal aorta, including part of the origin of the left subclavian artery when it arose just proximal to the coarctation. The suture line was always interrupted in 2 or more places. In 8 patients, the coarctation was resected and replaced by a tubular graft (Teflon® in 6 patients, homograft in 2). In 1 patient, the left subclavian artery was anastomosed to the distal aorta. In another patient with severe aortic valvular stenosis and relatively mild aortic coarctation, occlusion of the coarcted segment caused systolic pressure in the arm to increase to 260 mm Hg and the distal aorta to collapse; therefore, the coarctation was not resected.

Of the 70 patients undergoing operative repair of aortic coarctations, 3 (4%) died early after operation and each of them had multiple associated cardiovascular anomalies: A 15-month-old boy with ventricular septal defect, patent ductus arteriosus, preductile aortic coarctation, a large left-to-right shunt, and equal pulmonary and femoral arterial pressures died 4 hours after banding of the pulmonary trunk, ligation of the ductus, and anastomosis of the left subclavian artery to the distal aorta. A 20-year-old man with the Marfan syn-

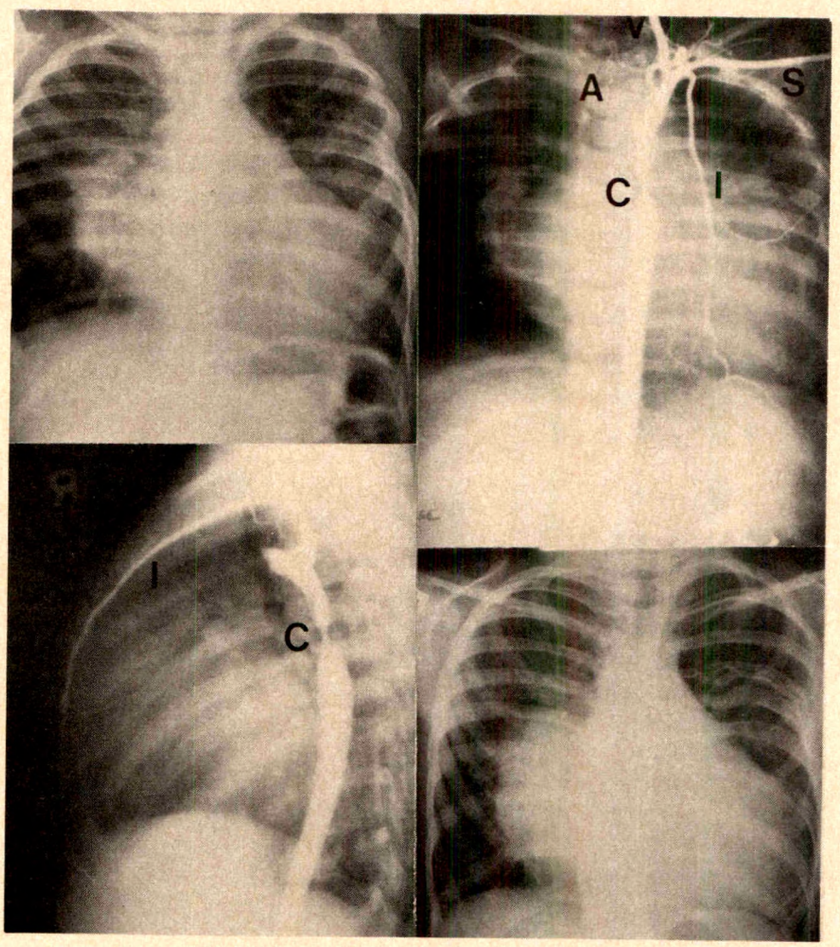



**FIGURE 10.** Chest roentgenograms and arteriograms in a girl with aortic coarctation and mitral regurgitation. Her younger sister died at 4 days of age with aortic coarctation and other congenital cardiovascular malformations. Slow growth, respiratory infections, and a precordial murmur prompted evaluation when she was 17 months of age. The arm blood pressure was 215/115 mm Hg, and she had congestive heart failure. The mitral valve was purely regurgitant and the pulmonary arterial pressure was 105/50 mm Hg. A typical aortic coarctation was resected. Postoperatively, systemic arterial pressure fell to 115/65 mm Hg, but 3 months later signs of infective "endocarditis" developed. While she was being treated for 10 weeks with antibiotic drugs, the femoral pulses gradually disappeared, the blood pressure increased to 205/145 mm Hg, congestive heart failure reappeared, and a chest radiogram (at 24 months) (**upper left**) again disclosed marked generalized cardiomegaly. Films taken in the anteroposterior (**upper right**) and lateral (**lower left**) projections after injection of contrast material into the left subclavian artery (S) showed a large internal mammary artery (I) and a tortuous anterior spinal artery (A) serving as collateral vessels around the aortic recoarctation (C). The vertebral artery (V) was large. The "recoarctation," which showed healing arteritis, was resected and a direct end-to-end anastomosis performed. The arm arterial pressure decreased to 110/80 mm Hg in 36 hours. Signs of mitral regurgitation persisted postoperatively and atrial fibrillation appeared before age 5 years. In addition, the electrocardiogram showed right axis deviation and biventricular hypertrophy. When 7 years old, the patient had striking generalized cardiomegaly with marked left atrial enlargement (**lower right**). She had severe mitral regurgitation and a pulmonary arterial pressure of 35/15 mm Hg, but no pressure gradient between brachial and femoral arteries. Congestive heart failure persisted intermittently, and she died from a respiratory infection at age 16 years.

drome, a severely regurgitant bicuspid aortic valve, mitral regurgitation, and a 1,000 g heart bled from dilated intercostal arteries after replacement of the coarctation with a Teflon graft. A 7-year-old boy with the scimitar syndrome, patent ductus arteriosus, preductile aortic coarctation, a moderate-size left-to-right shunt, and equal pulmonary arterial and descending aortic pressure died from obliterative pulmonary arterial disease and extensive intraalveolar hemorrhage 8 weeks after operation.

*Transient paradoxical postoperative hypertension*, diastolic blood pressure >20 mm Hg higher than the preoperative level, occurred in 41 patients (58%): in 31 (79%) of the 39 patients aged ≤15 years, in 10 (34%) of 29 patients aged >15 years, and in none of 6 patients aged >35 years. In 7 patients the postoperative diastolic blood pressure was >40 mm Hg higher than preoperative pressure. The systolic blood pressure also increased in 40 of the 41 patients. In 29 of the 41 patients, the increase in diastolic pressure exceeded the increase in systolic blood pressure. Seven (all boys ≤15 years of age) of the 41 patients had postoperative abdominal pain (4 patients), vomiting (3 patients), abdominal tenderness (2 patients), occult fecal blood (2 patients), epistaxis (1 patient) and/or subscapular pain (1 patient), when their systemic blood pressures were elevated above preoperative levels (an average of 43 mm Hg systolic and 41 mm Hg diastolic). Two patients also had generalized seizures.

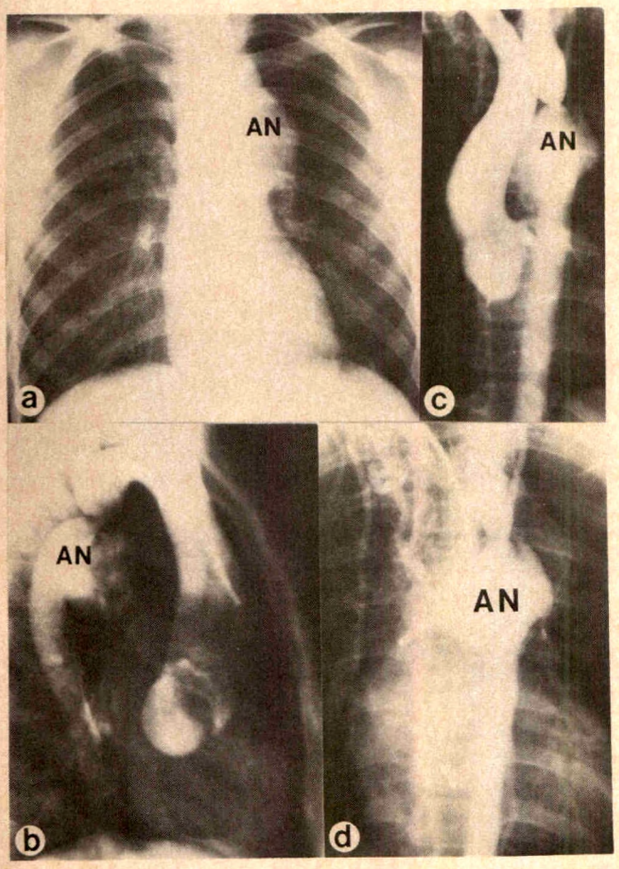



**FIGURE 11.** Posteroanterior chest X-ray (**a**), lateral aortogram (**b**) (taken 3 seconds after injection of contrast material into ascending aorta), and anteroposterior aortograms (**c** and **d**) taken 3 (**c**) and 5.5 (**d**) seconds after injection showing an aortic aneurysm (AN), infected by alpha streptococcus, just distal to a previously unrecognized coarctation in a 12-year-old boy.

Other postoperative complications occurred in 11 (38%) of the 29 patients >15 years of age (including 8 of 13 patients aged >25 years), and in 5 (13%) of 39 aged ≤15 years. The only complication associated with significant permanent sequelae was infective endocarditis in an 8-year-old boy who had septic cerebral emboli and residual hemiparesis and seizures. Thoracotomy was required for control of postoperative bleeding in 6 patients (including 2 of the 4 in whom aortic aneurysms had been resected) and for control of postoperative chylothorax in 1. Eight patients (including 3 requiring postoperative thoracotomy) had recurrent laryngeal nerve damage. In the 6 older patients (aged 19 to 49 years), difficulty with phonation occurred, and in 5 it was transient. One patient, a 49-year-old woman whose aneurysms above and below the coarctation were resected, also had transient left Horner's syndrome and diaphragmatic paralysis. Two patients, aged 8 and 17 years, had dysphagia without dysphonia; in 1 patient the entire left vagus nerve had been knowingly destroyed during removal of a rapidly expanding poststenotic aortic aneurysm infected with alpha streptococcus (Fig. 11). Superficial wound dehiscence, pneumothorax, and atelectasis occurred in 1 patient each.

Two patients required second operations for aortic coarctation. A 20-year-old man who had hypertension and diminished femoral pulses immediately after operation had a 50 mm Hg peak systolic pressure gradient across the proximal anastomosis of the Teflon graft used to replace the coarcted aortic segment, and 3 weeks after the first operation the graft was replaced and the proximal anastomosis made larger. Subsequent blood pressures were normal. An 18-month-old girl became normotensive and had good femoral pulses after resection of an aortic coarctation and end-to-end anastomosis of the aorta, but 2 months later she had infective aortitis accompanied by systemic hypertension (205/145 mm Hg) and gradual disappearance of the femoral pulses (Fig. 10). At age 24 months, the inflammatory narrowing at the site of previous anastomosis was resected, and an end-to-end anastomosis of the aorta was performed. The blood pressure subsequently was normal, and direct pressure measurements 5 years later revealed no gradient across the anastomosis.

By hospital discharge, either systolic or diastolic blood pressure had decreased to below preoperative levels in 58 (87%) of the 67 surviving patients and both pressures had decreased in 42 (63%). Whereas preoperative systolic pressures had been >140 mm Hg in 47 (70%) and diastolic pressures >90 mm Hg in 29 (43%), postoperative pressures were above these levels in only 11 (16%) and 7 (10%) patients, respectively (Table VII).

Of the 67 survivors, 60 have been followed up from 1 month to 15 years after discharge (mean follow-up 4.7 years). Although 53 (88%) of the 60 had preoperative

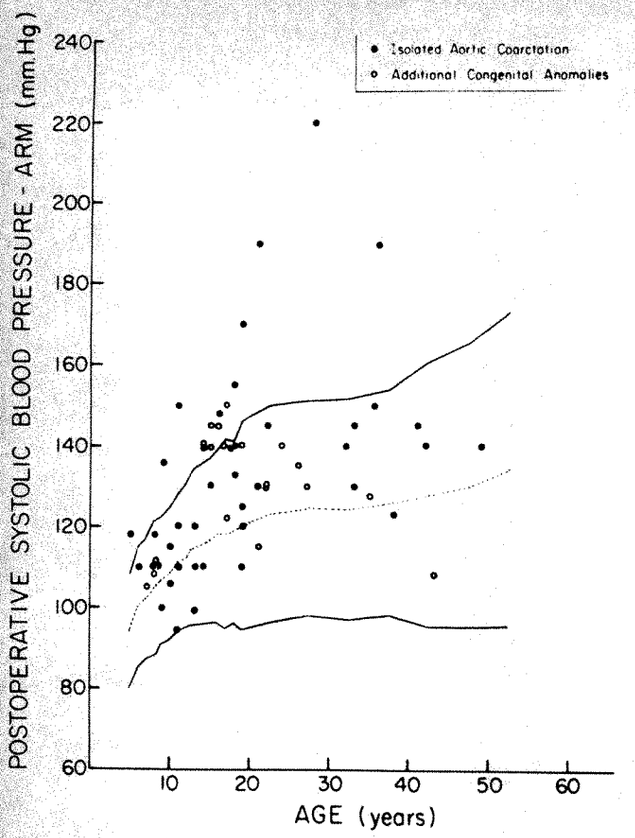



**FIGURE 12.** Systolic blood pressure recorded in the arm by cuff late postoperatively (1 month to 15 years; mean 4.7 years) in 60 patients after resection of aortic coarctation. Mean systolic pressure (±2 standard deviations) for the general population is indicated as in Figure 7.[46-48]

systolic blood pressures >97.5% of the general population, at the most recent postoperative follow-up only 15 (25%) had systolic pressures above these limits (Fig. 12), and in 9 of the 15 the pressure was 10 to 45 mm Hg lower than it was preoperatively. Furthermore, only 3 of the 15 patients have diastolic pressures that are unequivocally increased for their ages. Two of them underwent arterial puncture; the brachial-to-femoral arterial peak systolic gradients were 5 and 15 mm Hg, respectively. The third patient has good leg pulses, whereas none were palpable preoperatively. Despite lowering of blood pressure by operation, the distribution of pressures postoperatively differs from that in the general population (Fig. 12).

Of 11 patients ≥30 years of age with operative correction of aortic coarctation, all had had systolic and 8 had diastolic hypertension preoperatively, but in all 11 patients blood pressure decreased after operation, with the systolic blood pressure at discharge above normal in only 1. Of 9 patients followed up 3 months to 10 years, 1 still had systolic hypertension and 1 had diastolic hypertension.

In 18 patients, 12 of whom were operated on before age 11 years, intraarterial pressures were measured 5 to 15 years (average 11) after operation, which in 17 patients was resection with direct anastomosis. Peak systolic pressure gradients were absent in 8 patients, <10 mm Hg in 5, and 10 to 35 mm Hg in 5. In all patients the mean gradients were <12 mm Hg. In 5 patients pressure gradients were measured directly twice postoperatively (initially 0.3, 11, 12, 12, and 84 months postoperatively; and subsequently 10, 12, 14, 15, and 15 years postoperatively). The values obtained at the 2 studies were virtually identical.

In addition to the 3 patients who died after operation for coarctation, 7 others died later. Three died after operations for associated anomalies, and each of them had mild aortic coarctation: in 1 an earlier attempted resection of the coarctation had been abandoned because the distal aorta collapsed when the coarctated segment was occluded, and in the other 2 aortic coarctation was first discovered at necropsy. Two patients with mild coarctation died from Histoplasma capsulatum aortic valvular endocarditis and carcinoma of the breast. One patient died from coronary arterial occlusion 1 year postoperatively, and 1 patient, who required repeat operation and also had severe congenital mitral regurgitation, died at age 16 years (Fig. 10).

## Discussion

In this study the pathoanatomic features were remarkably uniform. In each patient the coarctation was juxtaductal, and in all but 1 patient the narrowing was discrete and caused by invagination of the media of the posterior aortic wall. Initimal jet lesions frequently caused further narrowing of the aortic lumen and in 4 patients led to complete occlusion.

Gupta and Wiggers[1] and McClenathan et al[2] demonstrated that the cross-sectional area of the aortic isthmus must be reduced 45 to 65% in the dog before any pressure differences are detected above and below the constriction. In contrast, turbulence may be produced by reductions in cross-sectional area as little as 25% and could play a role in the pathogenesis of poststenotic dilatation or even aneurysm formation in patients with mild coarctation. Once the aortic lumen has been narrowed to a critical size, most blood reaches the descending aorta by collateral vessels. The pressure gradient between the ascending and descending aorta then depends primarily on the resistance to flow in these collateral vessels. In the present study, patients whose resected aortic coarctations had luminal diameters ≤1.5 mm usually had rib notching on chest roentgenograms and extensive collateral vessels (seen on angiography), and no correlation existed between luminal diameter and mean gradient across the coarctation. Patients with luminal diameters >2.0 mm usually did not have rib notching or extensive collateral vessels, and the luminal diameter correlated inversely with the mean gradient across the coarctation. The luminal diameter at which collateral flow exceeds flow across the coarctation can be estimated using a modification of the Gorlin formula[3] and, in the intact aorta distended by systemic arterial pressure, is probably 1.5 to 4 mm depending on several factors, including the cardiac output.

*In older children and adults*, the increased pressure work performed by the left ventricle in patients with isolated aortic coarctation is accompanied by left ventricular hypertrophy without dilatation.[4] Ejection

fraction and cardiac output are usually in the high normal range.[4] Left ventricular filling pressures are normal or mildly increased at rest, but may increase to abnormal levels when afterload is markedly increased by exercise.[5] Renal, splanchnic, and leg blood flows are normal at rest,[6,7] but blood flow to the legs may not increase appropriately with exercise. Hemodynamic function may be altered markedly by associated anomalies.

In contrast, in symptomatic newborns with coarctation, left ventricular volume is normal but ejection fraction and systemic cardiac output are markedly reduced, presumably as a result of the sudden imposition of an increase in afterload as the ductus closes and the coarctation becomes obstructive. Left ventricular mass is normal, and a large volume of blood shunts left to right through the foramen ovale. Within weeks to months, the left ventricle hypertrophies and dilates slightly, and the ejection fraction and cardiac output improve.[8]

The high prevalence (43% of total group, 83% of patients 1 to 5 years old) and wide variety of associated congenital cardiovascular anomalies in our patients and in others[9–13] with aortic coarctation are striking. Patent ductus arteriosus, ventricular septal defect, various forms of hypoplastic left heart syndrome, and transposition of the great arteries are commonly associated with coarctation. In our patients, all of whom were >1 year of age, aortic valvular disease was the most common associated anomaly. Of 11 aortic valves examined directly, only 2 were both tricuspid and functioned normally. In patients with coarctation, high prevalence rates of aortic valvular malformations, especially bicuspid valves, are common[14–16], and high prevalence rates of mitral valvular disease have been noted by other investigators[17–20] in patients with coarctation.

One or more episodes of overt cardiac failure occurred in 15 (42%) of our 36 patients with associated anomalies, but in none of the 48 without them. Although described in patients with isolated juxtaductal aortic coarctation,[21,22] congestive heart failure is uncommon, especially after the neonatal period. Similarly, growth retardation, electrocardiographic abnormalities other than borderline voltage criteria for left ventricular hypertrophy, and moderate or marked cardiomegaly on chest roentgenograms are unusual in patients with coarctation alone and should always prompt a search for additional cardiovascular malformations.

Despite the pathognomonic features—arterial hypertension in the arms, delayed and diminished (or absent) femoral arterial pulses, and a systolic ejection murmur heard both between the scapulae and anteriorly—that are present in most patients with aortic coarctation, the diagnosis continues to be missed frequently. The reasons vary. Although it is almost always well above average for the patient's age in significant coarctation, systolic blood pressure may not be >140 or 150 mm Hg, a level considered the upper limit of normal for adults. Thus, that a systolic blood pressure of 125 mm Hg is abnormal for a 6-year-old child may not be appreciated, and further investigation may not be undertaken. Diastolic pressure usually is increased proportionally less than systolic pressure in patients with coarctation. When additional malformations are present, findings related to them may obscure or direct attention away from those resulting from the coarctation. With well-developed collateral vessels and a condition such as aortic regurgitation that causes a large aortic pulse pressure, femoral pulses may feel normal unless carefully compared with arm pulses. Delays in diagnosing coarctation usually result from failure to consider it.

In patients with aortic coarctation, the prognosis depends largely on the presence and type of associated malformations. Those who become symptomatic in the first months of life usually (up to 90% or more) have 1 or more additional malformations. The few patients with isolated coarctation who present with cardiac failure in the first months of life usually respond to digitalis and diuretic drugs and undergo elective operative repair when they are older.[13,22] Infants with associated malformations and cardiac failure rarely respond adequately to medical management, and without operation most die in infancy. Thus, prompt cardiac catheterization and operative correction of the coarctation (with ligation of the ductus and, if a moderate-to-large ventricular septal defect is present, banding of the pulmonary trunk) are mandatory. Despite this aggressive treatment, at least one third fail to survive 2 years.[9,13,23,24]

*When coarctation is first discovered after the patient is 2 years of age*, the prognosis is much less bleak than when symptoms occur in infancy. Nevertheless, life expectancy is considerably lower than that in the general population, even if additional malformations do not exist. Natural history data from before the operative era suggest that of the patients surviving infancy, 26% died by age 20 years, 65% by age 40 years, and 92% by age 60 years.[14,25,26] The mean age at death was 34 years. Congestive heart failure, aortic rupture, infective endocarditis, and intracranial hemorrhage accounted for 76% of deaths. These data come not only from the era before operation but, for the most part, also from the era before antibiotics and effective oral diuretic and antihypertensive agents were available. Prognosis has improved vastly with operative repair, but the life expectancy of patients treated operatively is still far below that of the general population.

There is general agreement that, except for minor narrowings, all juxtaductal aortic coarctations should be repaired operatively. In symptomatic infants with associated anomalies, operation often is lifesaving and should not be delayed. However, in asymptomatic patients, the optimal time for repair is a matter of conjecture. The longer the operation is delayed, the more likely it is that some complication will arise, and in older adults operative mortality and morbidity are increased and long-term results are less than optimal.[27] However, residual or recurrent coarctation with the need for a second operation is more likely to occur in those patients who were operated on in infancy.[13] Age 8 to 12 years has been suggested as the optimal time for elective repair.[28]

*The type of operative repair* is somewhat dependent on the patient's age. Resection with end-to-end anastomosis remains the standard operative technique. The

suture line is usually interrupted in 1 or more places to allow for growth of the aorta and its lumen as the child grows. In infants aortoplasty, usually with the aid of a Dacron® patch or a subclavian flap, may be the preferable procedure.[29-31] The Blalock-Park procedure[32] of transecting the left subclavian artery and anastomosing the proximal end to the distal aorta gives less satisfactory results and is rarely used now. In patients with coexisting tubular hypoplasia of the aorta, in whom the narrowed segment may be quite long, and in some older patients in whom the aorta may be too inelastic for a tension-free anastomosis to be performed, a patch, a flap, or a tubular synthetic graft is used.

Except in infants, patients >40 years of age, and those with associated anomalies, juxtaductal aortic coarctation can be corrected with a risk of death in the early postoperative period of approximately 1%. Because dilated collateral arteries are unavoidably damaged during operation, bleeding remains a significant postoperative problem. Similarly, postoperative difficulty in phonation, usually transient, is common because of the anatomic relation of the recurrent laryngeal nerve to the coarctation and the ligamentum arteriosum. Infective endarteritis (involving the anastomotic site), endocarditis (involving usually the aortic valve), and spinal cord damage[33,34] are less common but more serious complications.

*An increase in blood pressure during the first days after operation to above preoperative levels* is the most common postoperative complication of coarctation resection.[35] In contrast to other complications, which occurred more frequently in our older patients, paradoxical hypertension was seen more frequently in patients <16 years of age. It usually caused no symptoms, but occasionally was accompanied by abdominal pain, distention, nausea, and vomiting requiring nasogastric suction. Rarely, intestinal infarction may occur. These problems can be prevented by keeping postoperative blood pressure in the normal or near-normal range. The pathogenesis of paradoxical hypertension remains incompletely understood.

*Blood pressures in the arms are below preoperative levels in most patients by the time of discharge from the hospital.*[36-38] Furthermore, blood pressure continues to decrease subsequently. Nevertheless, as a group, these patients remain mildly hypertensive compared with the general population.[5,12,27,36-40] With exercise, striking elevations in systolic pressure may occur.[5,40]

*The cause of residual hypertension after coarctation repair* has been the subject of much speculation.[39-41] In a few patients, residual coarctation of significant degree is the cause, and this is most likely to occur when operation is performed during infancy.[41] In addition, mild degrees of residual coarctation are common. Karnell[39] performed postoperative aortography in 81 patients, and in each the diameter of the aortic isthmus, corrected for body surface area, was less than the mean of the diameters in control subjects.

Sehested et al[42] found the precoarctational aortic wall more rigid than the postcoarctational wall and postulated that this influences baroreceptors to tolerate a higher-than-normal pressure. They further postulated that this resetting of the baroreceptors might account not only for paradoxical hypertension in the early postoperative period, but also for sustained mild hypertension late postoperatively. Evidence of increased sympathetic activity many months postoperatively supports this hypothesis.[42,43] In addition, Samanek et al[44] studied patients an average of 11.5 years after coarctation resection and found resting and maximal blood flow reduced and vascular resistance increased in the arm muscles, whereas these were normal in the leg muscles. These findings imply permanent changes in the arteries and/or arterioles subjected to elevated pressure many years earlier, and such changes may contribute to persistent hypertension postoperatively.

Although the prognosis in patients with aortic coarctation is vastly improved by operative correction, these patients as a group do not have a normal life expectancy even when the coarctation is isolated.[15,16,27,39,45] The reasons for this are abundant. Residual hypertension is one. A second is that about 75% of patients have a biscuspid or other malformed aortic valve that predisposes to the development of aortic stenosis, regurgitation, or infective endocarditis, alone or in combination. Third, patients with aortic coarctation are subject to vascular accidents involving the central nervous system (subarachnoid hemorrhage from rupture of a Berry aneurysm, intracerebral hemorrhage, thromboembolic strokes, and paraplegia from spinal cord damage) and to dissecting and saccular aneurysms of the aorta and intercostal arteries. Although resection of the coarctation and its attendant lowering of blood pressure would be expected to, and probably does, decrease the frequency of these complications, it does not eliminate them.[27] Finally, because of long-standing hypertension, coronary atherosclerosis is probably more prevalent in these patients than in the general population. The data of Maron et al[27] suggest that the prognosis after operation for "uncomplicated" coarctation is better in those operated on before 25 years of age. Thus, early diagnosis is essential. Continued careful follow-up of all patients after operative repair is also mandatory, because most have further cardiovascular problems.

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## References

1. **Gupta TC, Wiggers CJ.** Basic hemodynamic changes produced by aortic coarctation of different degrees. Circulation 1951;3:17–31.
2. **Edmunds LH Jr, McClenathan JE, Hufnagel CA.** Subclinical coarctation of the aorta. Ann Surg 1962;156:180–189.
3. **Gorlin R, Gorlin SG.** Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. Am Heart J 1951;41:1–29.
4. **Graham TP Jr, Lewis BW, Jarmakani MM, Canent RV Jr, Capp MP.** Left heart volume and mass quantification in children with left ventricular pressure overload. Circulation 1970;41:203–212.
5. **Taylor SH, Donald KW.** Circulatory studies at rest and during exercise in coarctation of the aorta before and after operation. Br Heart J 1960;22:117–139.
6. **Wakim KG, Slaughter O, Clagett OT.** Studies on the blood flow in the extremities in cases of coarctation of the aorta: determinations before and after excision of the coarctate region. Proc Staff Meet Mayo Clinic 1948;23:347–351.

7. **Werkö L, Ek J, Bucht H, Karnell J.** Cardiac output, blood pressures and renal dynamics in coarctation of the aorta. Scand J Clin Lab Invest 1956; 8:193–200.
8. **Graham TP Jr, Atwood GF, Boerth RC, Boucek RJ Jr, Smith CW.** Right and left heart size and function in infants with symptomatic coarctation. Circulation 1977;56:641–647.
9. **Glass IH, Mustard WT, Keith JD.** Coarctation of the aorta in infants. A review of twelve years' experience. Pediatrics 1960;26:109–121.
10. **Tawes RL Jr, Aberdeen E, Waterston DJ, Bonham Carter RE.** Coarctation of the aorta in infants and children. A review of 333 operative cases, including 179 infants. Circulation 1969;39,40 Suppl I:I-173–I-184.
11. **Becker AE, Becker MJ, Edwards JE.** Anomalies associated with coarctation of aorta. Particular reference to infancy. Circulation 1970;41:1067–1075.
12. **Chiariello L, Agosti J, Subramanian S.** Coarctation of the aorta in children and adolescents: surgical treatment and review of 120 patients. Chest 1976;70:621–626.
13. **Hesslein PS, Gutgesell HP, McNamara DG.** Prognosis of symptomatic coarctation of the aorta in infancy. Am J Cardiol 1983;51:299–303.
14. **Abbott ME.** Coarctation of the aorta of the adult type. II. A statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of the descending arch in subjects above the age of two years. Am Heart J 1928;3:392–421,574–618.
15. **Smith DE, Matthews MB.** Aortic valvular stenosis with coarctation of the aorta with special reference to the development of aortic stenosis upon congenital biscuspid valves. Br Heart J 1955;17:198–206.
16. **Edwards JE.** The congenital bicuspid aortic valve. Circulation 1961;23: 485–488.
17. **Shone JD, Sellers RD, Anderson RC, Adams P Jr, Lillehei CW, Edwards JE.** The developmental complex of "parachute mitral valve," supravalvular ring of left atrium, subaortic stenosis, and coarctation of aorta. Am J Cardiol 1963;11:714–725.
18. **Auger P, Wigle ED.** Coarctation of the aorta associated with severe mitral insufficiency. Am J Cardiol 1968;21:190–195.
19. **Easthope RN, Tawes RL Jr, Bonham-Carter RE, Aberdeen E, Waterston DJ.** Congenital mitral valve disease associated with coarctation of the aorta. Am Heart J 1969;77:743–754.
20. **Glancy DL, Roberts WC.** Congenital obstructive lesions involving the major pulmonary veins, left atrium, or mitral valve: a clinical, laboratory, and morphologic survey. Cathet Cardiovasc Diagn 1976;2:215–252.
21. **Bahn RC, Edwards JE, DuShane JW.** Coarctation of the aorta as a cause of death in early infancy. Pediatrics 1951;8:192–203.
22. **Lang HT Jr, Nadas AS.** Coarctation of the aorta with congestive heart failure in infancy-medical treatment. Pediatrics 1956;17:45–57.
23. **Pelletier C, Davignon A, Ethier MF, Stanley P.** Coarctation of the aorta of the aorta in infancy. Postoperative follow-up. J Thorac Cardiovasc Surg 1969;57:171–179.
24. **Sinha SN, Kardatzke ML, Cole RB, Muster AJ, Wessel HU, Paul MH.** Coarctation of the aorta in infancy. Circulation 1969;40:385–398.
25. **Reifenstein GH, Levine SA, Gross RE.** Coarctation of the aorta: a review of 104 autopsied cases of the "adult type," 2 years of age or older. Am Heart J 1947;33:146–168.
26. **Campbell M.** Natural history of coarctation of the aorta. Br Heart J 1970; 32:633–640.
27. **Maron BJ, Humphries JO, Rowe RD, Mellits ED.** Prognosis of surgically corrected coarctation of the aorta. A 20-year postoperative appraisal. Circulation 1973;47:119–126.
28. **Gross RE.** Surgery for coarctation of the aorta in infants. Am J Cardiol 1970;25:507–508.
29. **King H, Waldhausen JA.** Angioplasty in infants with coarctation. Circulation 1963;27:890–894.
30. **Waldhausen JA, Nahrwold DL.** Repair of coarctation of the aorta with a subclavian flap. J Thorac Cardiovasc Surg 1966;51:532–533.
31. **Reul GJ Jr, Kabbani SS, Sandiford FM, Wukasch DC, Cooley DA.** Repair of coarctation of the thoracic aorta by patch graft aortoplasty. J Thorac Cardiovasc Surg 1974;68:696–704.
32. **Blalock A, Park EA.** The surgical treatment of experimental coarctation (atresia) of the aorta. Ann Surg 1944;119:445–456.
33. **Doppman JL, DiChiro G, Glancy DL.** Collateral circulation through dilated spinal cord arteries in aortic coarctation and extraspinal arteriovenous shunts. An arteriographic study. Clin Radiol 1969;20:192–197.
34. **Berendes JN, Bredee JJ, Schipperheyn JJ, Mashhour YAS.** Mechanisms of spinal cord injury after cross-clamping of the descending thoracic aorta. Circulation 1982;66:Suppl I:I-112–I-116.
35. **Sealy WC.** Indications for surgical treatment of coarctation of the aorta. Surg Gynecol Obstet 1953;97:301–306.
36. **Wright JL, Burchell HB, Wood EH, Hines EA Jr, Clagett OT.** Hemodynamic and clinical appraisal of coarctation four to seven years after resection and end-to-end anastomosis of the aorta. Circulation 1956;14:806–814.
37. **March HW, Hultgren HN, Gerbode F.** Immediate and remote effects of resection on the hypertension in coarctation of the aorta. Br Heart J 1960;22:361–373.
38. **Schuster SR, Gross RE.** Surgery for coarctation of the aorta: a review of 500 cases. J Thorac Cardiovasc Surg 1962;43:54–70.
39. **Karnell J.** Coarctation of the aorta. Circulation 1968;38:Suppl V:V-35–V-44.
40. **James FW, Kaplan S.** Systolic hypertension during submaximal exercise after correction of coarctation of aorta (abstr). Circulation 1974;50:Suppl II:II-27.
41. **Hartmann AF Jr, Goldring D, Hernandez A, Behrer MR, Schad N, Ferguson T, Burford T.** Recurrent coarctation of the aorta after successful repair in infancy. Am J Cardiol 1970;25:405–410.
42. **Sehested J, Baandrup U, Mikkelsen E.** Different reactivity and structure of the prestenotic and post-stenotic aorta in human coarctation: implications for baroreceptor function. Circulation 1982;65:1060–1065.
43. **Benedict CR, Grahame-Smith DG, Fisher A.** Changes in plasma catecholamine and dopamine beta-hydroxylase after corrective surgery for coarctation of the aorta. Circulation 1978;57:598–602.
44. **Samanek M, Goetzova J, Fiserova J, Skovranek J.** Differences in muscle blood flow in upper and lower extremities of patients after correction of coarctation of the aorta. Circulation 1976;54:377–381.
45. **Simon AB, Zioto AE.** Coarctation of the aorta. Longitudinal assessment of operated patients. Circulation 1974;50:456–464.
46. **Graham AW, Hines EA Jr, Gage RP.** Blood pressures in children between the ages of five and sixteen years. Am J Dis Child 1945;69:203.
47. **Master AM, Dublin LI, Marks HH.** The normal blood pressure range and its clinical implications. JAMA 1950;143:1464–1470.
48. **Hamilton M, Pickering GW, Roberts JAF, Sowry GSC.** The etiology of essential hypertension. 1. The arterial pressure in the general population. Clin Sci 1954;13:11.

# Hemodynamics and Intracardiac Conduction After Operative Repair of Tetralogy of Fallot

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**Electrophysiologic studies were performed in 47 children aged 3 to 18 years, 15 of whom had cardiac arrhythmias 1 to 15 years after repair of tetralogy of Fallot. Six exhibited sinus or atrioventricular nodal dysfunction, 8 had ventricular extrasystoles, and 1 had supraventricular tachycardia. Hemodynamic and electrophysiologic data were obtained at postoperative catheterization. Although electrophysiologic responses were abnormal in a proportion of both the children with and those without arrhythmia, hemodynamic values were similar. Three of 6 children with impaired sinus impulse generation or atrioventricular nodal conduction had a prolonged A-H interval, and in 3 Wenckebach heart block developed at low pacing rates. Ventricular ectopic rhythm was not associated with any particular abnormality of basic intracardiac conduction intervals. Thus, arrhythmias and conduction abnormalities are not consistently related to residual right ventricular hypertension. Abnormalities in electrophysiologic function are common after repair of tetralogy of Fallot in patients with sinus rhythm and may have prognostic implications for these patients.**

Tetralogy of Fallot is a common congenital heart defect for which reparative open heart surgery has been performed in thousands of patients over the past 2 decades. The immediate risk of the surgery has steadily declined; however, a small but alarming incidence of late sudden unexpected deaths represents a continuing source of concern. Bifascicular block,[1–4] transient complete heart block,[4,5] ventricular ectopic rhythm,[6] especially with right ventricular hypertension,[7–9] and late development of left axis deviation[10] have been associated with sudden unexpected death.

This investigation attempts to determine whether intracardiac hemodynamics relate to the intracardiac conduction properties in children after repair of tetralogy of Fallot. Also, because arrhythmias have been implicated in late mortality, it was hoped to determine whether those children with arrhythmias have specific conduction abnormalities that may serve to identify those requiring increased surveillance. The study was begun in 1975 to collect electrocardiographic information and to correlate this with postoperative hemodynamics and electrophysiologic functions at cardiac catheterization.

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## Methods

Forty-seven children were studied after operative repair of tetralogy of Fallot. None had arrhythmia preoperatively on standard electrocardiography. In 13 children the indications for admission included findings of residual heart disease or electrocardiographic abnormality; the remaining 34 were admitted electively. There were 24 male and 22 female patients, aged 3 to 18 years. Surgery had been performed 1 to 15 years previously (average 4.3). All children had a routine 12-lead electrocardiogram.

After informed consent had been obtained, cardiac catheterization was performed and included hemodynamics, cineangiography, and determination of basic intracardiac conduction intervals, right ventricular activation time, and sinus node recovery time to rapid atrial pacing. Thirty-one patients had programmed atrial extrastimulation studies, and 21 had programmed ventricular stimulation. Thirty patients also had

**TABLE I Arrhythmias in 15 Patients After Operative Repair of Tetralogy of Fallot (Group A)**

| Case | Age (yr) at Op | Age (yr) at Study | ECG Axis | Rhythm | RV Pressure (mm Hg) |
|---|---|---|---|---|---|
| 1 | 5 | 10 | 0° RBBB | Sinus arrest, Mobitz II | 44/4 |
| 2 | 3 | 7 | +120°RBBB | Sinus arrest, junctional bradycardia | 32/6 |
| 3 | 3 | 6 | −20° RBBB | Spontaneous Wenckebach | 102/7 |
| 4 | 4 | 6 | −30° RBBB | Spontaneous Wenckebach | 56/8 |
| 5 | 3 | 4 | +120° RBBB | Junctional bradycardia, P-R = 0.22 s, PVC | 90/8 |
| 6 | 2 | 4 | Indet RBBB | Sinus and junctional bradycardia | 24/6 |
| 7 | 4 | 5 | +160° RBBB | PVC, bigeminy | 66/3 |
| 8 | 7 | 18 | −30° RBBB | PVC, bigeminy | 40/6 |
| 9 | 6 | 12 | 0° RBBB | PVC, bigeminy | 20/4 |
| 10 | 7 | 17 | −30° RBBB | PVC | 44/10 |
| 11 | 5 | 7 | +140° RBBB | PVC, PAC | 80/10 |
| 12 | 6 | 11 | Indet RBBB | PVC, PAC | 36/12 |
| 13 | 5 | 12 | +75° RBBB | PVC, PAC | 46/4 |
| 14 | 4 | 8 | +90° RBBB | PVC, PAC | 28/4 |
| 15 | 3 | 7 | +110° RBBB | SVT | 34/6 |

* PVC = ventricular extrasystoles; RBBB = right bundle branch block; RV = right ventricular; SVT = supraventricular tachycardia.

ambulatory electrocardiographic monitoring and 29 had exercise stress testing using the modified Bruce protocol.

The materials and methods used for catheterization and electrode placement have previously been described.[11] Agents used for sedation included Demerol®, Phenergan®, Thorazine®, and pentobarbital sodium. Basic intervals and apical activation were compared with those of age-matched preoperative children studied in this laboratory.[12] Sinus node recovery time was measured from the last paced atrial deflection to the first spontaneous atrial beat and then divided by the resting sinus cycle length and expressed as a percentage. The majority of preoperative children have values for this percentage <160% in our laboratory.[12] The response to rapid atrial pacing was monitored for development of Wenckebach heart block. The cycle length at which Wenckebach periodicity occurred was compared with the reference distribution for our laboratory.[12] Values for Wenckebach periodicity were considered abnormal if they fell outside this reference. Definitions of basic intervals, right atrial effective refractory period, atrioventricular nodal effective refractory period, right ventricular effective refractory period, and right ventricular apical activation time have been cited[13] previously.

## Results

**Electrocardiographic findings:** Various arrhythmias were discovered by scalar electrocardiography (11 cases), ambulatory monitoring (3 cases), or exercise stress testing (1 case), The arrhythmias are listed in Table I and characterize Group A. Six children had various manifestations of sinus or atrioventricular nodal dysfunction, including sinus arrest, spontaneous Mobitz type I or II atrioventricular block, and junctional bradycardia (Table I). One child had supraventricular tachycardia and 8 had ventricular ectopic rhythm, which consisted of uniform single ectopic beats or bigeminy that were suppressed or unaffected by exercise. There were 32 children without arrhythmia and these comprise Group B (Table III). The average age of children in Group A was 8.9 years, of Group B 7.7 years, and of the study group as a whole 8.1 years. Twelve-lead scalar electrocardiograms revealed right bundle branch block in 96% of all cases and in all 15 cases in Group A.

**TABLE II Electrophysiologic Data: Group A**

| Case | SCL | A-H (ms) | H-V (ms) | RAERP (ms) | AVN ERP | RV ERP | SNRT (%) | $S_1S_1$ at Wenckebach | PRBBB |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 818 | 126* | 50 | 165 | 410* | 245 | 118% | None | + |
| 2 | 500 | 66 | 57*(54) | 220 | AL | ND | 170%* | 300 | − |
| 3 | 600 | 88 | 26 | 215 | F = 570 S = 450 | 270 | 105% | 470* | + |
| 4 | 680 | 230* | 41 | ND | ND | ND | 140% | 500* | + |
| 5 | 625 | 151* | 39 | 160 | AL | 160 | 208*% | 330 | − |
| 6 | 645 | 102 | 35 | 210 | 400 | ND | 138% | 500* | − |
| 7 | 590 | 80 | 42 | 220 | 275 | ND | 120% | 310 | + |
| 8 | 740 | 65 | 48 | ND | ND | ND | 148% | 0 | − |
| 9 | 816 | 70 | 35 | 230 | 390 | ND | 166*% | 410* | − |
| 10 | 850 | 76 | 65*(55) | ND | ND | ND | 135% | 0 | − |
| 11 | 610 | 80 | 58*(54) | ND | ND | ND | 108% | 350 | − |
| 12 | 748 | 90 | 49 | 280* | AL | 240 | 150% | 350 | + |
| 13 | 770 | 105 | 44 | 190 | 350 | ND | 157% | 350 | − |
| 14 | 522 | 69 | 44 | 220 | F = 295 S = AL | 220 | 153% | 0 | − |
| 15 | 706 | 85 | 30 | 240* | 300 | 220 | 129% | 350 | + |

* Abnormal valve; parentheses indicate mean value + 2 standard deviations.
AL = atrial limited; apex = RV apex pacing; AVN = atrioventricular nodal; DAVN = dual atrioventricular nodal pathways; ERP = effective refractory period; F = fast atrioventricular nodal pathway; LAD = left axis deviation; ND = not done; Op = operation; out = RV outflow pacing; P = paced; PAC = atrial extrasystoles; PRBBB = proximal right bundle branch block; preop = preoperative; RA = right atrial; S = slow atrioventricular nodal pathway; SCL = sinus cycle length; SNRT = sinus node recovery time; $S_1S_1$ = interstimulus interval; other abbreviations as in Table I.

**TABLE III Hemodynamic and Electrophysiologic Data in Arrhythmia-Free Patients (Group B)**

| Case | Age (yr) at Op | Age (yr) at Study | RVP (mm Hg) | SCL (ms) | Intervals (ms) | | | ERP (ms) | | | SNRT as % SCL | $S_1S_1$ at Wencke-bach (ms) | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | P-A | A-H | H-V | RA | AVN | RV | | | |
| 16 | 5 | 13 | 48/8 | 880 | 30 | 60 | 30 | 260* | AL | 260 | 118 | 320 | ... |
| 17 | 3 | 4 | 30/8 | 500P | | | | 180 | AL | | | | LAD, PRBBB, |
| | | | | 615 | 16 | 63 | 41 | 160 | 290 | 290* | 117 | None | split His |
| 18 | 3 | 7 | 26/7 | 900 | 15 | 102 | 50*(45) | 290* | AL | ND | 150 | 350 | PRBBB, split His |
| 19 | 3 | 18 | 27/6 | 608 | 16 | 72 | 42 | 250* | 205 | 260 | 128 | None | |
| 20 | 5 | 10 | 44/14 | 750 | 20 | 60 | 40 | 190 | 305 | ND | 139 | 345 | PRBBB |
| 21 | 1 | 5 | 58/2 | 720 | 19 | 40 | 47 | 230 | AL | 410* | 160* | 365* | PRBBB |
| 22 | 5 | 9 | 20/6 | 814 | 29 | 89 | 39 | 270 | AL | 370* | 150 | 480* | ... |
| | | | | 600P | | | | 250* | 320 | 290 | | | |
| 23 | 2 | 3 | 48/6 | 610 | 22 | 45 | 35 | 260* | 300 | ND | 160* | None | LAD preop, PRBBB |
| 24 | 6 | 17 | 42/8 | 500P | | | | 260* | AL | 220 | | | AVN, |
| | | | | 810 | 25 | 83 | 50 | 175 | AL | 290 | 135 | 300 | reentry |
| 25 | 2 | 7 | 34/6 | 540 | 18 | 93 | 40 | 220 | AL | 270 out | 171* | None | Split His |
| | | | | | | | | | | 230 apex | | | |
| 26 | 5 | 11 | 24/7 | 720 | 30 | 62 | 35 | 200 | AL | 250 | 138 | 200 | PRBBB, split His |
| 27 | 3 | 4 | 17/5 | 390P | | | | 145 | 260 = F | 220 | | | |
| | | | | 478 | 25 | 65 | 40 | 140 | 240 = S | 260 | 104 | None | DAVN |
| 28 | 2 | 4 | 39/4 | 450P | | | | 250 | 300 | 230 out | 113 | | |
| | | | | 557 | 39 | 60 | 44 | 165 | 300 | 190 apex | | 480* | |
| 29 | 3 | 5 | 33/8 | 580 | 25 | 80 | 30 | 220 | AL | 320* | 139 | None | ... |
| | | | | 480P | | | | 190 | AL | ... | | | PRBBB, LAD |
| | | | | | | | | | F = 430 | | | | Multiple |
| 30 | 4 | 6 | 40/8 | 680 | 29 | 70 | 50*(45) | 180 | S = 335 | 250 | 121 | 400* | AVN |
| | | | | | | | | | S = 315 | | | | pathways |
| | | | | | | | | | S = 300 | | | | |
| 31 | 3 | 4 | 32/6 | 693 | 21 | 69 | 45 | 200 | F = 310 | 310 | 136 | 290 | DAVN, |
| | | | | | | | | | S = AL | | | | AVN |
| | | | | 490P | | | | 200 | F = 290 | 225 | | | reentry |
| | | | | | | | | | S = AL | | | | |
| 32 | 1 | 4 | 20/4 | 541 | 0 | 78 | 36 | 190 | AL | 300 out | 156 | 330 | |
| | | | | | | | | | | 280 apex | | | |
| | | | | 400P | | | | 240 | AL | | | | Ventricular reentry |
| 33 | 4 | 8 | 38/8 | 620 | 23 | 70 | 40 | ... | ... | ... | 150 | 375* | PRBBB |
| 34 | 3 | 5 | 84/12 | 680 | 20 | 90 | 45 | ... | ... | ... | 100 | None | ... |
| 35 | 1 | 4 | 68/16 | 560 | 18 | 50 | 40 | ... | ... | ... | 110 | None | LAD, PRBBB |
| 36 | 3 | 7 | 42/5 | 800 | 21 | 77 | 45 | ... | ... | ... | 138 | 375* | ... |
| 37 | 3 | 5 | 40/8 | 490 | 20 | 60 | 64*(49) | ... | ... | ... | 156 | 300 | ... |
| 38 | 2 | 4 | 56/12 | 620 | 25 | 84 | 55*(49) | ... | ... | ... | 120 | None | PRBBB |
| 39 | 3 | 5 | 36/12 | 540 | 10 | 60 | 25 | ... | ... | ... | 153 | 333 | PRBBB |
| 40 | 3 | 7 | 50/10 | 720 | 18 | 70 | 60*(57) | ... | ... | ... | 164* | None | PRBBB + LAD |
| 41 | 6 | 10 | 36/10 | 840 | 21 | 80 | 35 | ... | ... | ... | 133 | None | ... |
| 42 | 5 | 13 | 30/8 | 740 | 13 | 62 | 35 | ... | ... | ... | 100 | None | ... |
| 43 | 5 | 10 | 108/10 | 638 | 24 | 42 | 37 | ... | ... | ... | 103 | None | ... |
| 44 | 3 | 8 | 38/10 | 680 | 12 | 70 | 55 | ... | ... | ... | 100 | None | ... |
| 45 | 6 | 13 | 36/4 | 920 | 18 | 68 | 42 | ... | ... | ... | 83 | None | LAD preop |
| 46 | 5 | 9 | 24/2 | 674 | 29 | 80 | 30 | ... | ... | ... | 125 | 375* | ... |
| 47 | 5 | 8 | 60/13 | 714 | 22 | 90 | 35 | ... | ... | ... | 120 | 428* | PRBBB |

LAD = left axis deviation; ND = not done; PRBBB = proximal right bundle branch block; other abbreviations as in Tables I and II.

Four children in Group A and 4 in Group B had left axis deviation that was not present preoperatively.

**Hemodynamic findings:** The majority of children had good hemodynamics postoperatively (Tables I and III), although mild pulmonary valve stenosis or pulmonary insufficiency, or both, were common. Four children in Group A and 4 in Group B had severe pulmonary stenosis, with right ventricular pressure ≥60 mm Hg. Two children in Group A and 1 in Group B required reoperation after these studies. Tricuspid valve regurgitation was found on right ventricular cineangiography in 4 children each in Groups A and B. Right atrial mean pressure was increased >8 mm Hg in 1 child in Group A (Case 11) and 2 in Group B. Right ventricular end-diastolic pressure was increased (>8 mm Hg) in 3 children in Group A and 10 children in Group B, and may reflect residual pulmonary insufficiency, right ventricular dysfunction, or decreased right ventricular compliance. Right ventricular aneurysm was defined angiographically by dilatation of the right ventricular outflow area to twice the diameter of the main pulmonary artery as visualized on the frontal view and was present in 2 children in Group A and 9 in Group B. Pulmonary stenosis was considered mild to moderate when right ventricular pressure was <60 mm Hg. Significant pulmonary insufficiency was defined by at least a grade 2/6 diastolic murmur at the pulmonary area. Three children had small residual ventricular septal defects. The residual cardiac defects are summarized in Table IV.

**TABLE IV Residual Cardiac Lesions After Operative Repair of Tetralogy of Fallot (47 Cases)**

| | Group A | | Group B | |
|---|---|---|---|---|
| | n | % | n | % |
| Significant PS (RVSP >60 mm Hg) | 4 | 27 | 4 | 13 |
| Significant PI | 9 | 60 | 26 | 81 |
| Significant TI | 4 | 27 | 4 | 13 |
| Mild/moderate PS | 8 | 53 | 16 | 50 |
| Residual VSD | 1 | 0.07 | 2 | 13 |
| RV aneurysm | 2 | 13 | 9 | 28 |
| Total | 15 | . . . | 32 | . . . |

No significant differences on chi-square analysis.
PI = pulmonary insufficiency; PS = pulmonary stenosis; RV = right ventricular; RVSP = right ventricular systolic pressure; TI = tricuspid insufficiency; VSD = ventricular septal defect.

**TABLE V Abnormal Intracardiac Conduction Findings**

| | Group A | | Group B | |
|---|---|---|---|---|
| | n | % | n | % |
| SNRT >160% | 3/15 | 30 | 4/32 | 13 |
| Wenckebach at $S_1S_1$ ≥365 ms | 4/15 | 26 | 8/32 | 25 |
| A-H over 2 SD for age | 3/15 | 20* | 0/32 | 0 |
| H-V over 2 SD for age | 3/15 | 20 | 5/32 | 16 |
| Proximal RBBB | 6/15 | 40 | 13/32 | 32 |
| LAD + PRBBB | 4/15 | 27 | 4/32 | 13 |
| RAERP over 1 SD for rate | 2/11 | 18 | 6/20 | 30 |
| RVERP over 1 SD for rate | 0/6 | 0 | 4/15 | 27 |

* p = 0.05 (chi-square).

**Electrophysiologic data:** These data are similar to conduction studies reported previously[14–16] after operative repair of tetralogy of Fallot. In addition, similar percentages of abnormal electrophysiologic findings were present in Group A as a whole and Group B (Tables II, III, and V). However, when the subgroup of cases of arrhythmia with impaired sinus or atrioventricular nodal conduction was analyzed separately, a higher aggregate number of cases had abnormal conduction values as compared with cases with ventricular ectopic rhythm or patients in Group B. There was no single pattern or abnormal measurement of conduction in the 6 children with impaired function (cases 1 to 6), although each had at least 1 abnormal value in the studies performed (Table II). Three children had a prolonged A-H interval of atrioventricular nodal dysfunction (cases 1, 4, and 5). One had a prolonged H-V interval consistent with His-Purkinje disease (case 2). In 3 children Wenckebach heart block developed at abnormally low paced rates (cases 3, 4, and 6) and in case 3 the block occurred below the His bundle. Only 2 of the 4 children (cases 2 and 5) suspected of having sinus node dysfunction had prolongation of the sinus node recovery time, suggesting either that this measurement is not sensitive, that vagal slowing may account for the observed bradycardia, or that the circumstances of the study did not reflect the clinical situation because of sedation or other factors.

## Discussion

Fifteen of 47 patients with postoperative tetralogy of Fallot manifested significant cardiac arrhythmias. In the 6 children with impaired sinus generation or atrioventricular nodal conduction, various electrophysiologic abnormalities were noted including prolonged A-H or H-V interval, increased sinus node recovery time, atrioventricular nodal effective refractory period, or appearance of Wenckebach periodicity at low pacing rates. Atrial and ventricular effective refractory periods were normal in these children. More children in Group A had a prolonged A-H interval (p = 0.05); however, the frequency of the other abnormalities was not statistically different in Groups A and B. Specifically, H-V interval, sinus node recovery time, Wenckebach periodicity, and atrial, ventricular, and atrioventricular nodal effective refractory periods were found in similar proportions in patients with and without overt arrhythmias.

Children with ventricular ectopic rhythm had no consistent abnormality of basic conduction intervals. In 5 of 6 cases in Group B in which comparison was possible, the right ventricular effective refractory period was longer at the outflow region of the right ventricle than at the apex. Only 2 of the 8 children cases with extrasystoles had ventricular stimulation. Provocative measures such as multiple stimuli or burst ventricular pacing might have uncovered more abnormalities. Ventricular tachycardia was reported after repair of tetralogy of Fallot[17] which used a reentry circuit around the margin of the ventriculotomy. Kavey et al[18] noted that fewer patients in their series of cases of ventricular tachycardia had outflow patches. One may speculate that the interposition of fabric may tend to interrupt a potential ventricular reentrant pathway. The difference we observed in ventricular refractoriness may be potentially arrhythmogenic. Other potentially arrhythmogenic factors such as prolonged effective refractory period, presence of dual atrioventricular nodal pathways, and split His potentials (reported previously)[11,19] are of uncertain prognostic significance. In addition, the large proportion of children in Group B who had sinus rhythm and abnormal intracardiac conduction values may have latent conduction disease and will require continued medical follow-up to determine whether impaired conduction or ventricular arrhythmia appears.[20]

Despite the findings of other investigators that ventricular extrasystoles were more frequent when right ventricular hypertension persisted,[7–9] our data show no consistent relation. Two patients with impaired conduction and 2 with ventricular extrasystoles had a right ventricular systolic pressure >60 mm Hg, but the majority of patients with arrhythmia had good hemodynamic results. Although a direct relation between the rate of pacemaker depolarization and myocardial stretch was demonstrated in vitro,[21] the present findings do not support a mechanical factor as the likely mechanism in clinical cases of postoperative rhythm disturbances. Furthermore, the reported series of ventricular tachycardia[17,18,22] occurred in cases with no significant residual pulmonary stenosis. The increase in ventricular arrhythmias noted by James and co-workers[22] after exercise may represent increased ventricular excitability

due to sympathetic discharge in patients who have a latent reentry circuit around the ventriculotomy. The observation that several patients with ventricular extrasystoles and right ventricular hypertension had sudden death[7-9] may reflect the poor tolerance of patients with impaired hemodynamic function to the circulatory effects of arrhythmias. Ventricular ectopic rhythm or conduction impairment, residual hemodynamic stress, and myocardial injury may combine to bring about sudden death. Furthermore, the incidence of ventricular arrhythmia was increased in older patients especially in those with tetralogy of Fallot followed up 10 years or more,[2,6,9,10,22-24] suggesting a relation to late fibrosis in the myocardium. Recent methods of myocardial preservation during surgery and the practice of operating at an earlier age may change the future incidence of ventricular arrhythmias.

Conclusions from these data are threefold: (1) children with evidence of Mobitz type I or II atrioventricular block usually have electrophysiologic abnormalities; (2) right ventricular hypertension or residual heart disease does not correlate well with the occurrence of arrhythmias or with electrophysiologic abnormalities; (3) a large number of children after repair of tetralogy of Fallot have conduction abnormalities and normal sinus rhythm. Although the arrhythmias and the electrophysiologic findings were well tolerated in this series and in others,[15,23] a longer period of observation is necessary before the prognostic significance of these findings is known.

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## References

1. **Wolff GS, Rowland TW, Ellison RC.** Surgically induced right bundle branch block with left anterior hemiblock. An ominous sign in postoperative tetralogy of Fallot. Circulation 1972;46:587–594.
2. **Quattlebaum TG, Varghese DJ, Neill CA, Donahoo JS.** Sudden death among postoperative patients with tetralogy of Fallot. A follow-up study of 243 patients for an average of twelve years. Circulation 1976;54:289–293.
3. **Downing JW, Kaplan S, Bone KE.** Post-surgical left anterior hemiblock and right bundle branch block. Br Heart J 1972;34:263–270.
4. **Godman MJ, Roberts NK, Izukawa T.** Late postoperative conduction disturbances after repair of ventricular septal defect and tetralogy of Fallot. Analysis by His bundle recordings. Circulation 1974;49:214–221.
5. **Krongrad E.** Prognosis for patients with congenital heart disease and postoperative intraventricular conduction defects. Circulation 1978;57: 867–869.
6. **James FW, Kaplan S, Chou TC.** Unexpected cardiac arrest in patients after surgical correction of tetralogy of Fallot. Circulation 1975;52:691–694.
7. **Garson A, Gillette PC, Gutgesell HP, McNamara DG.** Stress-induced ventricular arrhythmia after repair of tetralogy of Fallot. Am J Cardiol 1980;46:1006–1012.
8. **Gillette PC, Yeoman MA, Mullins CE, McNamara DG.** Sudden death after repair of tetralogy of Fallot. Circulation 1977;56:566–571.
9. **Fuster V, McGoon DC, Ritter DG.** Factors affecting the long term results (11–21 years) of open heart surgery for tetralogy of Fallot (abstr). Am J Cardiol 1979;43:362.
10. **Deanfield JE, McKenna WJ, Hallidie-Smith KA.** Mechanism of sudden death in postoperative tetralogy of Fallot (abstr). Br Heart J 1979;42:235–236.
11. **Casta A, Wolff GS, Mehta A, Tamer D, Garcia OL, Pickoff AS, Ferrer PL, Sung RJ, Gelband H.** Dual atrioventricular nodal pathways: a benign finding in arrhythmia-free children with heart disease. Am J Cardiol 1980;46: 1013–1018.
12. **Wolff GS, Casta A, Kaiser G, Pickoff AS, Mehta AV, Tamer D, Garcia OL, Ferrer PL, Smith K, Gelband H.** Sinus and atrioventricular nodal function: preoperative and early postoperative assessment in children. J Thorac Cardiovasc Surg 1982;83:141–145.
13. **Roberts N, Gelband H.** Cardiac Arrhythmias in the Neonate, Infant and Child. New York: Appleton-Century-Crofts, 1977:151.
14. **Neches WH, Parle SC, Mathews RA, Lenox CC, Marin-Garcia J, Zuberbuhler JR.** Tetralogy of Fallot: postoperative electrophysiologic studies. Circulation 1977;56:713–719.
15. **Pahlajani DB, Serratto M, Mehta A, Miller RA, Hastreiter A, Rosen KM.** Surgical bifascicular block. Circulation 1975;52:82–87.
16. **Levin AR, Haft JI, Engle MA, Ehlers KH, Klein AA.** Intracardiac conduction intervals in children with congenital heart disease. Circulation 1977;55: 286–294.
17. **Horowitz LN, Vetter VL, Harken AH, Josephson ME.** Electrophysiologic characteristics of sustained ventricular tachycardia occurring after repair of tetralogy of Fallot. Am J Cardiol 1980;46:446–452.
18. **Kavey REW, Blackman MS, Sondheimer HM.** Ventricular dysrhythmias after repair of tetralogy of Fallot (abstr). Circulation 1980;62:III:III-72.
19. **Wolff GS, Tamer D, Garcia OL, Ferrer PL, Pickoff AS, Sung RJ, Gelband H.** His-Purkinje conduction findings after cardiac surgery in children. Circulation 1980;62:615–621.
20. **Pickoff AS, Mehta AV, Casta A, Ferrer PL, Wolff GS, Tamer DL, Garcia OL, Gelband H.** Echocardiographic assessment of right bundle branch injury following repair of tetralogy of Fallot. Circulation 1981;63:174–181.
21. **Blinks JR.** Positive chronotropic effect of increasing right atrial pressure in the isolated mammalian heart. Am J Physiol 1956;186:299–303.
22. **James FW, Kaplan S, Schwartz DC, Chou TC, Sandler ET, Naylor V.** Response to exercise in patients after total surgical correction of tetralogy of Fallot. Circulation 1976;54:671–679.
23. **Wessel HA, Paul MH, Berry TE, Cole RB, Muster AJ.** Prognostic significance of arrhythmia in tetralogy of Fallot after intracardiac repair. Am J Cardiol 1980;46:843–848.
24. **Rocchini AP.** Hemodynamic abnormalities in response to supine exercise in patients after operative correction of tetralogy of Fallot after early childhood. Am J Cardiol 1981;48:325–330.

# Terminal Cardiac Electrical Activity in Pediatric Patients

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**Ventricular fibrillation (VF) is a frequently reported terminal cardiac electrical activity in adults. Such data are unavailable for pediatric patients. Terminal cardiac electrical activity determined in 100 pediatric patients was bradycardic arrest throughout the death process in 88% of newborns, 67% of infants, and 64% of children. Although bradycardic arrest was more common, the incidence of ventricular tachyarrhythmias was higher in patients who had congenital heart disease, who had received cardiopulmonary resuscitation, who were beyond the neonatal period, and/or who weighed >2.23 kg. No definite associations could be established between arterial blood gases, electrolyte values, and type of terminal cardiac electrical activity. The development of VF may be related to cardiac mass and the developing autonomic nervous system and therefore is less likely to occur in patients with a small heart.**

Cardiac arrest is defined as the sudden cessation of cardiac output. The electrical phenomena associated with cardiac arrest include VF and bradycardic arrest. The latter term refers to ventricular standstill or asystole, in which mechanical and electrical activity have ceased, and to agonal rhythm, in which there are wide, bizarre ventricular complexes but no myocardial contractions, palpable pulse, or heart sounds. Terminal cardiac electrical activity may differ with different patient populations. The most common cause of cardiac arrest associated with anesthetic induction and surgical procedures is asystole, probably precipitated by marked vagal stimulation.[1] Medical and surgical patients admitted for cardiac disease and persons who die suddenly most often die in VF.[2,3] The final mechanism of cardiac arrest may be complex and may be affected by various additive events, such as electrolyte imbalance, metabolic acidosis, hypothermia, intrinsic cardiac electrical abnormalities, intrinsic or drug-induced autonomic activity, disturbances of central nervous system function, and myocardial ischemia.[4,5]

No information is available about the terminal electrical events in children who die suddenly or who are expected to die. Indeed, reported studies of the terminal cardiac electrical activity in adults who die suddenly may bear no relation to that in children who die suddenly or who are expected to die. Therefore, this study was undertaken to determine the types of terminal cardiac electrical activity that occur in hospitalized pediatric patients and to determine if there is any association with conditions that might facilitate the development of VF or bradycardic arrest, or both, such as acid-base and electrolyte disturbances.

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## Methods

**Patient population:** The prospective study population included 100 hospitalized pediatric patients, 56 boys and 44 girls, who died at Babies Hospital in New York (Table I). The patients were divided into 3 age groups: 54 newborn infants aged 1 to 28 days (median 3), 24 infants aged 28 days to 1 year (median 3 months), and 22 children aged 1 to 18 years (median 6.6).

In the newborn group, 18 patients (33%) had congenital heart disease and 17 patients (31%) had severe respiratory distress syndrome. Five patients had sepsis, 4 had intracranial hemorrhage, 3 had meconium aspiration, and 7 had other causes of death. Of the 54 newborns, 28 were premature. The infant group contained 13 patients (54%) with congenital heart disease. Others had renal failure (3 patients), bronchopulmonary dysplasia (2 patients), or various other causes of death (6 patients). Fifteen (68%) of the 22 children had congenital heart disease. Two patients died from Reye's syndrome and 5 from different causes. Digitalis blood levels were not obtained. No patient was receiving digitalis at the time of death, because patients dying from congenital heart disease either had restricted pulmonary blood flow or were postoperative. Digitalis was routinely discontinued 2 days before surgery, and postoperative congestive heart failure and low output were treated with pressor agents such as dopamine or isoproterenol.

**Recording of terminal cardiac electrical activity:** A 1-lead (usually lead II) electrocardiogram was obtained from cardiac monitors or portable recorders, or both. Recording was usually precipitated by deterioration of clinical status or by an arrhythmia and was terminated with cessation of all cardiac electrical activity. The electrocardiographic recording was continued throughout the entire death process and during cardiopulmonary resuscitation when applied. The duration of recordings was 20 to 90 minutes during resuscitation and another 5 to 15 minutes after blood pressure, respiration, and pulse were absent.

**TABLE I Patient Population**

| Cause of Death | N |
|---|---|
| **Newborns (1 to 28 Days)** | |
| Congenital heart disease | 18 |
| Respiratory distress syndrome | 17 |
| Sepsis | 5 |
| Intracranial hemorrhage | 4 |
| Meconium aspiration | 3 |
| Miscellaneous | 7 |
| Total | 54 |
| **Infants (28 Days to 1 Year)** | |
| Congenital heart disease | 13 |
| Renal failure | 3 |
| Bronchopulmonary dysplasia | 2 |
| Miscellaneous | 6 |
| Total | 24 |
| **Children (1 to 18 Years)** | |
| Congenital heart disease | 15 |
| Reyes syndrome | 2 |
| Miscellaneous | 5 |
| Total | 22 |

**Laboratory studies:** The last arterial pH and partial pressure of oxygen and carbon dioxide values obtained in patients were recorded. These results were divided into 3 groups: (1) those obtained <1 hour before death, (2) those obtained 1 to 4 hours before death, and (3) those obtained 4 to 24 hours before death. The same classification was applied to the last sodium, potassium, and chloride values.

**Statistical analysis:** Statistical analysis of the data was performed using a chi-square test or Fisher's exact test.

## Results

**Types of terminal cardiac electrical activity:** Two basic types of terminal cardiac electrical activity were observed. In 1, bradycardic arrest occurred without ventricular tachyarrhythmia. Electrical activity included a gradual slowing of the heart rate with deterioration of AV conduction and QRS, S-T, and T wave configuration until complete cessation occurred. In the other, ventricular tachycardia or VF, or both, were prominent.

Figure 1 depicts bradycardic arrest which occurred throughout the terminal electrical activity of a child who died from smoke inhalation. The sequence of electrical events was sinus tachycardia followed by ST-T wave changes increasing atrioventricular block with QRS and Q-T prolongation, and finally wide, bizarre QRS complexes at an extremely slow, irregular rate until complete standstill occurred.

In the other type of observed terminal cardiac electrical activity, ventricular tachycardia or VF occurred during the death process. The final electrical event was either bradycardic arrest or deteriorating VF until standstill. Figure 2 depicts recurrent VF in a 1 month old infant with congenital heart disease.

The terminal cardiac electrical activity in all 100 patients is summarized in Figure 3. Bradycardic arrest was present throughout the death process in 78% of patients. Ventricular tachycardia or VF was seen during terminal electrical activity in 22 patients, 16 of whom had bradycardic arrest as the final electrical event. Six

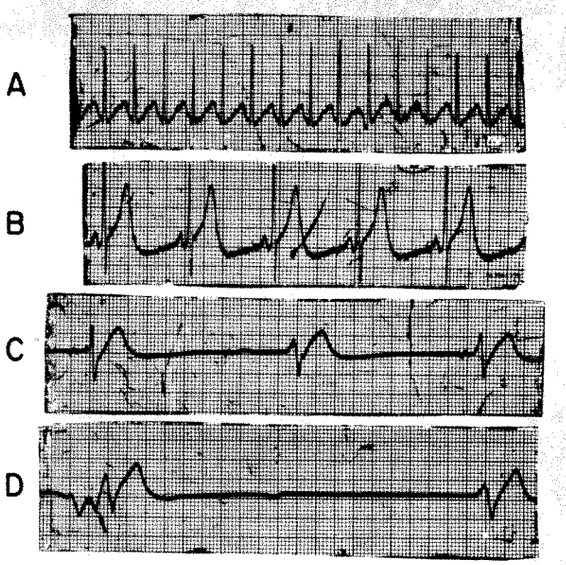



**FIGURE 1.** Successive electrocardiograms of a 5-year-old child who died from smoke inhalation. **A,** sinus tachycardia at a rate of about 200 beats/min. **B,** progressive sinus bradycardia with ST-T wave changes. **C,** atrioventricular dissociation with an idioventricular rhythm. **D,** a very slow terminal idioventricular rhythm with abnormally wide, bizarre QRS complexes.

patients had deteriorating and unremitting VF as the final electrical activity in the death process.

**Effect of age:** Bradycardic arrest was the most frequent terminal cardiac electrical activity in all groups (Fig. 4). Of the 54 newborns, 88% had bradycardic arrest throughout, whereas 67% of the 24 infants and 64% of the 22 children had this type of terminal activity. The difference in the terminal cardiac electrical activity of

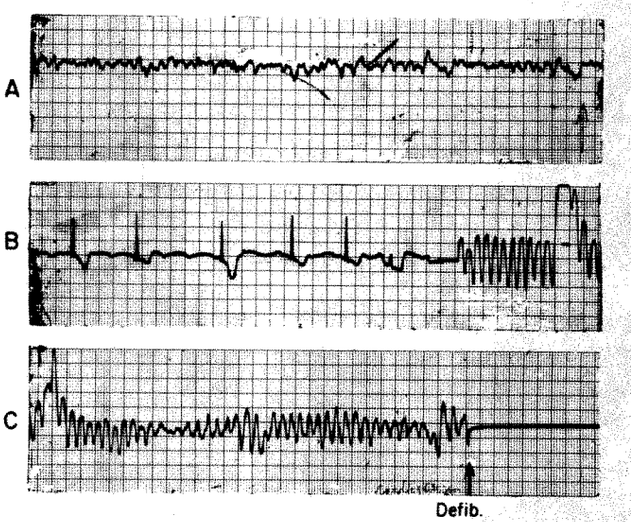



**FIGURE 2.** Successive rhythm strips obtained during prolonged cardiopulmonary resuscitation in a 1-month-old infant with cyanotic congenital heart disease. VF is evident in **A. B,** irregular ventricular contractions after cardioversion. The rhythm deteriorates to VF towards the end of this strip. **C,** continuation of VF with cardioversion (Defib.) to asystole.

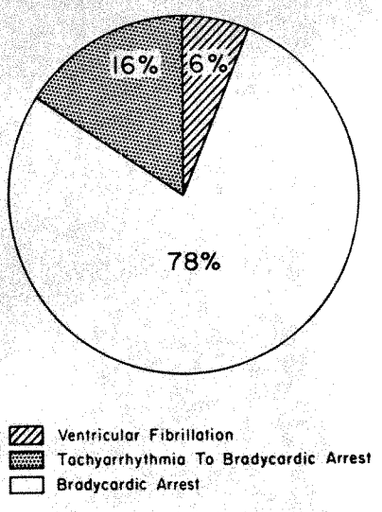



**FIGURE 3.** Summary of the terminal cardiac electrical activity in 100 patients. Bradycardic arrest occurred throughout the death process in 78% of patients. Sixteen percent had episodes of ventricular tachycardia or VF, with bradycardic arrest as the final electrical event. Unremitting VF was seen in 6%.

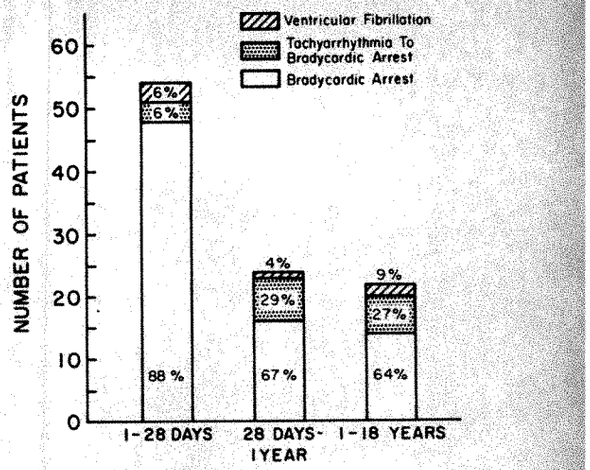



**FIGURE 4.** Terminal cardiac electrical activity among newborns aged <28 days, infants aged 28 days to 1 year, and children aged >1 year. Bradycardic arrest was the most common pattern in all age groups.

newborns versus that in older pediatric patients is statistically significant ($p < 0.01$), but no significant difference exists between the 2 older groups. Thus, 12% of newborns and 35% of the combined older groups had ventricular tachyarrhythmias, suggesting an increased tendency to develop ventricular tachyarrhythmias after the newborn period.

**Relation to patient weight:** The relation of weight to terminal cardiac activity also was examined. Because autopsies were performed in only a small number of children, cardiac mass could not be obtained directly. Patients' weight ranged from 630 g to 45 kg (median 3.25 kg). Ventricular tachycardia and VF did not occur in the 32 patients weighing <2.23 kg. Only 3 (9%) of these patients had congenital heart disease.

**Relation to congenital heart disease:** Forty-six patients had congenital heart disease and 54 patients had other terminal diseases (Fig. 5). Bradycardic arrest was the most common terminal cardiac electrical activity, but ventricular tachyarrhythmias were seen in 35% of patients with and 11% of those without congenital heart disease. Three of the 6 patients with congenital heart disease and VF died in the operating room. No patient without congenital heart disease had VF as the final cardiac electrical event.

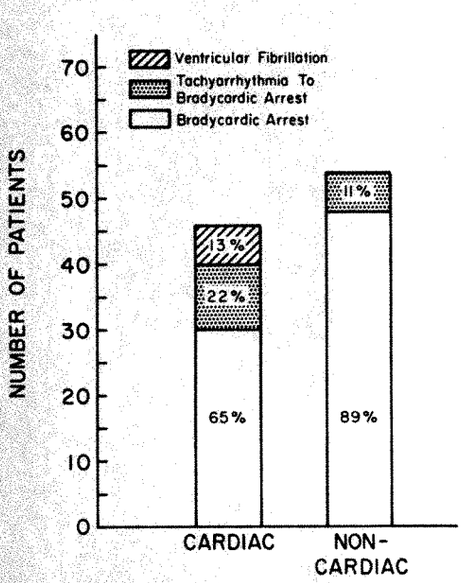



**FIGURE 5.** Relation of congenital heart disease to terminal cardiac electrical activity. Although bradycardic arrest was most common in both groups, ventricular tachyarrhythmia occurred more frequently in patients with congenital heart disease than in those with other diagnoses ($p < 0.01$).

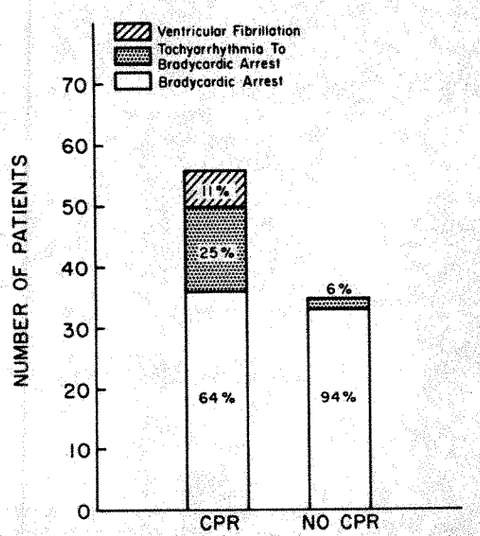



**FIGURE 6.** Relation of cardiopulmonary resuscitation (CPR) to terminal cardiac electrical activity. Bradycardic arrest occurred most frequently in both groups, but ventricular tachyarrhythmias were seen more often in patients who experienced resuscitative efforts ($p < 0.005$).

**TABLE II Arterial Blood Gases Before Death***

| Hours Before Death | pH | | $pCO_2$ | | $pO_2$ | |
|---|---|---|---|---|---|---|
| | Range | Mean | Range | Mean | Range | Mean |
| Newborns (1 to 28 days) | | | | | | |
| 0–1 | 6.67–7.34 | 6.96 (8) | 28–98 | 53 (6) | 25–170 | 67 (7) |
| 1–4 | 6.94–7.42 | 7.17 (9) | 22–74 | 48 (9) | 18–108 | 58 (7) |
| 4–24 | 7.01–7.36 | 7.18 (5) | 38–95 | 64 (5) | 21–44 | 37 (5) |
| Infants (28 days to 1 yr) | | | | | | |
| 0–1 | 6.60–7.48 | 7.06 (6) | 22–170 | 79 (6) | 30–145 | 63 (6) |
| 1–4 | 6.99–7.58 | 7.37 (6) | 29–72 | 43 (6) | 49–86 | 69 (5) |
| 4–24 | 7.18–7.56 | 7.34 (6) | 29–50 | 38 (6) | 30–185 | 98 (6) |
| Children (1 to 18 yr) | | | | | | |
| 0–1 | 7.12–7.52 | 7.29 (6) | 27–60 | 41 (6) | 35–161 | 69 (6) |
| 1–4 | 7.29–7.53 | 7.41 (2) | 28–53 | 41 (2) | 37–76 | 57 (2) |
| 4–24 | 7.21–7.70 | 7.40 (6) | 27–69 | 44 (6) | 50–140 | 78 (6) |

* Figures in parentheses represent number of values obtained.
$pCO_2$ and $pO_2$ = partial pressure of carbon dioxide and oxygen, respectively.

**Relation to cardiopulmonary resuscitation:** Among 56 patients who had cardiopulmonary resuscitation, 64% died with bradycardic arrest, 25% had a transient tachyarrhythmia, and 11% had VF as the terminal cardiac electrical activity (Fig. 6). In contrast, 94% of patients with end-stage terminal illness or brain death who did not experience resuscitative efforts died with bradycardic arrest.

**Arterial blood gases and electrolytes:** Arterial blood gas and serum electrolyte values are given in Tables II and III. No definite associations could be established between pH, partial pressure of oxygen and carbon dioxide, sodium, potassium, and chloride values and the type of terminal cardiac electrical activity. Ventricular tachyarrhythmias were observed infrequently in acidotic patients, but because these patients were most often neonates, this relation could not be separated from the possible additive effects of age and weight.

## Discussion

Bradycardic arrest was the most common terminal cardiac electrical activity in all pediatric patients studied irrespective of diagnosis, resuscitative efforts, or acid-base and electrolyte status. No comparable data are available for terminal hospitalized adult patients. The data were most striking among newborns, 88% of whom had bradycardic arrest as the terminal rhythm.

The propensity to develop tachyarrhythmias increased with age. The percentage of patients dying from congenital heart disease also increased with age. Cardiac patients were 3 times more likely to have tachyarrhythmias than were noncardiac patients (35 versus 11% of each group). In addition, deteriorating VF did not occur as the terminal cardiac electrical activity in any patient without congenital heart disease. Nevertheless, when the noncardiac patients are considered by themselves, the tendency to develop tachyarrhythmias increases with age (Fig. 7). Moreover, the same trend also is evident within cardiac patients after they are analyzed alone. Therefore, age and not the mere presence of congenital heart disease appears to be a dominant factor in determining the propensity to develop a certain kind of terminal electrical activity.

Our clinical observations support electrophysiologic data suggesting that induction and maintenance of VF is related to cardiac mass and therefore less likely to occur in smaller hearts. In 1887, McWilliams[6] found that VF could exist more easily in larger hearts than

**TABLE III Serum Electrolyte Values Before Death***

| Hours Before Death | Sodium (mEq/liter) | | Potassium (mEq/liter) | | Chloride (mEq/liter) | |
|---|---|---|---|---|---|---|
| | Range | Mean | Range | Mean | Range | Mean |
| Newborn | | | | | | |
| 0–1 | . . . | . . . | . . . | . . . | . . . | . . . |
| 1–4 | 138–142 | 139 (3) | 5.8–9.0 | 7.0 (4) | 70–92 | 80 (3) |
| 4–24 | 139–157 | 146 (4) | 2.8–5.9 | 4.3 (4) | 76–88 | 83 (3) |
| Infants | | | | | | |
| 0–1 | 138–161 | 149 (5) | 3.2–7.7 | 5.3 (6) | 83–95 | 89 (4) |
| 1–4 | 119–146 | 136 (4) | 2.7–8.1 | 5.0 (4) | 90–92 | 91 (2) |
| 4–24 | 128–146 | 139 (6) | 3.0–5.8 | 4.1 (7) | 86–99 | 93 (6) |
| Children | | | | | | |
| 0–1 | 154–160 | 157 (2) | 3.9–5.0 | 4.5 (2) | 85–111 | 98 (2) |
| 1–4 | 131–146 | 140 (3) | 5.1–5.8 | 5.4 (4) | 86–94 | 90 (4) |
| 4–24 | 130–154 | 138 (9) | 3.3–4.9 | 3.9 (9) | 82–125 | 95 (9) |

* Figures in parentheses represent number of values obtained.

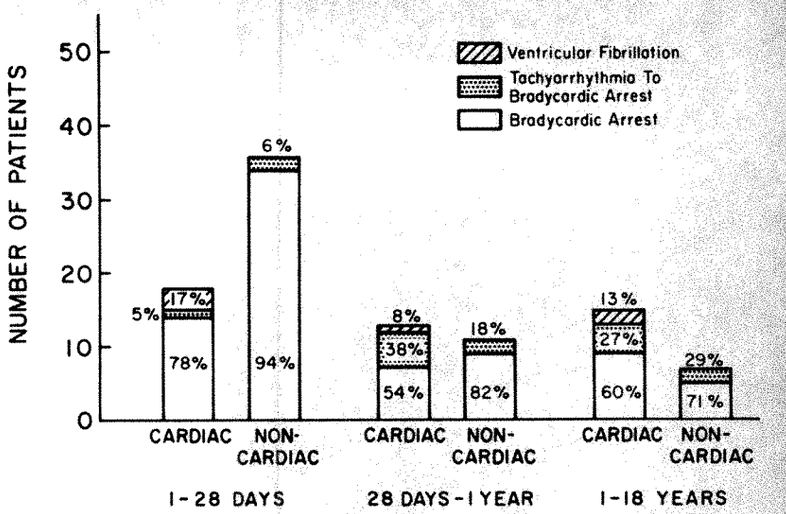



**FIGURE 7.** Terminal cardiac electrical activity in cardiac versus noncardiac patients, in newborn, infant, and child groups. The tendency to develop tachyarrhythmia increased similarly with age in both cardiac and noncardiac patients.

smaller ones. In 1914, Garrey[7] showed that pieces of muscle from a fibrillating left ventricle of a dog stopped fibrillating when the surface area was reduced to less than 4 $cm^2$. When only one fourth of the ventricular mass remained, it too stopped fibrillating. If fibrillation is more difficult to initiate and maintain in the small heart of young animals, the same may be true for the relatively small heart of infants and children. The possible effects of a critical cardiac mass on the development of VF is most evident when the relation of weight to terminal cardiac electrical activity is investigated. Although ventricular tachyarrhythmias occurred in patients as young as 1 day of age, none occurred in any of the 32 patients <2.23 kg.

The developing autonomic nervous system may play an important role in the age-related changes in cardiac rhythm. Studies[8] show that parasympathetic and alpha-adrenergic activity is dominant at an early period of gestation. Beta-adrenergic activity in the myocardium matures much later. Rosen et al[9] demonstrated that there are age-related changes in alpha- and beta-adrenergic responsiveness of the heart that may influence the occurrence of a particular arrhythmia. The late development of beta-adrenergic effects will cause a decrease in the VF threshold that would alter ventricular vulnerability to VF.[10] The fact that alpha- and beta-adrenergic activities are opposite in nature and mature asynchronously suggests that they may strongly influence the mechanism and type of arrhythmia that occurs in the neonate, infant, or child. The early dominance of the parasympathetic system and alpha-adrenergic activity may further explain why bradycardic arrest is the most common terminal cardiac electrical activity in infants. Such consideration cannot be applied when maturation of the autonomic nervous system has already been completed.

In contrast to adult medical and surgical patients hospitalized for cardiac disease, most of whom have VF as the terminal rhythm,[2] most children with congenital heart disease still had bradycardiac arrest as the terminal cardiac electrical activity. In our patient population, ventricular tachyarrhythmias were seen more often with congenital heart disease than with other terminal diseases. The increased muscle mass and cardiac hypertrophy associated with congenital heart disease may contribute to the increased tendency to develop a terminal cardiac tachyarrhythmia.

Many variables may contribute to the development of a certain type of terminal cardiac electrical activity.[4-13] These abnormalities are seldom found in isolation and their interrelationship is extremely complex and cannot be ascertained by clinical observations alone. Nevertheless, terminal tachyarrhythmias were seen more often in patients with congenital heart disease and in those who received cardiopulmonary resuscitation. Catecholamine administration during cardiopulmonary resuscitation may also contribute to the development of tachyarrhythmias. All 6 patients who died in unremitting VF had congenital heart disease and received unsuccessful cardiopulmonary resuscitation.

## References


1. **Briggs BD, Sheldon DB, Becher HK.** Cardiac arrest. Study of a 30-yr. period of operating room deaths at Massachusetts General Hospital. JAMA 1956;160:1439–1444.
2. **Day HW, Averill K.** Recorded arrhythmias in an acute coronary care area. Dis Chest 1966;49:113–118.
3. **Myerburg RJ, Kessler KM, Zaman L, Conde CA, Castellanos A.** Survivors of prehospital cardiac arrest. JAMA 1982;247:1485–1490.
4. **Marriott HJL, Myerberg RJ.** Recognition and treatment of cardiac arrhythmias and conduction disturbances. In: Hurst JW, Logue RB, Schlant RC, Wenger NK, eds. The Heart. 4th ed. New York: McGraw-Hill, 1978: 637–694.
5. **Surawicz B.** Ventricular fibrillation. Am J Cardiol 1971;28:268–287.
6. **McWilliams JA.** Fibrillar contraction of the heart. J Physiol 1887;8:296–310.
7. **Garrey WD.** The nature of fibrillatory contraction of the heart in relation to tissue mass and form. Am J Physiol 1914;33:397–414.
8. **Friedman W.** The intrinsic physiologic properties of the developing heart. Prog Cardiovasc Dis 1972;15:87–111.
9. **Rosen MR, Hordof AJ, Ilvento JP, Danilo P Jr.** Effect of adrenergic amines on electrophysiological properties and automaticity of neonatal and adult canine Purkinje fibers: evidence for $\alpha$ and $\beta$ adrenergic action. Circ Res 1977;40:390–400.
10. **Reder RF, Rosen MR.** The role of the sympathetic nervous system in sudden cardiac death. Drug Therapy 1978;8:41–48.
11. **Grumbach L, Howard JW, Merrill VI.** Factors related to the initiation of ventricular fibrillation in the isolated heart. Effect of calcium and potassium. Circ Res 1954;2:452–459.
12. **Surawicz B.** Arrhythmias and electrolyte disturbances. Bull NY Acad Med 1967;43:1160–1180.
13. **Gerst PH, Fleming WH, Malm JR.** Increased susceptibility of the heart to ventricular fibrillation during metabolic acidosis. Circ Res 1966;19:63–70.

# Percutaneous Transluminal Angioplasty of Congenital Coarctation of the Aorta

DONALD R. SPERLING, MD, THOMAS J. DORSEY, MD, MARSHALL ROWEN, MD, and ALAN B. GAZZANIGA, MD

**Two cases of successful dilatation of congenital coarctation of the aorta using the Grüntzig technique are reported. In a 3-week-old boy and an 11-month-old girl, systolic gradients across the narrowed areas were lowered from 50 to 8 mm Hg and from 23 to 8 mm Hg. Although the femoral pulses later disappeared in the younger patient, surgery was avoided. The second patient's gradient has remained minimal for 8 months and no surgery has been performed.**

The use of catheters to dilate vascular obstructions has increased since the original description by Dotter and Judkins[1] in 1964. Coaxial dilatation was followed by the use of balloon-tipped catheters in 1973 and 1974.[2,3] Grüntzig and Hopff[4] reported their initial experience with coronary arterial dilatation in 50 patients in 1979. The same technique also has been used to dilate a constriction in the distal abdominal aorta[5] and has been applied to relief of stenosis of the renal artery in a 3-year-old girl.[6] These catheters have been used to dilate artificially created branch pulmonary arterial stenoses in newborn lambs.[7] This study describes the use of the Grüntzig technique to dilate congenital coarctation of the aorta in 2 patients.

## Methods

A 5Fr Grüntzig dilatation catheter was inserted percutaneously into the femoral artery. This catheter has an inflatable balloon 5 mm in diameter and 2 cm in length. The catheter was passed across the coarctation into the ascending aorta for pressure recording and injection of contrast material through the end hole of the catheter (Fig. 1 and 2). The gradient across the coarctation was measured just before the balloon was placed across the area of narrowing (Fig. 3). The 2 radiopaque clips inherent in the catheter were used to delineate the limits of the balloon for orientation. The balloon was inflated by hand over a 3-second period with half-strength Renografin® to 75 lb/in$^2$ measured with use of a gauge. Full inflation time was 10 seconds and deflation time was 3 seconds. This was repeated 3 times over a 10 to 15 minute period. Postdilatation angiograms and pressure measurements were obtained (Fig. 2, 3, and 4). No complications occurred during or after the procedure.

## Comments

The 2 patients described in Table I and Figures 1 to 5 clearly demonstrate that acute dilatation of coarctation of the aorta is possible. Whether relief of the constriction will persist is unknown, although the pressure differential by cuff measurement has remained decreased for 5 and 8 months, respectively, after the procedure in these patients. The absence of femoral pulses with an 18 mm Hg sphygmomanometer pressure gradient between the right arm and left leg indicates persisting or recurrent obstruction in Patient 1, but early surgery was avoided. Dilatation in the moribund neonate with acute congestive heart failure secondary to the coarctation syndrome in conjunction with prostaglandin $E_1$[8] also is to be considered and may avoid early coarctation surgery. The 8-month success in our second patient suggests that the procedure may obviate surgery completely in some cases.

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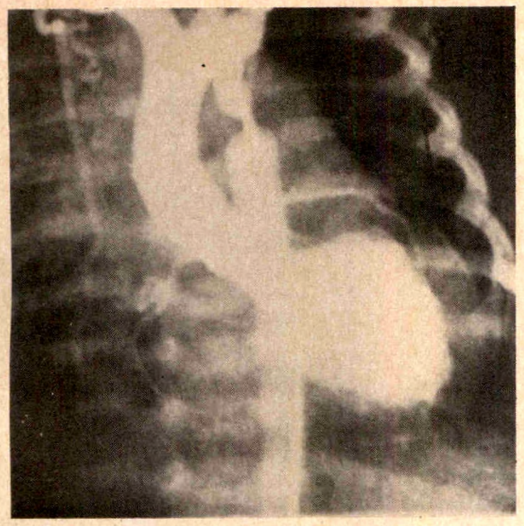


**FIGURE 1.** Patient 1. Aortogram demonstrating short narrowed segment distal to the subclavian artery.

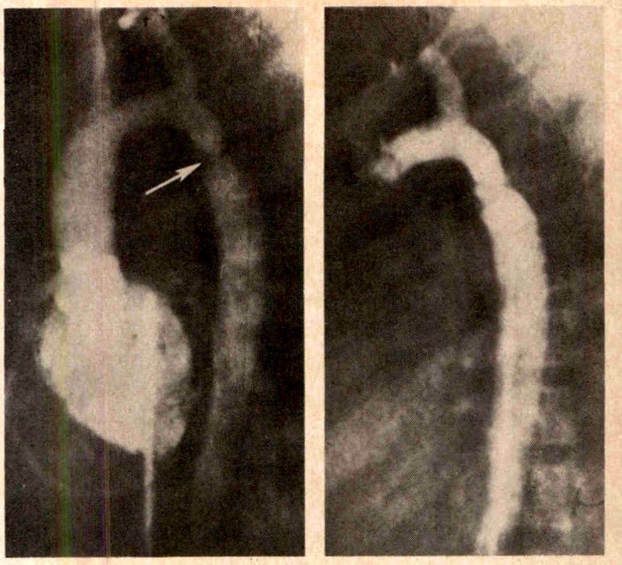


**FIGURE 2.** Patient 2. Aortograms before (**left**) and after (**right**) dilatation.

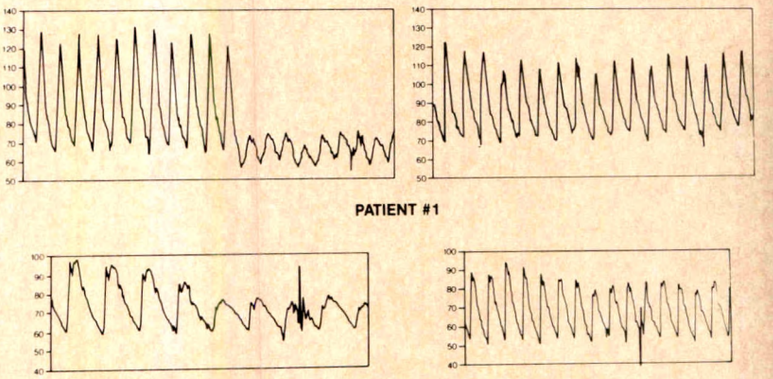



**FIGURE 3.** Pressure measurements before (**left**) and after (**right**) dilatation.



**FIGURE 4.** Patient 1. Postdilatation aortogram.

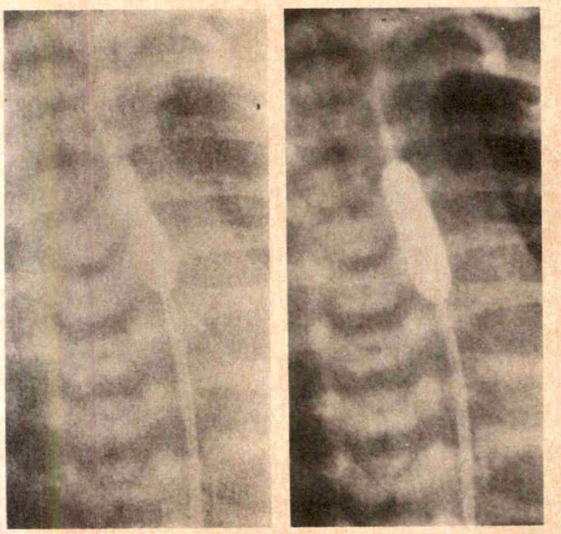


**FIGURE 5.** Patient 1. Dilatation sequence during inflation (**left**). Note coarctation indentation. Full inflation (**right**).

**TABLE I Patient Data**

| Patient | Age | | Cardiac Catheterization Pressure (mm Hg) Above Coarctation | Below Coarctation | Femoral Pulses | Cuff Blood Pressure (mm Hg) Right Arm | Left Leg |
|---|---|---|---|---|---|---|---|
| 1 | 17 days | Before D | 124/68 | 74/59 | 0 | 100/80 | 40/Flush |
| | | After D | 122/72 | 114/72 | 0 (late) | 120/77 | 102/67 |
| 2 | 1 year | Before D | 98/60 | 75/60 | 0 | 110/70 | 50/Flush |
| | | After D | 89/53 | 81/53 | + | 93/83 | 97/78 |

D = dilatation.

The use of balloon dilatation of other congenital heart conditions must be considered. Postsurgical applications may be dilatation of a narrowed Blalock-Taussig shunt or a narrowed aorta after coarctectomy or patch angioplasty.[9] Artificially created peripheral pulmonary stenoses have been relieved in lambs[7]; perhaps this will also be possible in humans. A narrowly obstructed area in an anomalous pulmonary vein is a potential application. Dilatation of isolated pulmonary valvular stenosis or the pulmonary valve in tetralogy of Fallot are also potential applications of this procedure.

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## References

1. **Dotter CT, Judkins MP.** Transluminal treatment of arteriosclerotic obstruction. Description of a new technique and report of its application. Circulation 1964;30:654–670.
2. **Porstman W.** Ein neuer korsett-ballonkatheter zur transluminalen rekanalisation nach Dotter unter besonderer berucksichtigung von obliterationen an der beckenarterien. Radiol Diagn (Berl) 1973;14:239–244.
3. **Grüntzig A, Hopff H.** Perkutane rekanalisation chronischer arterieller verschlusse mit einem neuen dilatationskatheter. Modifikation der Dotter-technik. Dtsch Med Wochenschr 1974;99:2502–2505.
4. **Grüntzig AR, Senning A, Siegenthaler WE.** Non-operative dilatation of coronary artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979;301:61–68.
5. **Tegtmeyer CJ, Wellons HA, Thompson RN.** Balloon dilation of the abdominal aorta. JAMA 1980;244:2636–2638.
6. **McCook TA, Mills SR, Kirks DR, Heaston SK, Seigler HF, Malone RB, Osofsky SG.** Percutaneous transluminal renal artery angioplasty in a 3½-year-old hypertensive girl. J Pediatr 1980;97:958–960.
7. **Lock JE, Niemi T, Einzig S, Amplatz K, Burke B, Bass JL.** Transvenous angioplasty of experimental branch pulmonary artery stenosis in newborn lambs. Circulation 1981;64:886–893.
8. **Heymann MA, Berman W, Rudolph AM, Whitman V.** Dilatation of the ductus arteriosus by prostaglandin $E_1$ in aortic arch abnormalities. Circulation 1979;59:169–173.
9. **Thibault WN, Sperling DR, Gazzaniga AB.** Subclavian artery patch angioplasty. Treatment of infants and young children with aorta coarctation. Arch Surg 1975;110:1095–1098.

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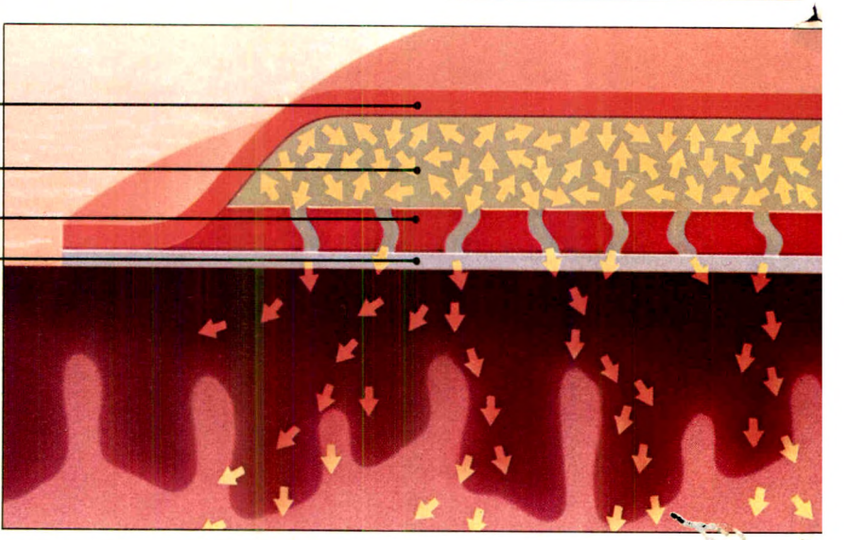
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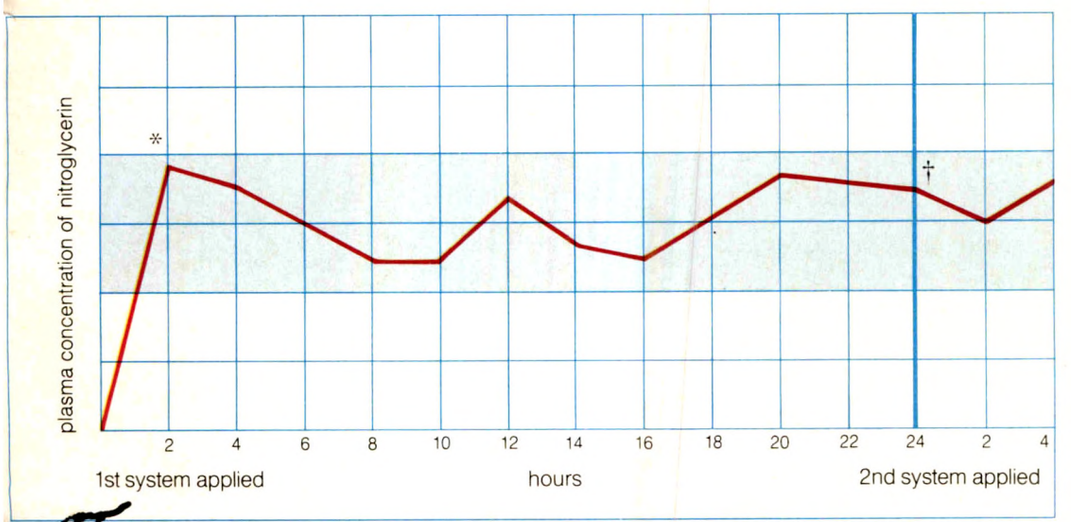
Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

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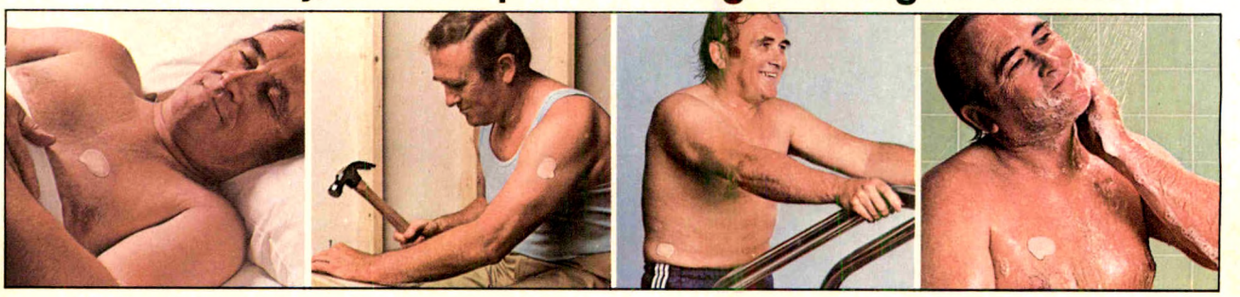
†After 24 hours, system is removed and a new one is applied to another site. Renewal of the system does not result in any significant alteration in the plasma levels, as long as the change is made without delay.

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## Once-a-day, 24-hour protection against angina attacks



System can be applied anywhere except distal extremities. Doesn't compromise daily activities.

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**Transdermal Therapeutic System**

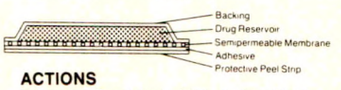
### DESCRIPTION

Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semipermeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 10 and 20 $cm^2$ respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system; 0.5 mg nitroglycerin is delivered *in vivo* for every $cm^2$ of system size.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface toward the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene/vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:




### ACTIONS

When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

### INDICATIONS AND USAGE

Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

### CONTRAINDICATIONS

Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

### WARNINGS

In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

### PRECAUTIONS

Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

### ADVERSE REACTIONS

Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

### DOSAGE AND ADMINISTRATION

Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

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# Subepicardial Adipose Tissue Producing Echocardiographic Appearance of Pericardial Effusion

## Documentation by Computed Tomography and Necropsy

JEFFREY M. ISNER, MD, BARBARA L. CARTER, MD, WILLIAM C. ROBERTS, MD, and MARK S. BANKOFF, MD

**An isolated anterior echo-free space is generally regarded as a false-positive echocardiographic finding for pericardial effusion. Even when an anterior echo-free space is accompanied by a posterior echo-free space, the echo-free spaces have been occasionally reported to be falsely positive for pericardial effusion, principally in patients with cardiac neoplasms. The basis for these findings has never been adequately explained. In the present study, evaluation by computed tomographic imaging or necropsy examination of 5 patients in whom there was either an anterior or posterior echo-free space or both demonstrated that subepicardial adipose tissue is the echocardiographic imitator of pericardial effusion.**

The presence by cardiac ultrasound of an anterior echo-free space in the absence of a posterior echo-free space represents a combination of findings known to imitate, but seldom indicate, a pericardial effusion.[1,2] Although speculated to result from subepicardial adipose tissue,[1,3,4] an isolated anterior echo-free space has never been established with certainty to result from subepicardial fat. The present report documents by necropsy examination in 1 patient and computed tomographic imaging of the chest in 2 other patients that subepicardial adipose tissue is the basis for the finding of an isolated anterior echo-free space. Furthermore, necropsy findings and results of computed tomography in 2 additional patients suggest that subepicardial adipose tissue is the basis for echocardiograms previously reported as being falsely positive for pericardial effusion in patients with a cardiac neoplasm.

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## Methods

**Computed tomographic imaging** of the chest was performed on a Siemen's Somatom-2 whole body scanner that utilizes a rotating gantry. A complete section scan with a slice thickness of 8 mm was performed in 5 seconds using 125 kV and 46 mA. At least 2 separate windows of varying contrast were viewed at each level. The scale for transparency was −1,000 Hounsfield Units (HU) for air, 0 for water, and +1,000 HU for bone; the attenuation coefficient for any given site was determined by multiple cursor sampling.

**M-mode echocardiography** was performed on either a Smith-Kline or Unirad ultrasonoscope with a 2.55 MHz transducer. Particular care was taken to prevent directing the ultrasonic beam too far medially. A switched-gain ("damping") mechanism[5] was used to evaluate the pericardial space in each patient. Two-dimensional real-time echocardiography was performed with either a mechanical (Hoffrel 201) or phased array (Hewlett-Packard) sector scanner.

Pertinent clinical and necropsy findings in the 4 patients are summarized in Table I and in Figures 1 to 6.

## Discussion

Although the finding of an echo-free space *posterior* to the left ventricular free wall has come to represent the echocardiographic sine qua non for pericardial effusion, the initial description of the use of ultrasound for diagnosing pericardial effusion involved an isolated echo-free space *anterior* to the right ventricular free

**TABLE I Clinical and Necropsy Findings in 5 Patients With Echo-Free Spaces Due to Fat**

| Pt | Age (yr) & Sex | Wt (kg) | Ht (cm) | Prednisone Therapy | Echo-Free Space: Anterior M-Mode | Anterior 2D | Posterior M-Mode | Posterior 2D | Results of Computed Tomography: Ant Fat | Post Fat | Pericardium | Necropsy Findings: Ant Fat | Post Fat | Peri Fluid | Heart Wt |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 88F | 80 | 150 | 0 | + | + | 0 | 0 | + | 0 | NI | – | – | – | – |
| 2 | 56M | 90 | 188 | + | + | – | 0 | – | – | – | – | + | Sm | 0 | 440 |
| 3 | 60F | 114 | 170 | 0 | + | – | + | – | – | – | – | + | + | 0 | 430 |
| 4 | 75F | 50 | 150 | 0 | + | + | 0 | 0 | + | Sm | Thick | – | – | – | – |
| 5 | 66M | 117 | 173 | + | + | + | + | 0 | + | Sm | NI | – | – | – | – |

+ = present; 0 = absent; – = not done; Ant = anterior; F = female; Ht = height; M = male; NI = normal; Peri = pericardial; Post = posterior; Pt = patient; Sm = small; Wt = weight.




**FIGURE 1.** M-mode echocardiogram from Patient 1 shows an isolated anterior echo-free space (Ant EFS) anterior to the right ventricular free wall (RVFW). Chest computed tomogram shows that the echo-free space is due to subepicardial fat interposed between the pericardium (Peri) and right ventricle (RV). AML = anterior mitral leaflet; Ant = anterior; Ao = aorta; ecg = electrocardiogram; L = left; LVFW = left ventricular free wall; Post = posterior; R = right; VS = ventricular septum.

wall.[6] Subsequently, Feigenbaum et al[7,8] demonstrated that the extent of pericardial fluid accumulation must be quite large before an anterior echo-free space is observed, so that it is nearly always associated with a posterior echo-free space. In fact, an anterior echo-free space in the *absence* of a posterior echo-free space was one of the earliest patterns to be recognized as a false-positive finding in the echocardiographic diagnosis of pericardial effusion.[1]

Horowitz et al[2] suggested that such an isolated anterior echo-free space might result from either fibrous tissue or lung interposed between the heart and anterior chest wall. Teichholz[9] suggested that in addition to connective tissue and lung, adipose tissue might be responsible for separating the anterior wall of the right ventricle from the chest wall. Feigenbaum[3] agreed that epicardial fat was the most likely basis for the finding of an anterior echo-free space. While the admonitions of these and other investigators established that the finding of (1) an anterior echo-free space in the absence of a posterior echo-free space is an inadequate diagnostic criterion for the presence of a pericardial effusion, and (2) that the basis for such an isolated anterior

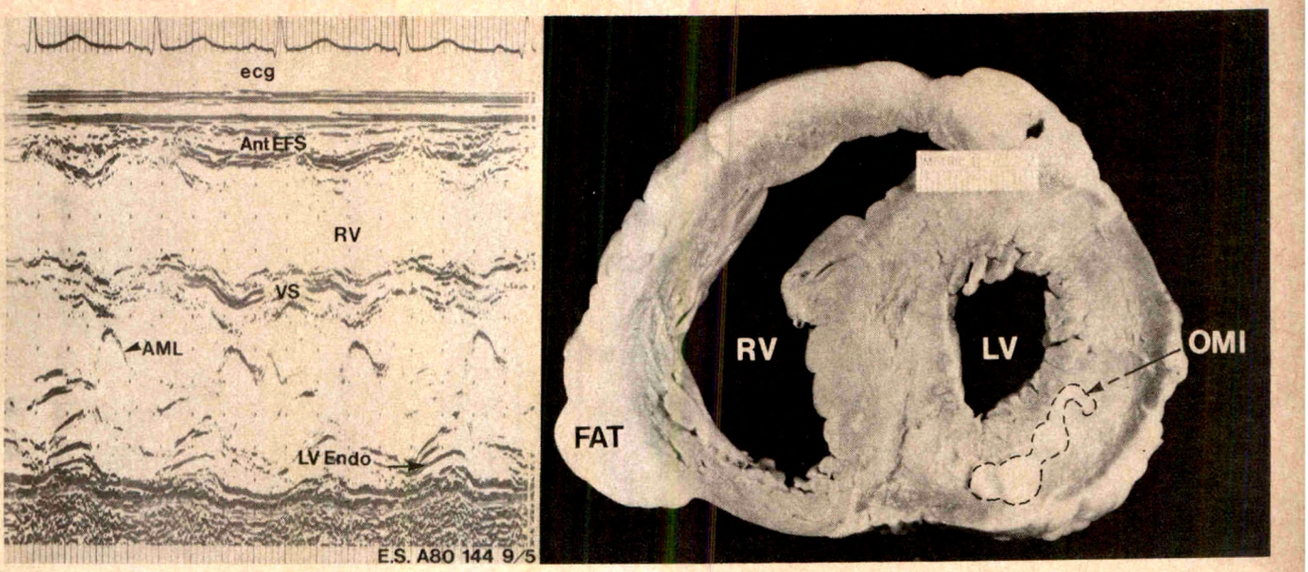



**FIGURE 2.** Patient 2. The anterior echo-free space on an M-mode echocardiogram was due to extensive subepicardial adipose tissue, greater over the anterior right ventricle (RV) than the posterior left ventricle (LV). AML = anterior mitral leaflet; Ant EFS = anterior echo-free space; ecg = electrocardiogram; Endo = endocardium; OMI = old myocardial infarction; VS = ventricular septum.

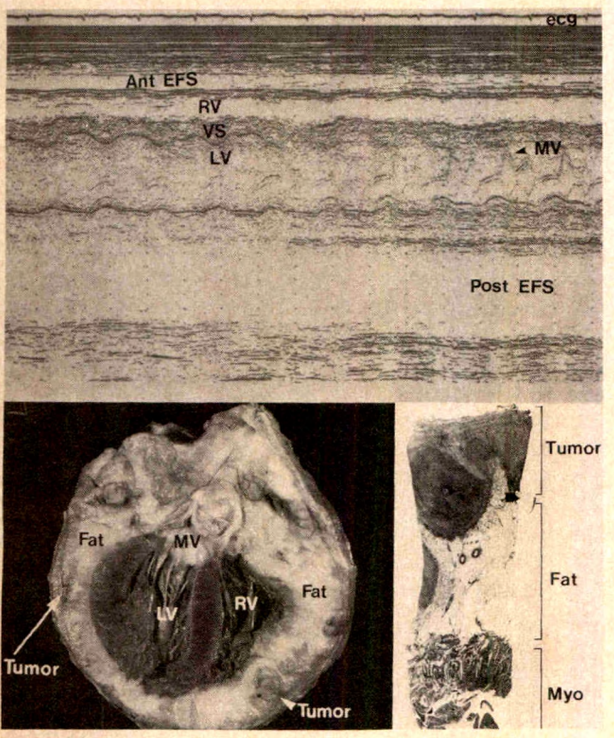



**FIGURE 3.** M-mode echocardiogram (**top panel**) from Patient 3 shows anterior (Ant) and posterior (Post) echo-free space (EFS). A "sweep" from left ventricle to left atrium showed no echo-free space posterior to the left atrium. At necropsy, gross examination of the heart (**bottom left panel**) disclosed no pericardial fluid. Instead, extensive subepicardial fat was interposed between underlying myocardium and metastatic bronchogenic carcinoma. The latter encased the heart in a nearly circumferential manner. Photomicrograph (**bottom right panel**) shows tumor, fat, and underlying myocardium (Myo). (Movat's pentachrome stain; original magnification × 6), reduced 38%. ecg = electrocardiogram; LV = left ventricle; MV = mitral valve; RV = right ventricle; VS = ventricular septum.

echo-free space was likely to be epicardial fat, documentation of the latter has not been previously established. The present study establishes by computed tomographic imaging and necropsy examination that the isolated anterior echo-free space is in fact due to the anterior epicardial fat.

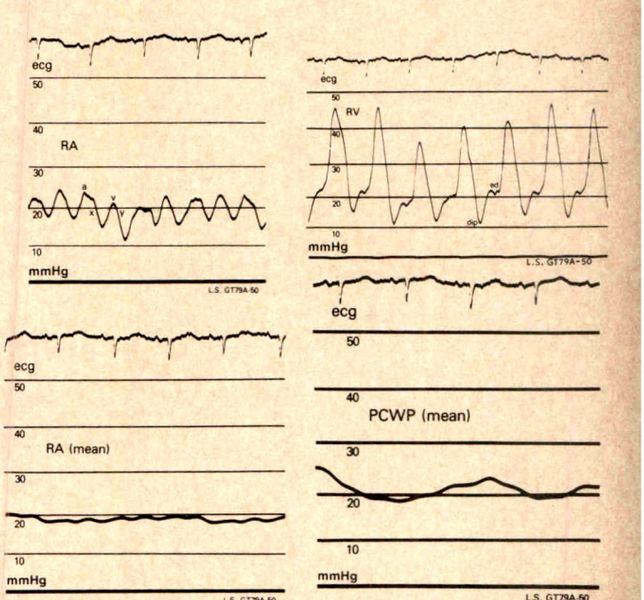



**FIGURE 4.** Hemodynamic recordings from Patient 3. The mean right atrial (RA), right ventricular (RV) end-diastolic, and mean pulmonary capillary wedge (PCWP) pressures are equal. The RA phasic trace (**top left**) has an M-shaped contour with a steep *y* descent. The RV pressure contour has an initial dip, followed by a short end-diastolic (ed) plateau. These hemodynamic findings documented constrictive/restrictive physiology secondary to tumor encasement of the heart. ecg = electrocardiogram.

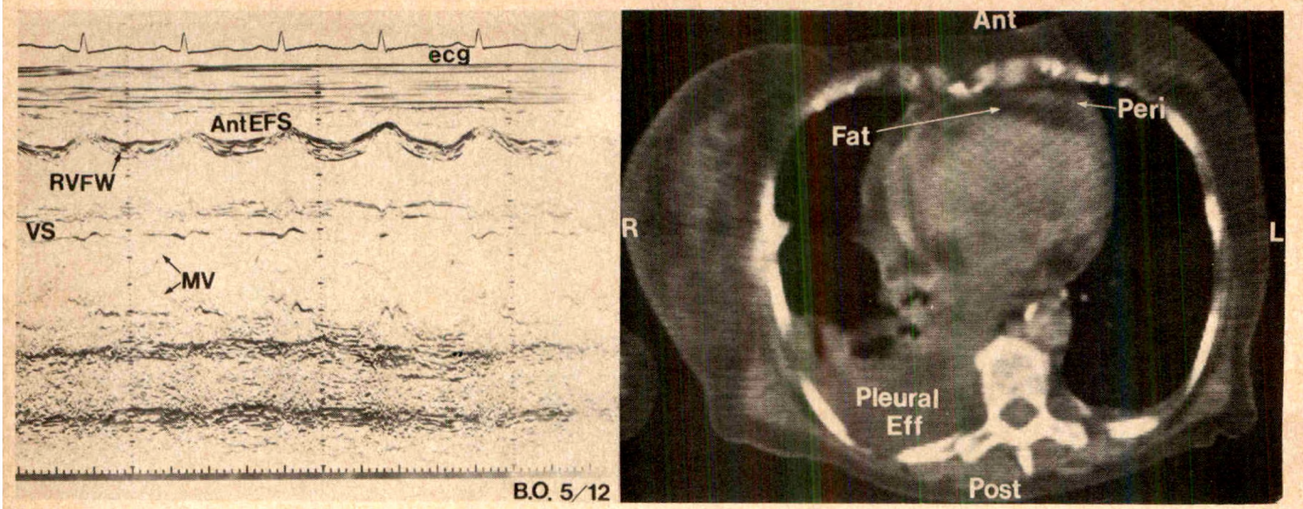



**FIGURE 5.** M-mode echo and computed tomographic scan from Patient 4. The M-mode echocardiogram shows an anterior relatively echo-free space (Ant EFS). Chest computed tomogram shows this to be due to fat underlying the pericardium (Peri); the pericardium itself is thickened by presumed metastatic bronchogenic carcinoma. The posterior echo-free space was related to the pleural effusion (Pleural Eff) seen on computed tomography. Ant = anterior; ecg = electrocardiogram; L = left; MV = mitral valve; Post = posterior; R = right; RVFW = right ventricular free wall; VS = ventricular septum.

The amount of subepicardial fat generally increases with age.[10] These deposits are characteristically most extensive over the anterior portion of the heart—in contrast to the *posterior* heart—a fact which explains the propensity for extensive subepicardial fat to produce an *anterior* echo-free space in the absence of a *posterior* echo-free space. While the extent of the fat is not necessarily related to the adipose content of other body tissues, the extent of subepicardial fat tends to be greater in obese individuals; 4 of our 5 patients were in fact obese (Table I). Endogenous or exogenous steroid excess (for example, long-term administration of high-dose steroid therapy) constitutes another setting in which an increased amount of subepicardial fat is commonly seen.[11] This factor may have played a role in the excessive amount of subepicardial adipose tissue in Patients 2 and 5 (Table I).

The unique capabilty of computed tomography to identify relative tissue density makes this diagnostic technique ideal for determining the basis of relatively sonolucent spaces visualized by cardiac ultrasound.[12] The relatively low attenuation coefficient of fat (−60 to −100 HU) established with certainty that the isolated anterior echo-free space in Patients 1 and 5 was due to subepicardial fat. A similar echocardiographic finding in Patient 2 was confirmed at necropsy. Although necropsy examination in the latter patient was performed over 1 year after the last M-mode echocardiogram, the absence of any posterior echo-free space on any of the multiple echocardiograms recorded and the finding at necropsy of normal visceral and parietal pericardia suggest that the anterior echo-free space resulted from the excessive amount of fat seen at necropsy rather than a transient pericardial effusion. In Patients 1, 2, and 5, the characteristically greater distribution of fat over the anterior, as opposed to the posterior, surface of the heart resulted in an isolated anterior echo-free space by cardiac ultrasound. In Patients 2 and 5, a small amount of posteriorly located fat appeared to result in a small posterior echo-free sliver with the boundary lines moving in parallel during systole and diastole. The finding of an anterior echo-free space that is out of proportion to an associated posterior echo-free space is therefore a valuable clue to the possibility that such echo-free spaces represent fat rather than fluid.

In contrast to the finding of an isolated anterior echo-free space, the finding of an isolated posterior echo-free space, provided it persists through ventricular diastole as well as systole, has been shown to be a reliable indicator of pericardial effusion.[2] As mentioned above, the finding of an anterior echo-free space in combination with a posterior echo-free space generally indicates a large effusion.[2,7,8] Even in the situation in which both an anterior and posterior echo-free space are observed together, however, echocardiograms may be falsely positive for a pericardial effusion, particularly as the result of a cardiac neoplasm.[13–16] The explanation for this association is poorly understood. In the patient reported by Lin et al,[15] the false-positive echo-free space seen anteriorly and posteriorly was attributed to the type of neoplasm encasing the heart (angiosarcoma with a rich vascular component). Millman et al[13] described 3 patients with metastatic carcinoma or lymphoma in whom a sonolucent space posterior to the left ventricle was unassociated with pericardial effusion at operation or necropsy. These authors also attributed the echo-free space to the neoplasm itself, suggesting that the acoustic impedence of the neoplasm might be the same as that of pericardial fluid. Come et al[16] reported 3 patients with metastatic tumor involving the pericardium. All 3 had a posterior echo-free space and 2 had both anterior and posterior echo-free spaces. In 1 patient, a 62-year-old man with lymphoma encasing the heart in whom there was both an anterior and posterior echo-

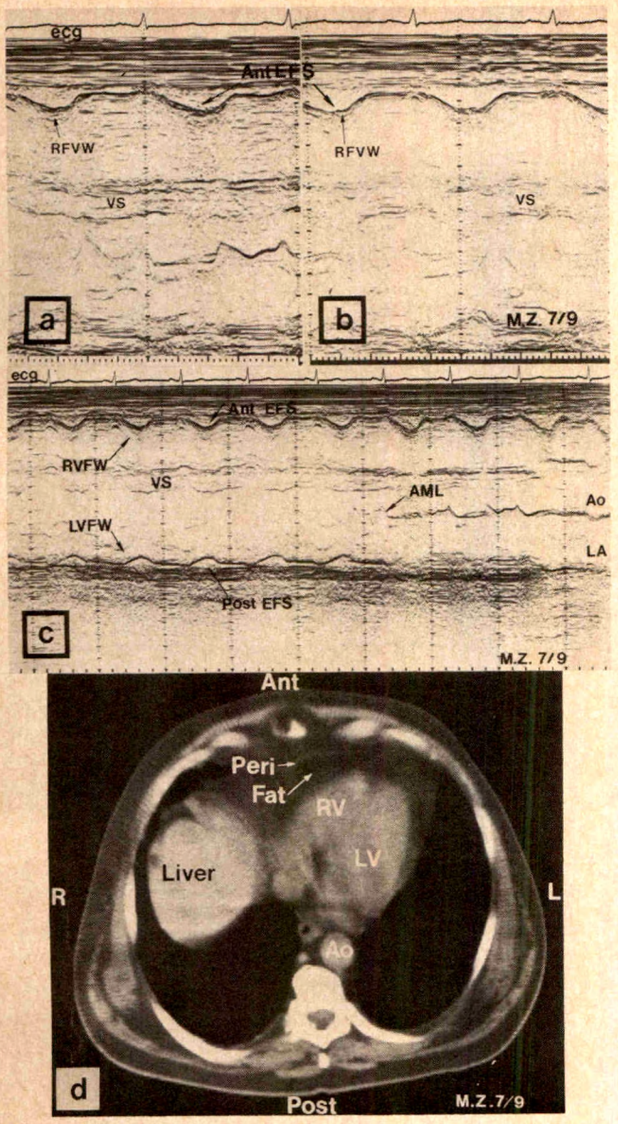



**FIGURE 6.** M-mode echocardiogram and computed tomographic scan from Patient 5. **a and b,** M-mode echocardiograms at 2 different gain settings each show an anterior (Ant) relatively echo-free space (EFS) anterior to the right ventricular free wall (RVFW). **c,** M-mode echocardiographic "sweep" from the left ventricular free wall (LVFW) to the left atrium (LA) shows a small posterior (Post) echo-free space in addition to an anterior echo-free space. **d,** computed tomographic scan shows that an anterior space on the M-mode echocardiogram is due to extensive subepicardial fat anterior to the right ventricle (RV), while a small posterior echo-free space is due to a small amount of fat posterolateral to the left ventricle (LV). AML = anterior mitral leaflet; Ao = aorta; ecg = electrocardiogram; L = left; Peri = pericardium; R = right; VS = ventricular septum.

free space, ". . . the epicardial fat pad was seen to lie several centimeters within the anterior heart border on the lateral film." In a second patient with metastatic squamous cell carcinoma, the posterior echo-free space ". . . was seen only at the junction of the left atrium and left ventricle . . .," that is, the atrioventricular sulcus where deposits of adipose tissue are generally extensive.

Necropsy findings and examination by computed tomographic imaging in Patients 3 and 4, respectively, demonstrate that subepicardial fat is the basis for the ability of neoplasms encasing the heart to simulate pericardial effusion on cardiac ultrasound. In Patient 3, generalized obesity was associated with extensive subepicardial fat that completely encased the heart, before superimposed encasement by metastatic bronchogenic carcinoma. The nearly circumferential deposits of subepicardial adipose tissue and the obliteration of the nonfluid filled pericardial cavity at necropsy demonstrate that fat was the basis for the echo-free space on this patient's echocardiogram. The tumor in this patient further simulated pericardial heart disease by causing physiologic constriction, a finding observed previously in patients with cardiac encasement by metastatic neoplasm.[14] In Patient 4, the capability of computed tomography to accurately identify tissue density again demonstrated that subepicardial adipose tissue interposed between encasing metastatic bronchogenic carcinoma and underlying myocardium was the basis for the echo-free space in this patient's M-mode and 2-dimensional echocardiograms.

Finally, the results of this computed tomographic and necropsy study suggest that caution must be observed in evaluating relatively sonolucent spaces in elderly obese patients who have no clinical evidence of pericardial heart disease. Findings in Patients 1, 4, and 5 also underscore the utility of computed tomography in clarifying the basis of an apparent echo-free space on cardiac ultrasound examination in patients in whom the finding is either unexpected or contrary to available clinical information.

## References

1. **Feigenbaum H.** Ultrasound diagnosis of pericardial effusion. First World Congress of Ultrasonic Diagnostics in Medicine, Vienna, June, 1969. Vienna Academy of Medicine Publishing Department. Chest 1969;55:59–62.
2. **Horowitz MS, Schultz CS, Stinson EB, Harrison DC, Popp RL.** Sensitivity and specificity of echocardiographic diagnosis of pericardial effusion. Circulation 1974;50:239–247.
3. **Feigenbaum H.** Echocardiography. 3rd ed. Philadelphia: Lea & Febiger, 1981:478–504.
4. **Ellis K, King DL.** Pericarditis and pericardial effusion: radiologic and echocardiographic diagnosis. Radiol Clin North Am 1973;11:393–413.
5. **Griffith JM, Henry WL.** Switched gain: a technique for simplifying ultrasonic measurement of cardiac wall thickness. IEEE Trans Biomed Eng 1975; 22:337–340.
6. **Edler I.** Diagnostic use of ultrasound in heart disease. Acta Med Scand 1955;308:32–36.
7. **Feigenbaum H, Waldhausen JA, Hyde LP.** Ultrasound diagnosis of pericardial effusion. JAMA 1965;191:107–110.
8. **Feigenbaum H.** Echocardiographic diagnosis of pericardial effusion. Am J Cardiol 1970;26:475–479.
9. **Teichholz LE.** Echocardiographic evaluation of pericardial diseases. Prog Cardiovasc Dis 1978;21:133–140.
10. **Roberts WC, Spray TL.** Pericardial heart disease. Curr Probl Cardiol 1977;2:1–71.
11. **Bulkley BH, Roberts WC.** The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy. A study of 36 necropsy patients. Am J Med 1975;58:243–264.
12. **Isner JM, Carter BL, Bankoff, MS, Konstam MA, Salem DN.** Computed tomography in the diagnosis of pericardial heart disease. Ann Intern Med 1982;97:373–379.
13. **Millman A, Meller J, Motro M, Blank HF, Horowitz I, Herman MV, Teicholz LE.** Pericardial tumor or fibrosis mimicking pericardial effusion by echocardiography. Ann Intern Med 1977;86:434–436.
14. **Foote WC, Jefferson CM, Price HL.** False-positive echocardiographic diagnosis of pericardial effusion. Result of tumor encasement of the heart simulating constrictive pericarditis. Chest 1977;71:546–549.
15. **Lin TK, Stech JM, Eckert WG, Lin JJ, Farha SJ, Hagan CT.** Pericardial angiosarcoma simulating pericardial effusion by echocardiography. Chest 1978;73:881–883.
16. **Come PC, Riley MF, Fortuin NJ.** Echocardiographic mimicry of pericardial effusion. Am J Cardiol 1981;47:365–370.

# Exercise-Induced Cardiac Dysfunction in Sickle Cell Anemia

## A Radionuclide Study

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**Cardiac performance was studied by radionuclide angiography at rest and during exercise in 22 adolescents with sickle cell (SC) anemia and the results were compared with those in 12 control subjects. At rest, cardiac contractility was normal; cardiac output and end-diastolic volume were increased. At maximal exercise, heart rate, cardiac output response, and work capacity were reduced; the reduction was related to the degree of anemia. Left ventricular end-diastolic volume decreased with exercise most markedly in patients with ischemic exercise electrocardiograms. An abnormal ejection fraction response to exercise occurred in 4 patients; electrocardiographic signs of ischemia developed in all 4, and wall motion abnormalities in 2. Those patients who had electrocardiographic signs of ischemia had a significantly lower heart rate, ejection fraction, and cardiac output response to exercise, and a lower hematocrit level than subjects with normal results on exercise electrocardiography. The increase in cardiac output was not sufficient to maintain a normal level of exercise. The decrease in end-diastolic volume suggests that diastolic function was abnormal during exercise. Cardiac dysfunction was manifested by an abnormal ejection fraction response, wall motion abnormalities, and incomplete left ventricular filling during exercise.**

Sickle cell anemia is associated with cardiomegaly,[1] left ventricular hypertrophy,[2] and decreased work capacity.[3] Controversy exists as to whether there is a specific pathologic process involving the myocardium which is associated with SC anemia. Despite pathologic data which suggest that there is no myocardial abnormality specific for SC disease,[4] there is mounting evidence of a functional abnormality. Rees et al[5] found decreased left ventricular contractility with echocardiography in one third of children tested. Alpert et al[3] demonstrated an ischemic electrocardiographic response in 15% of SC patients undergoing exercise testing. Cardiac dysfunction secondary to hemosiderosis has been demonstrated in thalassemic patients,[6] but no study of cardiac function has been reported for a large group of children with other types of anemia for comparison with the SC population. This study was undertaken to further characterize the functional abnormality seen in children and young adults with SC anemia.

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### Methods

Eleven male and 11 female adolescents and young adults with homozygous SC anemia were studied. Their ages ranged from 10 to 22 years (mean 15.3). No patient had had a crisis or transfusion in the 3 weeks before testing. Exercise testing without radionuclide evaluation had been performed in the past in 21 of 22. Eleven patients had previously abnormal or equivocal exercise electrocardiogram findings[3]; 10 had normal exercise electrocardiographic results previously. The patient who had not been exercised had an atrial septal defect and left ventricular aneurysm in addition to SC anemia. The current study was performed 5 to 6 years after the initial exercise test in 17 patients and 1 year after in 4 (Table I).

Extensive data are available from our laboratory for physical work capacity and heart rate response to exercise in healthy black children.[7] Radionuclide measurements for *normal children* during upright exercise are unavailable. For

**TABLE I Serial Exercise Data***

| Patient | Maximal Heart Rate (beats/min) | | | Work Capacity (kg-m/min/kg) | | | Exercise ECG Results | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1975 | 1980 | 1981 | 1975 | 1980 | 1981 | 1975 | 1980 | 1981 |
| 1 | 184 | 178 | ... | 6.6 | 10.2 | ... | B | B | ... |
| 2 | 170 | 153 | ... | 14.0 | 12.8 | ... | A | A | .. |
| 3 | ... | 150 | ... | ... | 5.3 | ... | ... | A | ... |
| 4 | 180 | 180 | ... | 10.3 | 9.2 | ... | B | N | ... |
| 5 | 195 | 170 | ... | 9.8 | 8.3 | ... | N | N | ... |
| 6 | 190 | 168 | ... | 10.1 | 9.0 | ... | A | N | ... |
| 7 | 144 | 135 | ... | 4.3 | 4.3 | ... | A | A | ... |
| 8 | 150 | 155 | ... | 10.4 | 8.4 | ... | B | N | ... |
| 9 | 180 | 173 | ... | 12.9 | 8.3 | ... | N | N | ... |
| 10 | 178 | 173 | ... | 8.3 | 7.1 | ... | A | A | ... |
| 11 | 200 | 205 | ... | 22.3 | 11.8 | ... | B | N | ... |
| 12 | 163 | ... | 170 | 8.0 | ... | 7.1 | N | ... | N |
| 13 | 190 | ... | 190 | 13.6 | ... | 10.8 | B | ... | N |
| 14 | 180 | ... | 190 | 6.4 | ... | 8.6 | A | ... | N |
| 15 | 173 | ... | 163 | 11.8 | ... | 10.5 | N | ... | N |
| 16 | 190 | ... | 173 | 11.0 | ... | 11.0 | B | ... | N |
| 17 | ... | 175 | 170 | ... | 14.0 | 12.9 | ... | N | N |
| 18 | 182 | ... | 180 | 10.3 | ... | 8.1 | N | ... | N |
| 19 | ... | 160 | 160 | ... | 10.7 | 12.9 | ... | N | N |
| 20 | ... | 175 | 180 | ... | 7.8 | 7.1 | ... | N | N |
| 21 | 179 | ... | 175 | 13.0 | ... | 8.8 | N | ... | N |
| 22 | ... | 159 | 140 | ... | 7.0 | 6.7 | ... | N | A |

* The earlier study is the nonradionuclide exercise test.
A = abnormal; B = borderline; ECG = electrocardiographic; N = normal.

this reason normal values were established for our laboratory. The control group included 12 adolescents referred to cardiac catheterization. The diagnoses included chest pain of undetermined cause, postoperative study after repair of a congenital heart defect, and mild valvular stenosis or insufficiency. All children were demonstrated to have normal left ventricular function at catheterization and had normal exercise test results. Six were black and 6 were white. No significant differences were noted in radionuclide measurements by race.

A continuous, graded *nuclear stress test* was performed with the subject sitting on a mechanically braked cycle ergometer (Monarch). Patients pedaled against a constant resistance during 3-minute stages, maintaining a speed of 60 to 70 rpm. Work loads were based by weight on those expected of normal subjects as described by Strong et al.[7] Subjects weighing <30 kg performed work loads of 75, 150, and 300 kg-m/min if they completed stages I to III, respectively. Those subjects weighing 30 to 40 kg performed work loads of 150, 300, and 450 kg-m/min. The larger subjects weighing 41 to 60 kg performed work loads of 300, 450, and 600 kg-m/min. Patients were exercised to exhaustion. Leads $V_5$, $V_1$, and aVF were monitored continuously. Myocardial ischemia was assessed by use of the P-R isoelectric line because of the low incidence of false-positive results with this method in previous studies on healthy black children.[8] A definitely ischemic test consisted of a downsloping S-T segment during the initial 60 to 80 ms with or without J-point depression, or a flat S-T segment (zero slope) with J-point depression. A borderline ischemic test consisted of a flat S-T segment without J-point depression, or an upsloping S-T with J-point depression. One test was interrupted (Patient 22) due to concern about the subject's condition. She had 2 mm J-point depression at the time in lead $V_5$ at a work load nearly equal to the maximal work performed during a previous exercise test.

Radionuclide studies were performed with a portable gamma camera (Technicare Sigma 420), interfaced with a portable computer (Medical Data Systems). A Brattle physiologic gate was used to trigger the system. Gated equilibrium radionuclide studies (MUGX) were performed at rest and

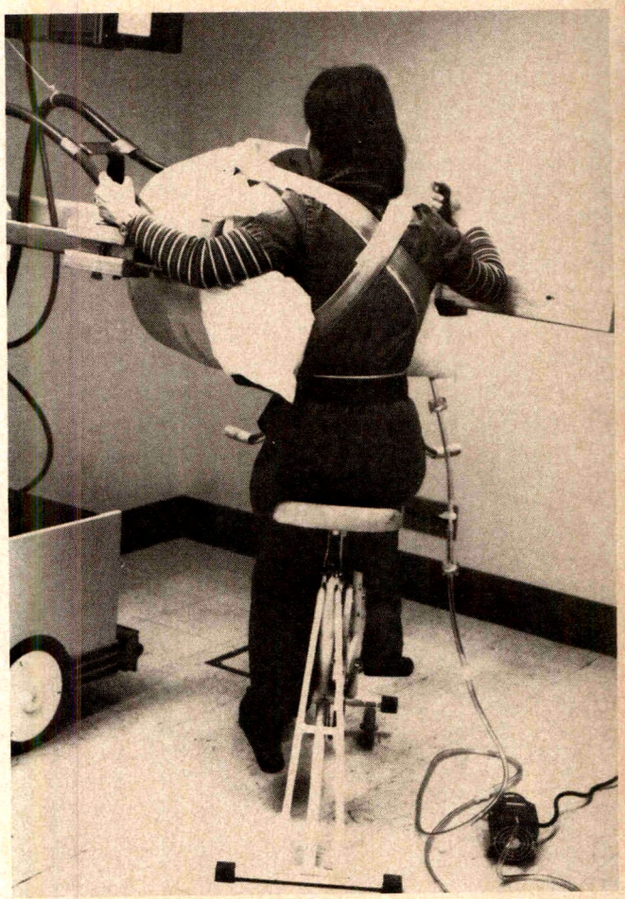


**FIGURE 1.** The adjustable wedge mold and harness permits appropriate positioning of the gamma camera and eliminates patient-detector motion. The mold is a plastic pillow filled with polystyrene beads which becomes hard in the molded configuration when a vacuum is applied. Three straps form the harness.

during the last 2 minutes of each 3-minute exercise stage. Technetium-99m albumin (0.3 mCi/kg) was administered intravenously just before positioning the patient on the bicycle (approximately 20 minutes before exercise). A high sensitivity, parallel hole collimator was placed within 2 cm of the chest wall. Zoom mode was not utilized. The patients were maintained in the proper left anterior obliquity (where the collimator was perpendicular to the interventricular septum), and motion was eliminated by using an adjustable wedge mold and harness (Fig. 1). Previous studies in our laboratory using radioopaque markers on exercising volunteers confirmed the elimination of motion with this device.[9] Left ventricular areas and background were automatically selected with the MUGX program.[10] This method was successfully applied to 96% of ejection fraction measurements. Ejection fraction and end-diastolic counts were determined at rest and during each exercise stage. Changes in end-diastolic counts from rest were assumed to reflect changes in ventricular volume, and changes in counts ejected/minute to reflect changes in cardiac output.[11] Cardiac cycles were divided into 14 frames. Count rates were adjusted to take into account varying times/frame and number of cycles processed as heart rate increased. Left ventricular end-diastolic volume and cardiac index at rest were expressed as unity, and volume and output during exercise were expressed as multiples of resting values. Wall motion abnormalities were detected by viewing the cineangiographic format of the equilibrium studies in a blinded fashion without knowledge of the ejection fraction data and subsequently by overlaying edge images from end-systole and end-diastole.

M-mode echocardiograms were obtained with an Irex echocardiograph just before exercise to assess left ventricular volume. Standard echocardiographic techniques were used.[12] Left ventricular volume was calculated from the end-diastolic dimension as described by Meyer et al.[13] Values derived from echocardiograms were compared with those performed in our laboratory of healthy black children of comparable body surface area.

**Statistical analysis:** Selected exercise and physical measurements were correlated with one another using Pearson's product moment correlation coefficient (r). Exercise data for the nonischemic SC group, the ischemic group, and the control group were compared using a $t$ test for 2 independent means. The null hypotheses that were tested were that the means did not differ, requiring a 2-tailed test significance. Changes in serial exercise data were tested with paired $t$ tests using 2-tailed tests of significance. The values shown represent the mean ± standard deviation.

## Results

**Resting measurements:** The mean upright resting radionuclide left ventricular ejection fraction was 0.60 ± 0.08 (control values 0.67 ± 0.08, p = NS). Resting heart rates (85 ± 9 beats/min) were normal.[7] Echocardiography revealed left ventricular enlargement in all patients (volume 114 ± 35 ml/m$^2$, normal for our laboratory 58 ± 25 ml/m$^2$). Since resting heart rates and ejection fractions were normal, the marked left ventricular volume overload would of necessity result in abnormally high stroke volumes and cardiac outputs. Though the elevated cardiac outputs and dilated ventricles were likely due to the anemia, these measurements did not correlate significantly with hematocrit.

**Serial exercise data (Table I):** A 5 to 6 year interval between tests in 17 patients, and 1 year interval in 4 revealed a significant decrease in maximal heart rate (p = 0.02). Maximal heart rate continued to be abnormally low, compared with values from our laboratory in normal black children (Table II) reported previously (previous exercise 176 ± 14 beats/min, nuclear exercise 170.5 ± 16). Though no change was noted in work capacity when all 21 studies were reviewed, a significant decrease was noted (p = 0.034) when only those with a

**TABLE II Comparison of Sickle Cell Patients With and Without Electrocardiographic Signs of Ischemia at Maximal Exercise With Reported Normal Values and With Radionuclide Data From the Control Group**

| Exercise Measurements | SC Anemia | | | | | Normal | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Abnormal Ex ECG | | | Normal Ex ECG | | Male | | Female | |
| | Mean | SD | p* | Mean | SD | Mean | SD | Mean | SD |
| Hematocrit | 20.7 | 2.1 | 0.036 | 24.8 | 3.4 | (40–54)† | | (37–47) | |
| Work capacity (kg-m/min/kg) | 7.7 | 3.6 | 0.144 | 9.6 | 1.8 | 17.2[7] | 3.5 | 14.4 | 3.1 |
| Maximal heart rate (beats/min) | 150 | 17 | 0.003 | 175 | 12 | 191[7] | 10 | 191 | 10 |

| Radionuclide Measurements | SC Anemia | | | | | Controls | | |
|---|---|---|---|---|---|---|---|---|
| | Abnormal Ex ECG | | | Normal Ex ECG | | | | |
| | Mean | SD | p | Mean | SD | Mean | SD | p§ |
| Maximal ejection fraction | 0.62 | 0.06 | 0.023 | 0.73 | 0.08 | 0.81 | 0.07 | 0.0008 |
| Maximal cardiac output‡ | 1.60 | 0.40 | 0.004 | 2.30 | 0.30 | 2.80 | 0.26 | 0.00001 |
| Left ventricular diastolic volume at maximal exercise‡ | 0.85 | 0.09 | 0.245 | 0.94 | 0.03 | 1.00 | 0.10 | 0.05 |

* Significant differences between SC patients with or without an abnormal Ex ECG (exercise electrocardiogram).
† Reported range for adolescents (Vaughan VC, McKay RJ, Nelson WE. Textbook of Pediatrics. Philadelphia: WB Saunders, 1975).
‡ Expressed as a multiple of fraction of the same measurement at rest.
§ Significant differences between sickle cell and control patients.
SD = standard deviation.

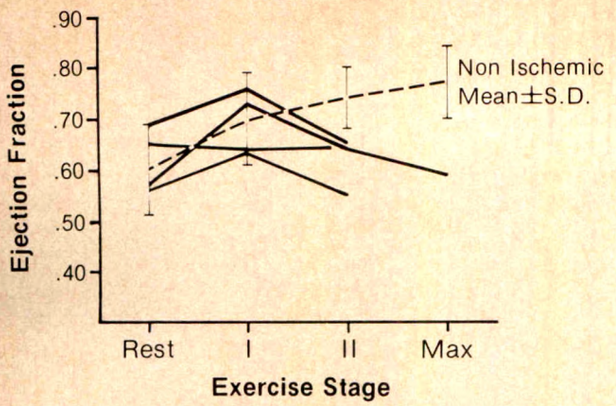



**FIGURE 2.** Ejection fraction response to exercise. The SC patients with electrocardiographic signs of ischemia during exercise are plotted individually. The **dashed line** represents the mean ± standard deviation (SD) for the SC patients with normal exercise electrocardiograms.

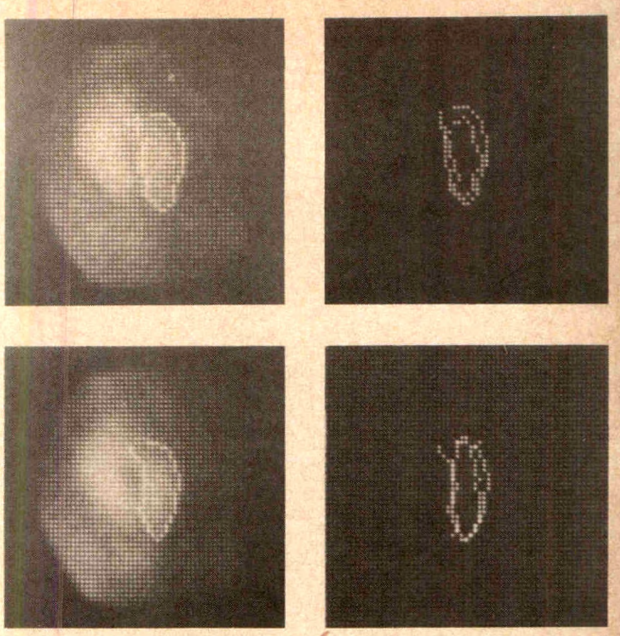


**FIGURE 3.** Gated equilibrium images at rest (**top panels**) and on maximal exercise (**bottom panels**) to demonstrate wall motion abnormalities. **Left panels,** the end-diastolic image is shown with the left ventricular edge, as defined by the automated edge detection program, superimposed. Note the decrease in diastolic chamber size from rest to maximal exercise. **Right panels,** the diastolic and systolic edge images are superimposed. Note that symmetrical contraction results in a concentric appearance at rest. At maximal exercise the apex is akinetic, resulting in a lack of separation of edges.

5 to 6 year follow-up were included. Though these were statistically significant changes, they were not clinically significant. Work capacity defined as kg-m/min/kg was decreased when compared with values in normal black children (before exercise in males 10.8 ± 2.7, females 10.4 ± 4.9; nuclear exercise in males 10.2 ± 1.9, females 8.2 ± 2.3). Work capacity was correlated with hematocrit ($r = 0.50$, $p < 0.02$).

The exercise electrocardiographic results during the radionuclide study showed definite ischemia in 5 and equivocal ischemia in 1, and was normal in 16 subjects. The exercise electrocardiogram of only 1 patient of 21 became abnormal during the 4.6 years (mean) study period, while 7 improved (Table I). It is unclear why 2 of 7 abnormal tests were subsequently normal, but the 5 borderline tests that became normal demonstrate the lack of reliability of the borderline category.

**Radionuclide data:** The exercise response of subjects without evidence of ischemia on their exercise electrocardiograms consisted of a stepwise increase in ejection fraction. The mean increase from rest to maximum was 0.14 ± 0.08. Maximal exercise was reached during stage II by 17 patients; 3 reached stage III and 2 reached stage IV. There were no significant differences in ejection fraction between subjects with normal and abnormal exercise electrocardiograms at rest and stage I of exercise. Subsequently, in 3 of 4 patients with electrocardiographic evidence of ischemia, ejection fraction decreased >5% in the presence of an increasing heart rate and effort. Ejection fractions were essentially unchanged from resting values at maximal exercise in these 4 patients (Fig. 2). The fifth ischemic test (Patient 22) was interrupted due to concern about the subject's condition before the ejection fraction could be obtained. Patients with electrocardiographic signs of ischemia had significantly lower heart rate, ejection fraction, and cardiac output responses to exercise as well as lower work capacity and hematocrit (Table II).

Observation of the cineangiographic mode of the gated equilibrium scans revealed wall motion abnormalities in 2 of the patients with ischemic tests. Patient 3 had a dyskinetic apical area at rest. Patient 10 had normal wall motion at rest; an akinetic area was identified at maximal exercise in the left anterior oblique projection (Fig. 3).

Cardiac output achieved was significantly correlated with heart rate ($r = 0.67$, $p < 0.003$). Work capacity was related to the percent increase in cardiac output from rest ($r = 0.50$, $p < 0.05$). The cardiac output response was most severely impaired in those patients with the lowest hematocrit levels ($r = 0.52$, $p < 0.03$). Though resting outputs were high, performance was related to the relative increase in output from rest, which was significantly less than expected (Table II).

Left ventricular end-diastolic volume (based on end-diastolic counts) was unchanged from resting values to stage I of exercise, but decreased from stage I to maximal exercise (assume resting volume = 1, stage I = 1.0 ± 0.10, maximal exercise = 0.91 ± 0.12) (Table III). Normally no change in diastolic volume is seen in our laboratory at maximal exercise. A decrease in end-diastolic volume at maximum was associated with a reduced cardiac output response ($r = 0.57$, $p < 0.02$). At maximum, the decrease in left ventricular volume was even more marked in the ischemic group than in the SC patients with normal exercise electrocardiographic results (Table II).

## Discussion

This study was designed to document and further define the cardiac dysfunction associated with SC anemia. Although Gerry et al[14] found no evidence of left

**TABLE III Radionuclide Data**

| | Rest | | Stage I | | | Maximal Exercise | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | HR | EF | HR | EF | LVV | HR | EF | LVV | CO | PWC | HCT |
| 1 | 80 | 0.61 | 129 | 0.69 | 0.93 | 178 | 0.70 | 1.14 | 2.9 | 10.2 | 23.2 |
| 2 | 68 | 0.69 | 130 | 0.76 | 1.00 | 153 | 0.66† | 0.92 | 2.0 | 12.8 | 20.7 |
| 3* | 90 | 0.57 | 128 | 0.73 | 1.21 | 150 | 0.59† | 0.70 | 1.2 | 5.3 | 18.2 |
| 4 | 90 | 0.57 | 155 | 0.78 | 0.98 | 180 | 0.76 | 0.87 | 2.3 | 9.2 | 20.2 |
| 5 | 89 | 0.63 | 130 | 0.68 | 1.16 | 170 | 0.74 | 0.86 | 1.9 | 8.3 | 20.8 |
| 6 | 84 | 0.58 | 129 | 0.65 | 0.91 | 168 | 0.64 | 0.92 | 2.0 | 9.0 | 23.3 |
| 7 | 89 | 0.56 | 130 | 0.63 | ... | 135 | 0.55* | 0.89 | 1.3 | 4.3 | 18.7 |
| 8 | 80 | 0.56 | 135 | 0.63 | 0.98 | 155 | 0.67 | 0.92 | 2.1 | 8.4 | 20.3 |
| 9 | 82 | 0.59 | 145 | ... | 1.15 | 173 | 0.65 | 1.12 | 2.6 | 8.3 | 25.3 |
| 10 | 88 | 0.65 | 148 | 0.64 | 0.85 | 173 | 0.64† | 0.75 | 1.5 | 7.1 | 20.0 |
| 11 | 100 | 0.47 | 152 | 0.66 | 0.98 | 205 | 0.74 | 0.90 | 2.9 | 11.8 | 30.0 |
| 12 | 92 | 0.66 | 140 | ... | ... | 170 | 0.73 | ... | ... | 7.1 | 21.5 |
| 13 | 105 | 0.65 | 135 | 0.69 | 0.95 | 190 | 0.87 | 0.91 | 2.2 | 10.8 | 25.0 |
| 14 | 85 | 0.46 | ... | ... | ... | 190 | 0.67 | ... | ... | 8.6 | 31.1 |
| 15 | 95 | 0.62 | 123 | 0.58 | 0.90 | 163 | 0.78 | 0.88 | 1.9 | 10.5 | 27.4 |
| 16 | 73 | 0.82 | 147 | 0.89 | 1.10 | 173 | 0.88 | 0.87 | 2.1 | 11.0 | 29.0 |
| 17 | 70 | 0.58 | 150 | 0.64 | 1.14 | 170 | 0.66 | 0.94 | 2.6 | 12.9 | 25.4 |
| 18 | 80 | 0.61 | 160 | 0.82 | 0.89 | 180 | 0.81 | 0.77 | 2.3 | 8.1 | 23.5 |
| 19 | 75 | 0.58 | 130 | 0.63 | ... | 160 | 0.67 | 0.89 | 2.2 | 12.9 | 27.0 |
| 20 | 90 | 0.63 | 180 | 0.70 | 0.92 | 180 | 0.68 | 1.11 | 2.4 | 7.1 | 21.8 |
| 21 | 84 | 0.53 | 175 | 0.82 | ... | 175 | 0.83 | ... | ... | 8.8 | 26.4 |
| 22 | 87 | 0.59 | 102 | 0.63 | ... | ... | Interrupted test | ... | ... | 6.7 | 23.6 |
| Mean | 85 | 0.60 | 141 | 0.70 | 1.0 | 171 | 0.72 | 0.91 | 2.1 | 9.1 | 23.7 |

* Excluded from data analysis due to additional abnormalities.
† Electrocardiographic evidence of ischemia.
CO = cardiac output expressed as a multiple of resting output; EF = radionuclide ejection fraction; HCT = hematocrit (%); HR = heart rate (beats/min); LVV = left ventricular diastolic volume expressed as a multiple of resting volume; PWC = physical work capacity (kg-m/min/kg).

ventricular dysfunction in an echocardiographic study of adult patients with SC disease and no myopathic changes in an autopsy series,[4] we have previously reported echocardiographic evidence for left ventricular dysfunction in children with SC anemia.[5] We have also noted a decreased working capacity and heart rate response to sitting bicycle exercise.[3] Electrocardiographic signs of ischemia were identified during exercise in 15% of children tested.[3]

In the current study, no progression in exercise electrocardiographic abnormalities was found in the 4.6 year follow-up period. Electrocardiographic signs of ischemia were, however, related to a specific cardiac dysfunction (abnormal ejection fraction response). This provided nonelectrocardiographic confirmation of an exercise-induced abnormality. The consistent association of ischemia and abnormal ejection fraction response supports the validity of the P-R isoelectric line method of defining electrocardiographic ischemia. Use of the P-Q junction to P-Q junction would have resulted in a greater number of electrocardiograms being interpreted as ischemic in the absence of an abnormal ejection fraction response. The cardiac dysfunction was associated with wall motion abnormalities in 2 of our patients.

The data presented provide insight into the hemodynamic response to exercise in a group of patients with SC anemia. At maximal exercise a normal adult should be able to triple resting cardiac output.[15] The patients with SC anemia had high resting outputs and were unable to raise their outputs to the extent that normal subjects do. Their working capacity was related to the relative increase in cardiac output from rest to maximum, rather than the absolute output. This is understandable since the high resting outputs were due to a reduced oxygen-carrying capacity seen with hemoglobins in the 7 to 8 g/100 ml range.[16] Meeting the increased demands of maximal exercise would logically require a tripling of the already high cardiac outputs. Work capacity and the relative increase in cardiac output with exercise were dependent on the degree of anemia.

Of interest is that those persons with the most severe anemia, poorest performance (reduced heart rate and cardiac output response and work capacity), and electrocardiographic signs of ischemia had a decrease in left ventricular end-diastolic volume at maximal exercise. In coronary disease[16] and in aortic stenosis,[17] when ejection fractions decrease during maximal exercise, left ventricular diastolic volume increases due to the reduced stroke volume and high residual volume. In aortic insufficiency left ventricular volume decreases, but this has been interpreted as being due to a lessening of regurgitation.[18] The decrease in left ventricular diastolic volume at maximum in our patients is likely to be due to incomplete left ventricular filling. Whether the incomplete ventricular filling is related either to diastolic unloading of the left ventricle or due to an abnormality of ventricular relaxation is not known.

We have documented cardiac dysfunction in the form of abnormal ejection fraction responses and wall motion abnormalities in association with electrocardiographic signs of ischemia in young patients with SC anemia. The dysfunction which is related to the severity of the anemia may also be associated with an abnormality of ventricular filling.

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## References


1. **Shubin H, Kaufman R, Shapiro M, Levinson DC.** Cardiovascular findings in children with sickle cell anemia. Am J Cardiol 1960;6:865–885.
2. **Uzsoy NK.** Cardiovascular findings in patients with sickle cell anemia. Am J Cardiol 1964;13:320–328.
3. **Alpert BS, Gilman PA, Strong WB, Ellison MF, Miller MD, McFarlane J, Hayashidera T.** Hemodynamic and ECG responses to exercise in children with sickle cell anemia. Am J Dis Child 1981;153:362–366.
4. **Gerry JL, Bulkley BH, Hutchins GM.** Clinicopathologic analysis of cardiac dysfunction in 52 patients with sickle cell anemia. Am J Cardiol 1978;42: 211–216.
5. **Rees AH, Stefadouros MA, Strong WB, Miller MD, Gilman P, Rigby JA, McFarlane J.** Left ventricular performance in children with homozygous sickle cell anemia. Br Heart J 1978;40:690–696.
6. **Leon MB, Borer JS, Bacharach SL, Green MV, Benz EJ Jr, Griffith P, Nienhuis AW.** Detection of early cardiac dysfunction in patients with severe beta-thalassemia and chronic iron overload. N Engl J Med 1979;301: 1143–1148.
7. **Strong WB, Spencer D, Miller MD, Salebhai ML.** The physical working capacity of healthy black children. Am J Dis Child 1978;132:244–248.
8. **Thaper MK, Strong WB, Miller MD, Leatherbury L, Salebhai ML.** Exercise electrocardiography of healthy black children. Am J Dis Child 1978;132: 592–595.
9. **Eubig C, Covitz W, Green RT.** Elimination of patient-detector motion during upright bicycle exercise (abstr). J Nucl Med 1980;21:61.
10. **Slutsky R, Karliner J, Ricci D, Kaiser R, Pfisterer M, Gordon D, Peterson K, Ashburn W.** Ventricular volumes by gated equilibrium radionuclide angiography: a new method. Circulation 1979;60:556–564.
11. **Sorensen SG, Ritchie JT, Caldwell JH, Hamilton GW, Kenney JW.** Serial exercise radionuclide angiography. Validation of count derived changes in cardiac output and quantitation of maximal exercise ventricular volume change after nitroglycerin and propranolol in normal men. Circulation 1980;61:600–607.
12. **Covitz W, Rees AH.** Echocardiography in infants and children. Paediatrician 1978;7:126–140.
13. **Meyer RA, Stockert J, Kaplan S.** Echographic determination of left ventricular volumes in pediatric patients. Circulation 1975;51:297–303.
14. **Gerry JL, Baird MG, Fortuin NJ.** Evaluation of left ventricular function in patients with sickle cell anemia. Am J Med 1976;60:968–972.
15. **Rerych R, Scholz P, Newman G, Sabiston D, Jones R.** Cardiac function at rest and during exercise in normals and patients with coronary heart disease. Ann Surg 1978;187:449–460.
16. **Varat MA, Adolph RJ, Fowler NO.** Cardiovascular effects of anemia. Am Heart J 1972;83:415–426.
17. **Covitz W, Eubig C, Strong W.** Radionuclide ejection fraction response to exercise in children with heart disease (abstr). Circulation 1980;62:Suppl III:III-116.
18. **Iskandrian AS, Hakki A, Kane SA, Segal BL.** Quantitative radionuclide angiography in assessment of hemodynamic changes during upright exercise: observations in normal subjects, patients with coronary artery disease and patients with aortic regurgitation. Am J Cardiol 1981;48:239–246.

METHODS

# Variability of Digitized Echocardiography: Size, Source, And Means of Reduction

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**Digitization of M-mode echocardiograms provides useful information on left ventricular function, but its variability has been assessed rarely. Inter- and intraobserver (technical) variability of readers digitizing the same cardiac cycles, and variability between beats, days, and subjects (biologic) was determined. Technical variability was small for both standard dimensions (correlation coefficient r values 0.82 to 1.00) and rates of change (r values 0.70 to 0.98). Biologic variability was large with expected normal differences between 2 measurements (95% confidence limits) of 11 to 55% and 37 to 106% for standard dimensions and rates of change, respectively. By averaging measurements of 5 beats from each of 2 days, the expected normal differences are reduced to 6 to 32% and 23 to 63% for standard dimensions and rates of change.**

**This study emphasizes the large biologic variability in rates of change of digitized left ventricular measurements. Normal variation between studies can be reduced and real physiologic or pathologic changes perceived best if many beats from more than 1 day are measured.**

M-mode echocardiography, by virtue of the high repetition rate of 1,000 pulses/second, displays cardiac structures "continuously" throughout the cardiac cycle. The method of digitization of M-mode records takes advantage of this excellent frequency response, and provides information on left ventricular function beyond that given by standard dimensions.[1]

Despite the more widespread use of digitization, the variability and reproducibility of measurements has been assessed rarely. Such information is needed to differentiate between normal random variation and a true physiologic or pathologic change in the derived measurements. We performed this study to explore the magnitude of technical variability between and within observers of digitized M-mode echocardiograms, and normal biologic variability between subjects, days, and beats.

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## Methods

For the assessment of inter- and intraobserver variability (technical variability or reproducibility) 3 to 5 cardiac cycles from patients with various cardiac physiology were independently analyzed by 2 "readers," and were reanalyzed by 1 of these readers several weeks later. There were a total of 35 cycles for analysis from 10 patients: 3 normal subjects, 2 normal subjects during a drug infusion (done for other purposes), 2 patients with mitral regurgitation, 2 patients with hypertrophic cardiomyopathy, and 1 patient with a congestive cardiomyopathy (Group 1). The same 35 cycles were analyzed by both observers.

To assess variability between subjects, days, and beats (biologic variability), we studied 10 normal healthy male

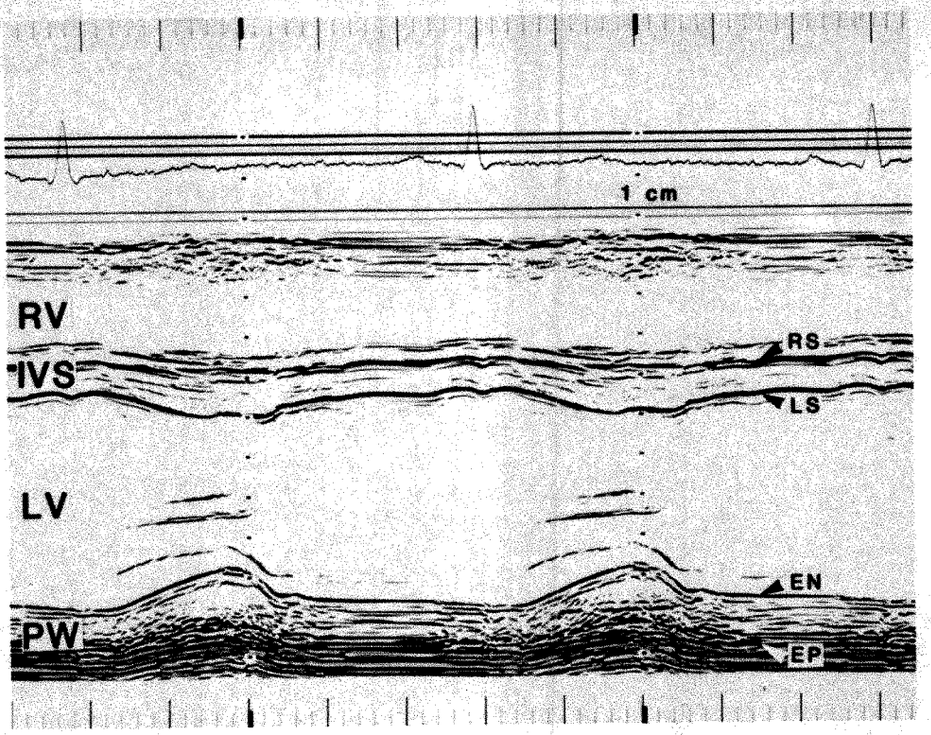



**FIGURE 1.** M-mode echocardiogram of the left ventricle in a normal subject. EN = posterior wall endocardium; EP = posterior wall epicardium; IVS = interventricular septum; LS = left side of septum; LV = left ventricular cavity; PW = posterior wall; RS = right side of septum; RV = right ventricle.

volunteers, all hospital personnel aged 21 to 30 years (mean 24), on 3 separate occasions several days apart (Group 2).

**Echocardiographic studies:** M-mode echocardiograms at the level of the left ventricular minor axis[2] were obtained using an Irex System II echocardiograph with a 2.25 MHz medium focus transducer and were recorded at 100 mm/s. Echocardiographic studies of the left ventricle were chosen for digitization if there were continuous echoes of the right and left sides of the septum and the endocardial and epicardial surfaces of the posterior wall throughout the cardiac cycle. In Group 2, 5 to 15 beats/day (12 ± 4, mean ± standard deviation) were analyzed on each of 3 separate days.

**Digitization:** The studies were digitized by tracing echoes from the right and left sides of the septum and the endocardial and epicardial surfaces of the posterior wall (Fig. 1) using a Hewlett-Packard 9874A digitizing table, interfaced with a Hewlett-Packard 2100 computer. The data were analyzed at 10 ms intervals with a moving average filter using a 3 point smoothing algorithm.[1] Each cardiac cycle was identified by 2 successive electrocardiographic Q waves and up to 5 cycles could be digitized. Each strip chart was calibrated by time (2 seconds) and depth (3 cm), which also ensured axis alignment of the strip chart with respect to the digitizing pad. From the digitized echocardiogram, the following standard left ventricular dimensions (in centimeters) were obtained in diastole (d) and systole (s): left ventricular internal dimension (LV), interventricular septal thickness (IVS), and posterior wall thickness (PW). Standard dimensions in diastole were taken at the onset of the electrocardiographic Q wave. Systolic dimensions were taken at the time that left ventricular dimensions were smallest. The peak rates of change of the left ventricle, interventricular septum, and posterior wall (in centimeters/second) were obtained as follows: peak left ventricular filling and emptying rates (d/dt LVd, d/dt LVs), peak interventricular septal and posterior wall diastolic thinning, and systolic thickening rates (d/dt IVSd, d/dt PWd, d/dt IVSs, d/dt PWs).

**Conceptual analysis and statistical methods:** A single measurement of a cardiac dimension is affected by the following factors: (1) *The subject:* There is a "normal" variability between subjects with normal hearts reflecting body size, sex, heredity, and so on. (2) *The day:* The same subject may show variability on different days. This may be due to several factors, including body position during the examination and different levels of autonomic tone. (3) *The beat:* Dimensions may differ between beats due to respiration, sinus arrhythmia, and so on. (4) *The reader* ("personality" factor): There will be variability between different readers digitizing the same tracing. This may be due to different types of style in moving the digitizing cursor, for example. (5) *The tracing* ("jitter" factor): There will be a difference in the measurements made by the same reader digitizing the same tracing on ≥2 occasions. This difference reflects the human interaction such as fine motor and eye-hand coordination required to digitize the tracing.

The purpose of this study was to estimate the magnitude of effects from these different variability factors in digitized echocardiographic measurements. The estimates cannot be derived simply by subtraction since only their combined effect is observed in any 1 observation. For instance, let us consider 1 normal subject whose mean left ventricular end-diastolic dimension of 10 beats on Day 1 is 5.2 cm, and measured by a different reader is 5.0 cm on Day 2. The difference between the mean values on the 2 separate days simultaneously embody normal differences due to reader variability, tracer variability, and normal variability between beats, as well as

any true difference in dimensions on the different days. The 10 beats on the 2 separate days may be truly identical (and thus the difference of 0.2 cm between the means does not represent day-to-day difference); on the other hand the reader, tracing, and beat factors may have cancelled out true day-to-day difference and the day-to-day difference may actually be much larger than 0.2 cm.

The separate variability factors were "teased out" using standard statistical methods[3] by a *variance components analysis* based on the following concept:

Consider 1 cardiac cycle of a left ventricular echocardiogram. Let us assume that the true value for end-diastolic cavity dimension (LVd) of this beat is X cm.

1. Reader A digitizes the cardiac cycle obtaining a value of $Y_1$ cm. He redigitizes it 9 times and obtains $Y_2$-$Y_{10}$ cm, with an average of $\overline{Y}$cm. The average jitter (*tracer variability*) could be estimated from the average of the differences between each Y measurement and $\overline{Y}$. (The applicable standard statistical methods actually use the root-mean-square rather than the arithmetic mean.)

2. Reader B digitizes the same tracing and obtains value $Z_1$ cm. Nine other readers digitize the same tracing and obtain values $Z_2$-$Z_{10}$. These readings will differ from one another partly because each contains "jitter," but additionally because various readers may systematically tend to provide somewhat higher or lower readings than do others. This possibility (checkable from the data) represents variability due to "personality" (*reader variability*).

3. Reader A digitizes 2 separate cardiac cycles from the same day and obtains two values $A_{b1}$ and $A_{b2}$. The difference between the values may represent jitter or true *interbeat variability*. Reader B digitizes the 2 cardiac cycles to obtain values $B_{b1}$ and $B_{b2}$. The difference between $A_{b1}$ and $B_{b1}$ embodies, in combination, jitter, personality, and possible true interbeat differences.

4. Similarly, if reader A digitizes a cycle from Day 1 and reader B a cycle from Day 2 then the difference reflects jitter, personality, and beats, as well as *interday variability*.

5. Finally, if reader A digitizes a cycle from normal subject M and reader B digitizes a cycle from normal subject N then the differences reflect jitter, personality, interbeat, and interday, as well as *intersubject variability*.

In summary, the variance components analysis works in the following way: In Group 1, the variance* between measurements made by the same observer of the same tracing was calculated (tracer variance – $\sigma^2$T). This component of variance estimates variability due to jitter. It was then suitably removed from the variability recorded between measurements of 2 different observers of the same tracing to obtain an estimate of reader variance ($\sigma^2$R). Both these factors were then suitably removed from the variability of beats recorded in Group 2 on any 1 day to obtain beat variance ($\sigma^2$B). $\sigma^2$T, $\sigma^2$R, and $\sigma^2$B were then all suitably removed from the variability recorded between days to obtain day variance ($\sigma^2$D). All 4 factors were then suitably removed from the variability recorded between subjects to obtain subject variance ($\sigma^2$S). (The details of "suitably removing" are made more specific later.)

**Variance components analysis equations:** An individual digitized measurement of a cardiac cycle of a given subject represents the true value for that given cycle ± the total variability due to each of the 5 factors. If several observations are averaged together, than that average will contain variability from all factors, and the *amount* of that variability for any factor will be related to how many different values of that factor enter into the average. Thus, if we estimate a cardiac dimension for a particular subject by recording 5 beats, on each of 3 days, each read twice by 4 readers, then the average of the $3 \times 5 \times 2 \times 4 = 120$ readings contains 120 jitter components averaged together, and 3 day components, 4 reader components, and 15 beat components. The variability of the average of the 120 readings we call $\sigma^2$, and it has the form:

$$\sigma^2 = \frac{\sigma^2 D}{3} + \frac{\sigma^2 B}{15} + \frac{\sigma^2 R}{4} + \frac{\sigma^2 T}{120}.$$

More generally, if $\overline{N}$ denotes the average of the D × B × R × T tracings (where on each of D days B beats are recorded and read by each of R readers T times), then the average has variance:

$$\sigma^2\overline{N} = \frac{\sigma^2 D}{D} + \frac{\sigma^2 B}{DB} + \frac{\sigma^2 R}{R} + \frac{\sigma^2 T}{DBRT}.$$

From this equation (equation 1), we may see that if we take the average value of an infinite number of tracings by an infinite number of readers of an infinite number of beats and on an infinite number of days we may arrive at a true number for that subject, as the total variability would be zero. If this were repeated for another subject, the difference between the true numbers would represent true intersubject variability, having eliminated the differences due to day, beat, reader, and tracing.

**Statistical significance of different measurments:** The difference between M1 and M2, 2 averaged measurements obtained by the same B, R, and T pattern from the same subject on 2 different days, will have variance equal to $2\sigma^2\overline{N}$ (since the difference involves the random error of 2 averages, each with variance $\sigma^2\overline{N}$). This standard error for (M1 – M2), the difference between the 2 average readings, permits deciding how large a value (M1 – M2) must be in order to be regarded as showing a real change, rather than merely exhibiting statistical fluctuation. *The argument is: If, indeed, no real change has occurred between the 2 days, then there is a 95% chance that (M1 – M2) will not exceed 1.96* $\sqrt{2\sigma^2\overline{N}}$ *= 2.8* $\sigma^2\overline{N}$*, and so if the difference in the 2 measurements exceeds that amount, it may be taken (with 95% confidence, or p <0.05) to indicate a real difference. For 99% confidence (p <0.01), the difference must be at least 2.58* $\sqrt{2\sigma^2\overline{N}}$ *= 3.64* $\sigma^2\overline{N}$.

## Results

**Technical variability:** Correlations between repeated readings of 1 reader, and between 2 readers, were high both for standard dimensions and peak rates of change as tabulated in Table I.

The variance attributable to the reader and tracing factors is shown in Table II. The variance is larger for peak rates of change than standard dimensions.

**Biologic variability:** The variance attributable to the subject, day, and beat factors is shown in Table III. Biologic variability is much larger than technical variability. As with technical variability, the variance of the peak rates of change was larger than for standard dimensions (Fig. 2). There was no significant correlation between cycle length and either dimensions or rates of change within the same subject or between different subjects.

**Estimated total variance:** From the individual components, $\sigma^2$D, $\sigma^2$B, $\sigma^2$R, and $\sigma^2$T, we estimated (from equation 1) the total variance for the mean of d/dt LVd derived from 20 observations, taken in various patterns (Table IV). Days and beats reduce the variance more

* Variance ($\sigma^2$) is a measure of variability, and represents the average squared deviation from the mean.

**TABLE I Correlation Coefficients of 2 Measurements of the Same Tracing of 35 Different Cardiac Cycles in 10 Subjects (Group 1) Within the Same Observer (Intra) and Between 2 Observers (Inter)**

| | Intra | Inter |
|---|---|---|
| Dimensions | | |
| LVd | 0.99 | 0.99 |
| LVs | 0.99 | 1.00 |
| IVSd | 1.00 | 1.00 |
| IVSs | 0.82 | 0.84 |
| PWd | 0.99 | 1.00 |
| PWs | 0.97 | 0.90 |
| FS | 0.99 | 0.99 |
| Rates of Change | | |
| d/dt LVd | 0.98 | 0.96 |
| d/dt LVs | 0.96 | 0.95 |
| d/dt IVSd | 0.80 | 0.73 |
| d/dt IVSs | 0.76 | 0.70 |
| d/dt PWd | 0.93 | 0.91 |
| d/dt PWs | 0.73 | 0.82 |

FS = fractional shortening: %(LVd − LVs/LVd × 100).

**TABLE II Technical Variability**

| Dimensions | Mean (cm) | $\sigma^2$R (cm)$^2$ | $\sigma^2$T (cm)$^2$ |
|---|---|---|---|
| LVd | 5.2 | 0.00 | 0.01 |
| LVs | 3.6 | 0.01 | 0.02 |
| IVSd | 1.4 | 0.00 | 0.00 |
| IVSs | 1.2 | 0.00 | 0.01 |
| PWd | 1.6 | 0.00 | 0.01 |
| PWs | 1.8 | 0.00 | 0.01 |
| FS | 32.5 | 1.33 | 1.61 |
| **Rates of Change** | **Mean (cm/s)** | **$\sigma^2$R (cm/s)$^2$** | **$\sigma^2$T (cm/s)$^2$** |
| d/dt LVd | 10.8 | 0.40 | 0.49 |
| d/dt LVs | 7.4 | 0.00 | 0.32 |
| d/dt IVSd | 2.9 | 0.04 | 0.42 |
| d/dt IVSs | 2.3 | 0.08 | 0.19 |
| d/dt PWd | 7.0 | 0.02 | 0.96 |
| d/dt PWs | 3.0 | 0.04 | 0.40 |

The estimated variance attributable to the reader ($\sigma^2$R) and tracing ($\sigma^2$T) are shown for peak rates of change and standard dimensions. Data were calculated from Group 1, and the Group 1 mean values are shown.

**TABLE III Biologic Variability**

| Dimensions | Mean (cm) | $\sigma^2$S (cm)$^2$ | $\sigma^2$D (cm)$^2$ | $\sigma^2$B (cm)$^2$ |
|---|---|---|---|---|
| LVd | 5.0 | 0.06 | 0.01 | 0.02 |
| LVs | 3.4 | 0.03 | 0.01 | 0.00 |
| IVSd | 0.8 | 0.01 | 0.00 | 0.01 |
| IVSs | 0.9 | 0.06 | 0.01 | 0.01 |
| PWd | 1.0 | 0.03 | 0.01 | 0.02 |
| PWs | 1.4 | 0.03 | 0.01 | 0.02 |
| FS | 31.0 | 2.33 | 2.14 | 4.26 |
| **Rates of Change** | **Mean (cm/s)** | **$\sigma^2$S (cm/s)$^2$** | **$\sigma^2$D (cm/s)$^2$** | **$\sigma^2$B (cm/s)$^2$** |
| d/dt LVd | 14.4 | 3.61 | 1.29 | 3.49 |
| d/dt LVs | 8.3 | 0.22 | 0.42 | 0.52 |
| d/dt IVSd | 4.2 | 0.50 | 0.73 | 1.29 |
| d/dt IVSs | 3.0 | 0.12 | 0.13 | 0.43 |
| d/dt PWd | 9.7 | 1.67 | 1.37 | 3.47 |
| d/dt PWs | 3.5 | 0.11 | 0.14 | 0.12 |

The estimated variance attributable to the subject ($\sigma^2$S), day ($\sigma^2$D), and beat ($\sigma^2$B) are shown for peak rates of change and standard dimensions. These data were derived from Group 2 after taking into account the estimated variance attributable to the reader and tracing derived grom Group 1 data. Mean values from Group 2 are shown.

than the number of readers or tracings. Table V shows the precision obtainable on the standard dimensions using 2 patterns, and Table VI shows the corresponding information for the peak rates of change.

**Statistical significance:** The difference between 2 averaged measurements for standard dimensions and peak rates of change for 2 patterns of B, R, and T to occur beyond 95 and 99% confidence limits were calculated and are shown in Tables VII and VIII. Differences of 46.5 and 37.2% in d/dt LVd (peak filling rate) and d/dt LVs (peak emptying rate) are required for 95% confidence with 1 day, 1 beat, 1 reader, and 1 tracing. With 2 days, 5 beats, 1 reader, and 2 tracings, these differences are reduced to 27.1 and 23.4%, respectively, for 95% confidence.

## Discussion

Biologic variability due to the subject, day, and beat is greater than technical variability due to the reader and the tracing he or she makes. Among biologic factors, the subject variance is the highest for standard dimensions and peak left ventricular filling rate, indicating, as might be expected, that intersubject variation is greater than intrasubject variation due to different days or beats for these measurements. For the other measurements, subject-to-subject variance is equal to or less than day-to-day or beat-to-beat variance, which may be a reflection of the homogeneity of Group 2; subject variance would have been greater for these measurements if Group 2 had been composed of patients with larger differences in these peak rates of change rather than normal young persons.

There is large beat-to-beat variation both for standard dimensions and peak rates of change as has been described previously.[4–6] There are several possible reasons for this variation. In a study of normal subjects paced at heart rates of 50 to 150 beats/min, there was a significant correlation between heart rate and left ventricular size and function.[7] However, in another study, no correlation between heart rate and left ventricular performance was found within the normal variation in heart rate of resting subjects.[4] We also did not find a significant correlation between heart rate and left ventricular performance. Shapiro et al[8] recently reported striking differences between rates of change recorded in different regions of the left ventricle; we also observed this (Fig. 2). Finally, beat-to-beat variation is likely to reflect variation due to respiration.[9] Day-to-day variation is less than beat-to-beat variation and may be due to a change in body position of the subject,[10] or different transducer angulation, or both.[4,10,11]

Guiding the digitizer over the recording of the septum and posterior wall throughout the cardiac cycle requires fine eye-hand coordination which is within most people's capabilities; however, mastering this takes a few sessions. There was more technical variability of septal

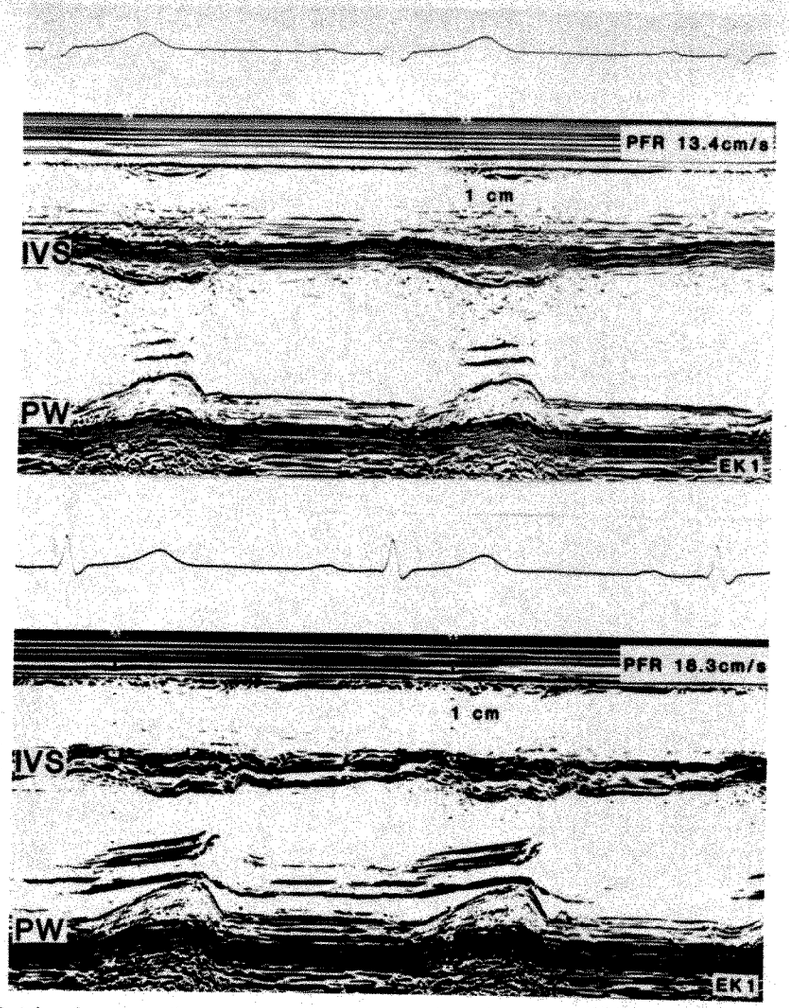



**FIGURE 2.** Two pairs of beats taken from a continuous recording (on the same day in the same subject) showing a large difference in peak filling rate. The part of the mitral valve apparatus recorded for each pair is quite different, indicating different transducer positions between beats. IVS = interventricular septum; PFR = peak filling rate (mean measurement for both beats at each level of the ventricle is shown); PW = posterior wall.

and posterior wall measurements than of left ventricular cavity measurements, as described previously,[12,13] and this is likely due to the difficulty often encountered in demarcating both the right side of the septum and epicardium. There was little technical variance in standard dimensions compared to peak rates of change, which showed relatively large biologic and technical variance. The extra element of eye-hand coordination involved in tracing the often rapid slopes of the septum and posterior wall probably explains the larger technical variability of peak rates of change compared with technical variability of standard dimensions.

Our results of the variance components of the standard dimensions are similar to a previous study in which the measurements were made directly by hand without digitizing the records.[13] This suggests that the technical variability of standard dimensions is not reduced by deriving these by digitization. Using 2-dimensional images to localize the area for M-mode sampling has been reported not to improve reproducibility of standard dimensions.[14] The effect of different sonographers performing the study has been shown to add little variability above the other components.[13]

By analyzing the contribution of each variance component, we were able to estimate the total expected variance for the combinations of different numbers of days, beats, readers, and tracings. In the comparison of measurements made at different times, large differences of $\geq 100\%$ are required in some of the peak rates of change to be beyond 99% confidence limits ($p < 0.001$) with only 1 day, 1 beat, 1 reader, and 1 tracing. Smaller differences are statistically significant with a combination of 2 days, 5 beats, 1 reader, and 2 tracings. Thus, by using such combinations, biologic variation is reduced and real physiologic or pathologic changes will be perceived best.

It is appreciated that our assessment of biologic variability refers to normal subjects. The biologic

variability of patients with stable heart disease may be different, although 2 studies[15,16] have shown that day-to-day variability of standard dimensions measured manually was similar to previous studies of normal subjects.[14]

**Implications:** Digitized M-mode echocardiograms provide information on left ventricular function beyond that given by standard dimensions. However, there is much biologic and technical variability in derived peak rates of change. Variance components for each variable

**TABLE IV Estimated Total Variance of Peak Left Ventricular Filling Rate for 20 Observations on the Same Subject (for Various Patterns of Taking the 20 Observations)**

| D | B | R | T | $\sigma^2\bar{N}$ |
|---|---|---|---|---|
| 1 | 1 | 1 | 20 | 5.20 |
| 1 | 1 | 2 | 10 | 5.00 |
| 1 | 10 | 2 | 1 | 2.06 |
| 2 | 1 | 1 | 10 | 2.84 |
| 2 | 2 | 1 | 5 | 1.94 |
| 2 | 2 | 5 | 1 | 1.62 |
| 2 | 5 | 1 | 2 | 1.91 |
| 5 | 2 | 1 | 2 | 1.03 |
| 5 | 2 | 2 | 1 | 0.83 |

$\sigma^2\bar{N}$ = total variance $(cm/s)^2$. D, B, R, and T = number of days, beats, readers, and tracings.

**TABLE V Estimated Total Coefficients of Variation (%)* for Dimensions**

| Dimensions | Pattern a | Pattern b |
|---|---|---|
| LVd | 4.0 | 2.4 |
| LVs | 5.8 | 4.6 |
| IVSd | 12.7 | 5.7 |
| IVSs | 18.6 | 11.8 |
| PWd | 19.8 | 11.7 |
| PWs | 14.2 | 8.4 |
| FS | 9.9 | 6.7 |

* Coefficient of variation was determined from $\sqrt{\text{variance}} \div \text{mean}$ value of each dimensions from Group 2. The variance was determined using pattern a = 1 day, 1 beat, 1 reader, 1 tracing; and pattern b = 2 days, 5 beats, 1 reader, 2 tracings.

**TABLE VI Estimated Total Coefficients of Variation (%)* for All Rates of Change**

| Peak Rate of Change | Pattern a | Pattern b |
|---|---|---|
| d/dt LVd | 16.5 | 9.8 |
| d/dt LVs | 13.5 | 8.1 |
| d/dt IVSd | 38.0 | 23.0 |
| d/dt IVSs | 30.1 | 18.4 |
| d/dt PWd | 25.0 | 14.2 |
| d/dt PWs | 23.9 | 16.4 |

* Coefficient of variation was determined from $\sqrt{\text{variance}} \div \text{mean}$ value of each peak rate of change from Group 2. The variance was determined using pattern a = 1 day, 1 beat, 1 reader, 1 tracing; and pattern b = 2 days, 5 beats, 1 reader, 2 tracings.

**TABLE VII Estimated Differences in Dimensions Between 2 Studies for Statistical Significance**

| | Pattern a | | | | Pattern b | | | |
|---|---|---|---|---|---|---|---|---|
| | p <0.05 | | p <0.01 | | p <0.05 | | p <0.01 | |
| Dimension | Δ | % Δ | Δ | % Δ | Δ | % Δ | Δ | % Δ |
| LVd | 0.6 | 11.2 | 0.7 | 14.1 | 0.3 | 6.3 | 0.4 | 8.2 |
| LVs | 0.6 | 16.2 | 0.7 | 20.9 | 0.4 | 12.9 | 0.6 | 16.6 |
| IVSd | 0.3 | 35.4 | 0.4 | 45.6 | 0.1 | 16.0 | 0.2 | 20.5 |
| IVSs | 0.5 | 51.6 | 0.6 | 53.4 | 0.3 | 32.3 | 0.4 | 42.0 |
| PWd | 0.6 | 55.4 | 0.7 | 71.3 | 0.3 | 32.7 | 0.4 | 42.1 |
| PWs | 0.6 | 39.8 | 0.7 | 51.1 | 0.3 | 23.0 | 0.4 | 30.2 |
| FS (%) | 8.6 | 27.7 | 11.0 | 35.6 | 5.8 | 18.8 | 7.5 | 24.1 |

Pattern a = 1 day, 1 beat, 1 reader, 1 tracing. Pattern b = 2 days, 5 beats, 1 reader, 2 tracings. Δ = centimeter difference between 2 studies required for significance at $p < 0.05$ or $p < 0.001$. % Δ = Δ/means Group 2.

**TABLE VIII Estimated Differences in Rates of Change Between 2 Studies for Statistical Significance**

| | Pattern a | | | | Pattern b | | | |
|---|---|---|---|---|---|---|---|---|
| | p <0.05 | | p <0.01 | | p <0.05 | | p <0.01 | |
| Rate of Change | Δ | % Δ | Δ | % Δ | Δ | % Δ | Δ | % Δ |
| d/dt LVd | 6.7 | 46.5 | 8.6 | 59.7 | 3.9 | 27.1 | 5.1 | 35.4 |
| d/dt LVs | 3.1 | 37.2 | 4.1 | 49.2 | 1.9 | 23.4 | 2.5 | 30.4 |
| d/dt IVSd | 4.4 | 106.3 | 5.7 | 137.7 | 2.6 | 63.3 | 3.4 | 82.3 |
| d/dt IVSs | 2.5 | 82.5 | 3.3 | 108.9 | 1.6 | 51.5 | 2.0 | 66.2 |
| d/dt PWd | 6.8 | 70.4 | 8.7 | 90.1 | 3.8 | 39.8 | 4.9 | 51.1 |
| d/dt PWs | 2.3 | 65.0 | 2.9 | 84.5 | 1.6 | 45.7 | 2.1 | 59.0 |

Pattern a = 1 day, 1 beat, 1 reader, 1 tracing. Pattern b = 2 days, 5 beats, 1 reader, 2 tracings. Δ = cm/s difference between 2 studies required for significance at $p < 0.05$ or $p < 0.01$. % Δ = Δ/means Group 2.

can be reduced by combining readings of several beats over 2 or more days.

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## References

1. **Gibson DG, Brown D.** Measurement of instantaneous left ventricular filling rate in man, using echocardiography. Br Heart J 1973;35:1141–1149.
2. **Popp RL, Filly K, Brown OR, Harrison DC.** Effect of transducer placement on echocardiographic measurements of left ventricular dimensions. Am J Cardiol 1975;35:537–550.
3. **Searle SR.** Linear Models. New York: John Wiley, 1971:475.
4. **Belenkie I.** Beat to beat variability of echocardiographic measurements of left ventricular end-diastolic diameter and performance. J Clin Ultrasound 1979;7:263–268.
5. **Bass NM, Whitlock RML.** Repeatability of left ventricular echocardiogram (abstr). Aus NZ J Med 1977;7:558.
6. **Bett JHN, Dryburgh LG.** Beat to beat variation in echocardiographic measurements of left ventricular dimensions and function. J Clin Ultrasound 1981;9:119–125.
7. **DeMaria AN, Neuman A, Schubart PJ, Lee G, Mason DT.** Systematic correlation of cardiac chamber size and ventricular performance determined with echocardiography and alterations in heart rate in normal persons. Am J Cardiol 1979;43:1–9.
8. **Shapiro E, Marier DL, St. John Sutton MG, Gibson DG.** Regional non-uniformity of wall dynamics in normal left ventricle. Br Heart J 1981;45: 264–270.
9. **Brenner JI, Waugh RA.** Effect of phasic respiration on left ventricular dimension and performance in a normal population. An echocardiographic study. Circulation 1978;57:122–127.
10. **Wong M, Shah PM, Taylor RD.** Reproducibility of left ventricular internal dimensions with M-mode echocardiography: effects of heart size, body position and transducer angulation. Am J Cardiol 1981;47:1068–1074.
11. **Stetadouros MA, Canedo MI.** Reproducibility of echocardiographic estimates of left ventricular dimensions. Br Heart J 1977;39:390–398.
12. **Monoson PA, O'Rourke RA, Crawford MH, White KH.** Measurements of left ventricular wall thickness and systolic thickening by M-mode echocardiography: interobserver and intrapatient variability. J Clin Ultrasound 1978;6:252–258.
13. **Feiner JM, Blumenstein BA, Schlant RC, Carter AD, Alimurung BN, Johnson MJ, Sherman SW, Klicpera MW, Kutner MH, Drucker LW.** Sources of variability in echocardiographic measurements. Am J Cardiol 1980; 45:995–1004.
14. **Pietro DA, Voelkel AG, Ray BJ, Parisi AF.** Reproducibility of echocardiography. A study evaluating the variability of serial echocardiographic measurements. Chest 1981;79:29–32.
15. **Clark RD, Korcuska D, Cohn K.** Serial echocardiographic evaluations of left ventricular function in valvular disease, including reproducibility guidelines for serial studies. Circulation 1980;62:564–575.
16. **Unverferth DV, Lewis RP, Leier CV, Magorien RD, Fulkerson PK.** Reproducibility of echocardiography in chronic congestive heart failure. J Clin Ultrasound 1980;8:479–482.

# Left Ventricular Isovolumic Pressure Decay and Diastolic Mechanics After Postextrasystolic Potentiation and During Exercise

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**Left ventricular contraction, relaxation, and diastolic mechanics were examined in subjects after postextrasystolic potentiation and compared with results during supine bicycle exercise. Twelve patients had ventricular extrasystoles induced during biplane left ventricular cineangiography (PES Group). Six patients with no or minimal cardiovascular disease underwent exercise (Exercise Group). From simultaneous high-fidelity pressure curves the time constant of relaxation (T), a theoretical baseline for isovolumic pressure decay ($P_B$), and the lowest diastolic pressure ($P_L$) were determined. Frame-by-frame volume analysis was completed in 6 patients from the PES Group and 4 in the Exercise Group to quantitate filling rates and to construct diastolic pressure-volume relations.**

**In the PES Group, the ejection fraction increased from 65 to 74% ($p < 0.001$) and end-systolic volume decreased from 38 to 29 ml/m$^2$ ($p < 0.001$). Pressure decay was altered with maximal negative first derivative of left ventricular pressure (dP/dt), decreasing from −1,553 to −1,273 mm Hg/s ($p < 0.001$), T increasing from 51 to 74 ms ($p < 0.001$), and $P_B$ decreasing from −6 to −19 mm Hg ($p < 0.001$). While $P_L$ occurred later in diastole (138 to 177 ms after maximal negative dP/dt, $p < 0.001$), it remained at the same level (8 versus 7 mm Hg). Peak filling rate was unaltered in the diastole after postextrasystolic potentiation, and no upward shift in the diastolic pressure-volume relation occurred.**

**In the Exercise Group, the ejection fraction increased from 65 to 75% ($p < 0.001$) and end-systolic volume decreased from 35 to 26 ml/m$^2$ ($p < 0.001$). With exercise, maximal negative dP/dt increased from −1,566 to −2,650 mm Hg/s ($p < 0.001$), T decreased from 50 to 26 ms ($p < 0.001$), and $P_B$ was unchanged. As a result, $P_L$ occurred earlier in diastole (120 to 96 ms, $p < 0.001$), achieved a lower value (9 to 4 mm Hg, difference not significant [NS]), and the peak filling rate increased from 588 to 1,107 ml/s, $p < 0.001$). At $P_L$, relaxation was complete during exercise but incomplete after postextrasystolic potentiation (3.7 versus 2.4 T elapsed, $p < 0.001$).**

**Postextrasystolic potentiation, like dynamic exercise, enhances shortening and augments restoring forces by producing a smaller end-systolic chamber. Yet, postextrasystolic potentiation delays inactivation and prolongs relaxation. Diastolic mechanics (early diastolic pressure, filling, pressure-volume relation) are not subsequently altered, suggesting that enhanced restoring forces counterbalance the delayed inactivation. With exercise, diastolic filling is enhanced both by more rapid pressure decay and by increased restoring forces. Thus, diastolic mechanics can be dissociated from systolic and are determined by the nature of the inotropic stimulus.**

Diastolic mechanics have been characterized by the predominant effect of left ventricular passive chamber properties. Diastolic mechanics are also determined by the preceding systole. The end-systolic volume produced by contraction may contain stored elastic energy which promotes restoration of the ventricle to its precontraction configuration. Similarly, pressure decay from systole may play an important role in determining diastolic pressures, filling rates, and pressure-volume relations.[1–5] We examined these influences on relaxation and diastolic function in man after 2 interventions producing distinctive alterations in cardiovascular function. Postextrasystolic potentiation is a positive inotropic intervention with enhanced shortening, producing a smaller end-systolic chamber capable of augmenting restoring forces. Yet, isolated muscle studies and animal studies have shown that postextrasystolic potentiation delays relaxation probably by delaying muscle inactivation.[6,7] Dynamic exercise also is a positive inotropic intervention producing a smaller end-systolic chamber with enhanced restoring forces available. In human subjects pressure decay is greatly aug-

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mented during dynamic exercise, and in isolated muscle and animal studies catcholamines promote inactivation and pressure decay.[6-10] Thus, the 2 interventions produce an increase in restoring forces but opposite effects on muscle inactivation. In our subjects, we assessed the net effect of these 2 common cardiovascular interventions on pressure decay and diastolic function as represented by diastolic pressures, filling dynamics, and pressure-volume relations.

## Methods

A total of 17 patients (16 men, 1 woman) were included in the study. Twelve patients participated in the postextrasystolic potentiation part of the study. Ten had significant coronary artery disease (>50% diameter narrowing: 8 with 3-vessel and 2 with 2-vessel disease) and 2 patients with atypical chest pain had no cardiovascular abnormalities. All 12 had normal resting ejection fractions (>57%), although 8 had mild to moderate regional wall motion abnormalities on the resting angiogram, which improved in 5 after postextrasystolic potentiation. The response to postextrasystolic potentiation was similar in all types of patients; they will be referred to as 1 group, the PES Group.

Five additional patients and 1 patient from the PES Group (Case 1) underwent supine bicycle exercise. In all the ejection fraction increased by >5%, and none had angina. All underwent catheterization to evaluate atypical chest pain (4 had no cardiovascular abnormalities, 1 had minimal coronary artery disease, and 1 had minimal mitral valve prolapse without mitral regurgitation). These patients comprise the Exercise Group.

**Catheterization and cineangiography:** Premedication consisted of 10 mg of chlordiazepoxide given orally 1 hour before catheterization. In the Exercise Group, 4 patients were receiving long-term administration of beta-adrenergic blockers; 4 patients, calcium antagonists; and 2 patients, long-acting nitrates. In the PES Group, 11 were taking beta-adrenergic blockers, 7 took calcium antagonists, and 11 took long-acting nitrates. Cardiovascular medications were withheld for 12 to 24 hours before study. Left ventricular pressure was measured with a Millar pigtail angiographic micromanometer introduced from the femoral artery. The pressures were recorded at a paper speed of 250 mm/s (Electronics for Medicine, VR16) with the dP/dt, dP/dt/P, and an intracardiac electrocardiogram from a right-sided catheter. Before both resting and exercise recordings, the pressure was calibrated against a fluid-filled system.

Biplane left ventricular cineangiography was performed in the right anterior oblique (30°) and left anterior oblique (60°) projections at a filming rate of 50 frames/s. Volumes were calculated using the area-length method. Each angiographic frame had a digital time which corresponded to time marks on the pressure recordings.

**Postextrasystolic potentiation protocol:** In 7 of the 12 patients in the PES Group, a single premature contraction was produced by right ventricular electrical stimulation with a right-sided pacing catheter. The extrasystole occurred immediately after the second well-opacified beat during cineangiography. Coupling interval was adjusted before the angiogram to insure systolic potentiation (as judged from maximal positive dP/dt) of the postextrasystolic beat. In the additional 5 patients, spontaneous extrasystoles (in 3 single, in 2 triplets) occurred during cineangiography with adequate visualization of a nonpotentiated and a potentiated beat to permit analysis. In 6 of the 12 patients, both the nonpotentiated and potentiated beats were evaluated from end-diastole to the next end-diastole to assess alterations in filling and diastolic pressure-volume relations (see later). All 12 patients had their feet in a semi-elevated position, attached to a bicycle device, as part of a separate study. For this reason, in part, end-diastolic pressures were increased due to the augmented preload.

**Exercise protocol:** All 6 patients in the Exercise Group had precatheterization bicycle exercise testing to determine achieved work load and exercise limitations. At catheterization, pressures were recorded before and after attaching the patients' feet to the bicycle device. Left ventricular end-diastolic pressure subsequently increased from 12 to 20 mm Hg ($p < 0.01$). The increase in preload and bradycardia in several patients account for the elevated end-diastolic pressures. All resting data presented here are during the first angiogram with the legs in this elevated position. After the resting angiogram and a subsequent 12- to 15-minute pause, exercise was begun at a low level. Patients underwent progressively higher work loads until limiting symptoms (fatigue in legs, no angina) occurred or until they achieved a predicted submaximal heart rate according to sex, age, and height. At the point of peak exercise pressure was again recorded and simultaneous cineangiography was completed. Coronary arteriography was performed after exercise using the Judkins technique.

**Data analysis:** Rest, postextrasystolic, and exercise data were derived from beats selected during simultaneous pressure measurement and left ventricular cineangiography. All beats analyzed were well opacified and within 5 seconds of the beginning of contrast injection. In the PES Group, a control, unpotentiated beat was compared with a potentiated beat. In the Exercise Group, all beats analyzed were sinus beats, and postextrasystolic beats were excluded. Resting beats were from midinspiration and exercise beats were average if any respiratory-related pressure changes were noted.

Pressure tracings were digitized for an entire cardiac cycle by an electronic digitizer (Numonics Corporation) interfaced with a digital computer (PDP 11/10). A previously described program produced a printout of pressure and dP/dt values with a time interval between 3 and 10 ms depending on the heart rate (each cycle being divided into 130 time intervals).[11] The time constant of relaxation (T, in milliseconds) was calculated as the negative reciprocal of the slope of the linear regression of pressure and dP/dt coordinates.[12] These coordinates were taken from the isovolumic relaxation period defined as from immediately after maximal negative dP/dt to the time pressure had decreased to 5 mm Hg above left ventricular end-diastolic pressure. The linear regression of pressure and dP/dt coordinates was also characterized by its pressure axis intercept. This extrapolated baseline pressure—$P_B$—was calculated at dP/dt = 0.

To study the completeness of relaxation in early diastole we used the technique of Weisfeldt et al,[1] which assumes pressure decay to be 97% complete at 3.5 times constants (T) after maximal negative dP/dt. The number of time constants elapsed was computed at the time of lowest diastolic pressure ($P_L$) in the rest and exercise states and also for control and postextrasystolic potentiated beats.

In order to assess the effects of postextrasystolic potentiation and exercise on diastolic dynamics, ventricular filling was quantitated using frame-by-frame angiographic volumes from mitral valve opening to end-diastole in 10 patients with adequate data (6 with postextrasystolic potentiation and 4 with exercise). The time of mitral valve opening was 20 ms before the time of the first frame showing the entry of unopacified blood into the left ventricle. The time of end-diastole was noted as the beginning of the rapid rise in left ventricular pressure immediately after the onset of the QRS complex. The time of mitral valve opening to end-diastole is the left ven-

**TABLE I Left Ventricular Pressure Data**

| | LVP (mm Hg) | | LVEDP (mm Hg) | | +dP/dt Max (mm Hg/s) | | −dP/dt Max (mm Hg/s) | | $P_L$ (mm Hg) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Patient | C | I | C | I | C | I | C | I | C | I |
| | | | | | Exercise Group | | | | | |
| 1 | 140 | 149 | 21 | 17 | 1,992 | 3,057 | 2,296 | 2,763 | 3 | 0 |
| 2 | 125 | 154 | 21 | 28 | 1,389 | 3,204 | 1,239 | 2,500 | 14 | 10 |
| 3 | 164 | 170 | 27 | 28 | 1,282 | 3,477 | 1,541 | 3,198 | 16 | 0 |
| 4 | 131 | 162 | 25 | 24 | 1,354 | 3,432 | 1,494 | 3,248 | 11 | 6 |
| 5 | 153 | 167 | 22 | 20 | 1,827 | 2,434 | 1,919 | 2,626 | 11 | 2 |
| 6 | 82 | 120 | 7 | 8 | 963 | 2,031 | 909 | 1,567 | 2 | 6 |
| Mean | 133 | 154 | 20 | 21 | 1,468 | 2,939 | 1,566 | 2,650 | 9 | 4 |
| ±SD | ±29 | ±18 * | ±7 | ±8 | ±398 | ±582 ‡ | ±490 | ±611 ‡ | ±6 | ±4 |
| | | | | | PES Group | | | | | |
| 1 | 153 | 155 | 22 | 26 | 1,827 | 1,864 | 1,919 | 1,447 | 11 | 12 |
| 2 | 126 | 118 | 22 | 21 | 1,386 | 1,460 | 1,197 | 920 | 12 | 10 |
| 3 | 149 | 153 | 18 | 23 | 1,663 | 2,040 | 1,569 | 1,314 | 2 | 7 |
| 4 | 140 | 143 | 25 | 26 | 1,553 | 1,682 | 1,666 | 1,689 | 10 | 7 |
| 5 | 139 | 127 | 31 | 38 | 1,309 | 1,342 | 1,457 | 1,115 | 10 | 11 |
| 6 | 151 | 144 | 29 | 31 | 1,243 | 1,347 | 1,370 | 1,178 | 13 | 12 |
| 7 | 125 | 99 | 21 | 21 | 1,389 | 1,752 | 1,239 | 920 | 14 | 11 |
| 8 | 103 | 89 | 11 | 13 | 1,373 | 1,546 | 1,389 | 910 | 3 | 4 |
| 9 | 182 | 175 | 23 | 24 | 1,796 | 1,969 | 1,972 | 1,838 | 10 | 5 |
| 10 | 128 | 120 | 12 | 9 | 2,064 | 2,540 | 1,604 | 1,292 | 2 | −2 |
| 11 | 146 | 131 | 33 | 30 | 1,198 | 1,206 | 1,564 | 1,264 | 13 | 8 |
| 12 | 145 | 137 | 10 | 14 | 1,367 | 1,394 | 1,693 | 1,394 | 1 | 3 |
| Mean | 141 | 133 | 21 | 23 | 1,514 | 1,679 | 1,553 | 1,273 | 8 | 7 |
| ±SD | ±19 | ±24 * | ±8 | ±8 | ±268 † | ±380 | ±241 ‡ | ±295 | ±5 | ±4 |

LVP = left ventricular pressure; LVEDP = end-diastolic pressure; SD = standard deviation; T = time constant of relaxation; $P_L$ = lowest diastolic pressure; * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$. All probabilities are for intervention (I) versus control (C) comparisons.

tricular filling time. This filling time was divided into a first and second half, the middle being mid-diastole. The average filling rate was calculated for the first half of diastole. In addition, instantaneous filling rates were calculated every 40 ms after mitral valve opening. The greatest value opening occurring early in diastole was termed the peak filling rate. End-diastolic volume index, end-systolic volume index, and ejection fraction were calculated in the usual fashion.

The left atrial-left ventricular pressure gradient is a major determinant of ventricular filling.[13] Since left atrial pressure was not measured, we noted the pressure at the time unopacified blood first entered the ventricle. This is termed the *driving pressure* and is an index of the pressure responsible for mitral valve opening.

Prolonged relaxation during ischemia has been implicated as a cause of the upward shift in the diastolic pressure-volume relation.[4] We assessed the possible influence of prolongation of relaxation induced by postextrasystolic potentiation on the diastolic pressure-volume relation in 6 patients. Angiographic biplane volumes every 20 ms were time-matched to simultaneous left ventricular pressures and the data graphically displayed.

**Statistics:** All tabular data are presented as means ±1 standard deviation. Figure data are means ±1 standard error. The statistical significance of differences between control and PES data and between rest and exercise data was tested with a paired *t* test. Differences between the PES and Exercise Groups were assessed with an unpaired *t* test.

## Results

Left ventricular pressure results are shown in Table I, volume data in Table II, and derived relaxation parameters in Table III. Figures 1 and 2 show representative pressure tracings.

Systolic performance was augmented in both postextrasystolic and exercise beats (Fig. 3). Postextrasystolic potentiation increased maximal positive dP/dt from 1,514 to 1,679 mm Hg/s ($p < 0.01$), ejection fraction increased from 65 to 74% ($p < 0.001$), and end-systolic volume decreased from 38 to 29 ml/m$^2$ ($p < 0.001$). Exercise increased heart rate from 66 to 118 beats/min and maximal positive dP/dt increased from 1,468 to 2,939 mm Hg/s ($p < 0.001$), which was greater than the level achieved by postextrasystolic potentiation ($p < 0.05$). Exercise increased ejection fraction from 65 to 75% ($p < 0.001$) and decreased end-systolic volume from 35 to 26 ml/m$^2$ ($p < 0.001$), nearly identical compared with postextrasystolic potentiation. With exercise, there was an insignificant increase in end-diastolic volume (99 to 105 ml/m$^2$) and end-diastolic pressure (20 to 21 mm Hg). With postextrasystolic potentiation, there was a small increase in end-diastolic volume (107 to 112 ml/m$^2$, $p < 0.001$) and pressure (21 to 23 mm Hg, NS). Peak left ventricular pressure increased with exercise from 133 to 154 mm Hg ($p < 0.05$) but decreased slightly with postextrasystolic potentiation (141 to 133 mm Hg, $p < 0.05$).

Relaxation was altered in opposite directions by postextrasystolic potentiation and exercise (Fig. 4). With postextrasystolic potentiation, maximal negative dP/dt decreased from −1,553 to −1,273 mm Hg/s ($p < 0.001$), T increased from 51 to 74 ms ($p < 0.001$), and $P_B$ decreased from −6 to − 19 mm Hg ($p < 0.001$). Exercise caused an increase in maximal negative dP/dt from −1,566 to −2,650 mm Hg/s ($p < 0.001$), T de-

**TABLE II Left Ventricular Volume Data**

| Patient | Heart Rate (beats/min) | | EF (%) | | EDVI (ml/m²) | | ESVI (ml/m²) | |
|---|---|---|---|---|---|---|---|---|
| | C | I | C | I | C | I | C | I |
| **Exercise Group** | | | | | | | | |
| 1 | 101 | 148 | 66 | 76 | 86 | 85 | 29 | 21 |
| 2 | 71 | 120 | 59 | 72 | 100 | 114 | 41 | 32 |
| 3 | 54 | 125 | 66 | 78 | 98 | 102 | 35 | 22 |
| 4 | 46 | 119 | 62 | 74 | 116 | 116 | 44 | 30 |
| 5 | 65 | 109 | 73 | 81 | 92 | 103 | 25 | 19 |
| 6 | 58 | 90 | 63 | 71 | 100 | 109 | 37 | 32 |
| | 66 ± 19 | 118 ± 19 | 65 ± 5 | 75 ± 4 * | 99 ± 10 | 105 ± 11 * | 35 ± 7 | 26 ± 6 * |
| **PES Group** | | | | | | | | |
| 1 | 65 | ... | 73 | 83 | 92 | 92 | 25 | 16 |
| 2 | 71 | ... | 57 | 66 | 111 | 115 | 48 | 37 |
| 3 | 66 | ... | 58 | 69 | 121 | 127 | 49 | 39 |
| 4 | 70 | ... | 68 | 72 | 117 | 123 | 37 | 35 |
| 5 | 54 | ... | 60 | 70 | 104 | 106 | 42 | 32 |
| 6 | 52 | ... | 59 | 69 | 117 | 124 | 48 | 39 |
| 7 | 51 | ... | 59 | 72 | 100 | 106 | 41 | 30 |
| 8 | 90 | ... | 65 | 79 | 88 | 102 | 31 | 22 |
| 9 | 70 | ... | 68 | 76 | 130 | 130 | 42 | 31 |
| 10 | 80 | ... | 77 | 79 | 77 | 80 | 19 | 16 |
| 11 | 47 | ... | 69 | 81 | 117 | 128 | 37 | 24 |
| 12 | 71 | ... | 66 | 76 | 107 | 111 | 37 | 27 |
| | 67 ± 12 | ... | 65 ± 6 | 74 ± 5 * | 107 ± 15 | 112 ± 16 * | 38 ± 9 | 29 ± 8 * |

EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; * $p < 0.001$. All probabilities are for intervention (I) versus control (C) comparisons.

creased from 50 to 26 ms ($p < 0.001$), and $P_B$ was unchanged. These changes in pressure decay are portrayed in Figure 5.

Early diastolic pressures were also different after postextrasystolic potentiation and exercise. In the diastole after the potentiated beat, the minimal diastolic pressure, $P_L$, occurred later after maximal negative dP/dt (138 to 177 ms, $p < 0.001$), relaxation was less complete at $P_L$ (2.7 to 2.4 T elapsed, NS), but the absolute value of $P_L$ was unchanged (8 to 7 mm Hg). Exercise caused $P_L$ to occur earlier (120 to 96 ms, $p < 0.001$), relaxation was completed at $P_L$ (2.4 to 3.7 T elapsed, $p < 0.05$), and $P_L$ decreased in 5 of 6 patients (9 to 5 mm Hg, NS).

Despite a prolonged T, the diastolic filling after the potentiated beat was not diminished in the 6 patients studied. The mean filling rate for the first half of diastole increased insignificantly (377 ± 163 ml/s to 409 ± 123 ml/s, NS) and early peak filling rate was unaltered (829 ± 325 ml/s to 829 ± 394 ml/s). There was no change in the other key determinant of early diastolic filling, the driving pressure. The pressure at mitral valve opening was 17 ± 8 mm Hg in the control beats and unchanged after the potentiated beats at 18 ± 8 mm Hg.

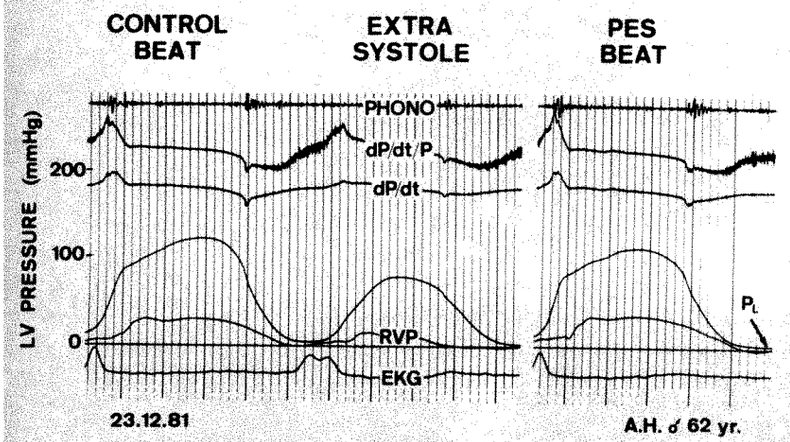



**FIGURE 1.** Patient 5. Left ventricular (LV) pressure tracing for a control beat and a postextrasystolic potentiated beat. An extrasystole was produced by a right ventricular pacing (RVP) catheter. The postextrasystolic beat had an increase in maximal positive dP/dt but a reduction in maximal negative dP/dt. The time constant of relaxation (T) was prolonged from 58 to 101 ms. $P_L$, the lowest diastolic pressure was not affected by this delay, but occurred later in diastole. EKG = electrocardiogram.

**TABLE III Left Ventricular Relaxation Data**

| Patient | T (ms) | | $P_B$ (mm Hg) | | T (s) Elapsed at $P_L$ | |
|---|---|---|---|---|---|---|
| | C | I | C | I | C | I |
| | | | Exercise Group | | | |
| 1 | 27 | 21 | −2 | −3 | 3.3 | 3.0 |
| 2 | 60 | 23 | −2 | 13 | 2.0 | 3.8 |
| 3 | 58 | 21 | 0 | 11 | 2.3 | 3.6 |
| 4 | 50 | 24 | 1 | −10 | 2.5 | 4.6 |
| 5 | 46 | 29 | −6 | −6 | 2.2 | 3.3 |
| 6 | 56 | 35 | −7 | 0 | 2.3 | 3.7 |
| | 50 ± 12 * | 26 ± 6 | −3 ± 3 | 1 ± 9 | 2.4 ± 0.5 † | 3.7 ± 0.5 |
| | | | PES Group | | | |
| 1 | 46 | 72 | −6 | −21 | 2.2 | 2.3 |
| 2 | 53 | 106 | 4 | −27 | 2.8 | 2.2 |
| 3 | 56 | 84 | −20 | −36 | 2.1 | 1.5 |
| 4 | 39 | 48 | 1 | −7 | 3.0 | 2.7 |
| 5 | 58 | 101 | −14 | −30 | 2.2 | 1.6 |
| 6 | 64 | 73 | −4 | −9 | 2.5 | 3.4 |
| 7 | 60 | 86 | −2 | −14 | 2.0 | 1.6 |
| 8 | 44 | 76 | −3 | −15 | 3.5 | 2.0 |
| 9 | 52 | 44 | −15 | −11 | 2.2 | 2.7 |
| 10 | 47 | 66 | 1 | −14 | 3.4 | 2.4 |
| 11 | 45 | 68 | −8 | −25 | 3.2 | 2.1 |
| 12 | 43 | 60 | −6 | −13 | 3.2 | 3.9 |
| | 51 ± 8 * | 74 ± 19 | −6 ± 7 * | −19 ± 9 | 2.7 ± 0.6 | 2.4 ± 0.7 |

$P_B$ = baseline pressure, $P_L$ = lowest diastolic pressure. T = time constant of relaxation; * $p < 0.001$; † $p < 0.05$. All probabilities are for intervention (I) versus control (C) comparisons.

During exercise, all 4 patients with data had an increase in mean filling rate for the first half of diastole (360 ± 120 ml/s to 684 ± 157 ml/s, NS) and early peak filling rate (586 ± 174 ml/s to 1,094 ± 350 ml/s, $p < 0.05$). There was no change in the driving pressure (13 ± 8 mm Hg to 15 ± 12 mm Hg, NS).

Pressure-volume relations from the diastole after the potentiated beat are presented for 6 patients in Figure 6. No upward shifts occurred despite the prolongation of T by an average of 50%. In 1 patient (Case 9) who did not have a prolonged T after postextrasystolic potentiation, but in whom end-systolic volume was reduced, there was a downward shift of the pressure-volume relation.

## Discussion

In humans, left ventricular relaxation is slower and prolonged after postextrasystolic potentiation, but accelerated and shortened during dynamic exercise. Relaxation, that is, pressure decay or force dissipation, is dependent upon a complex interplay of 2 major controlling systems, as described by Brutsaert et al.[14] The first is related to inactivation, which is the energy-requiring process of calcium reuptake by the sarcoplasmic reticulum. The second, load dependency, is determined by the nature and magnitude of the load, its timing relative to the contraction-relaxation sequence, its duration, and the uniformity of its distribution. Loads produced by acute aortic cross-clamping in experi-

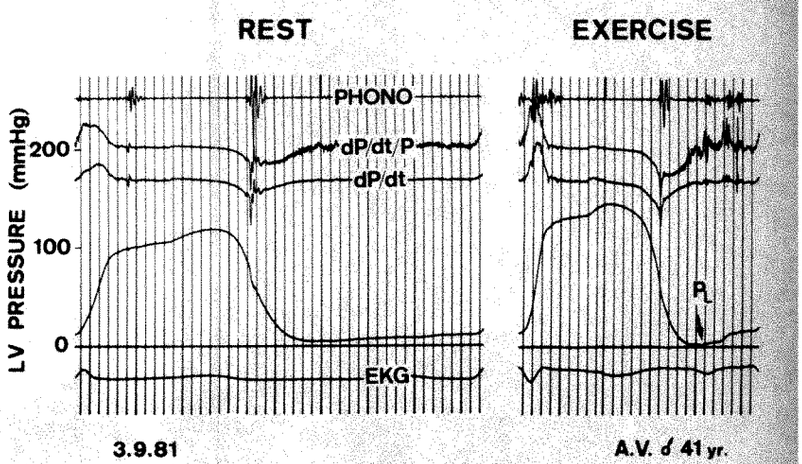



**FIGURE 2.** Patient 2. An example of the left ventricular (LV) pressure tracing at rest and during maximal supine bicycle exercise. The exercise beat had a greater maximal positive and negative dP/dt. The time constant of relaxation (T) decreased from 60 to 23 ms. The lowest diastolic pressure ($P_L$) occurred earlier after maximal negative dP/dt (87 versus 120 ms) and was lower. EKG = electrocardiogram; PHONO = phonocardiogram.

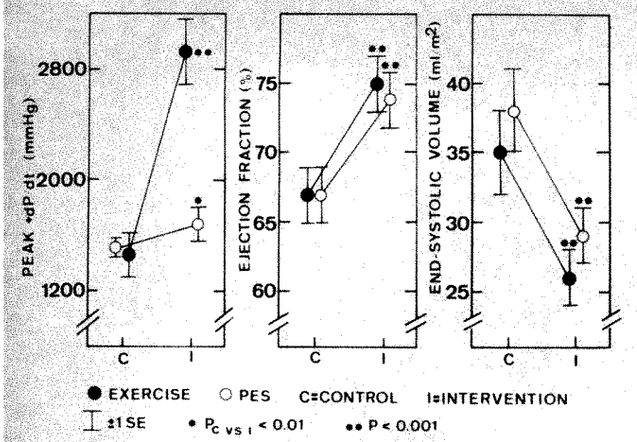



**FIGURE 3.** Systolic performance was augmented during exercise beats (**solid circles**) and postextrasystolic potentiated beats (PES) (**open circles**). Control data (C) and after the intervention (I: exercise or PES) are presented as means ±1 standard error. Maximal positive dP/dt and ejection fraction increased after both positive inotropic interventions. Both exercise and postextrasystolic potentiation caused a similar reduction in end-systolic volume and thus augmented restoring forces. * p <0.01; ** p <0.001. SE = standard error.

mental animals are applied throughout systole and appear to slow relaxation.[15] Loads applied in late systole on partially relaxed muscle may increase the rate of relaxation.[16] Relaxation, as assessed by both T and maximal negative dP/dt, is accelerated during dynamic exercise. Probably most important is the direct effect of catecholamines on the inactivation process, resulting in more rapid uptake of calcium by the sarcoplasmic reticulum. Augmented restoring forces, increased coronary blood flow, and enhanced synchrony of contraction probably contribute further to more rapid relaxation. The subsequent rapid inflow of blood early in diastole may further accelerate the return of the left ventricle to its precontraction configuration.[14]

Pressure decay is decelerated after postextrasystolic potentiation. Parmley and Sonnenblick[6] have suggested that the prolongation of tension decay after postextrasystolic potentiation in isolated muscle is probably due to a change in the uptake and the removal of activating calcium. The increase in the intracellular active calcium pool after an extrasystole potentiates contraction yet may saturate the system responsible for its removal. While the inactivation process is altered so as to prolong relaxation, loading conditions appear chiefly altered to produce the opposite. As with exercise, postextrasystolic potentiation augments restoring forces, and left ventricular systolic pressure is slightly lower. The increase in T occurs despite this, suggesting that delayed inactivation has the predominant effect. In the canine left ventricle, Blaustein et al[7] previously reported that postextrasystolic potentiation increases T despite changes in loading conditions which should decrease T.

Elastic recoil and diastolic suction are being reconsidered as potentially important mechanical determinants of diastolic function. Sonnenblick[17] suggested that the smaller, more deformed end-systolic shape of the left ventricle during exercise produces restoring forces which may augment ventricular filling. Muscle fibers shortening below slack length may produce internal restoring forces while the deformation of the left ventricular wall at end-systole may produce external restoring forces.[14] Hori et al[18] showed that negative

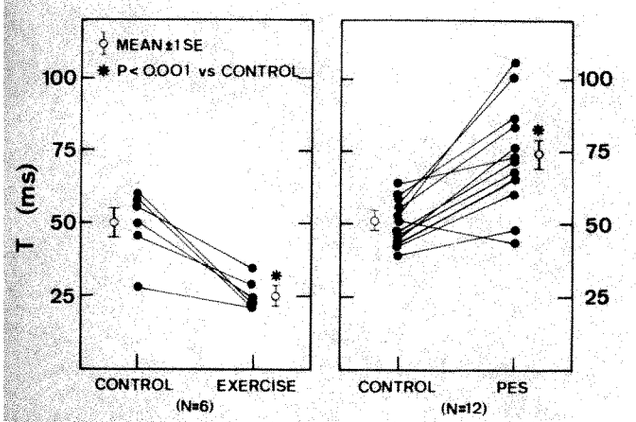



**FIGURE 4.** In the **left panel,** control (or rest) values of the time constant of relaxation (T) are compared with the exercise values. All 6 patients had more rapid pressure decay (50 to 26 ms, * p <0.001). The **right panel** compares control unpotentiated beats with postextrasystolic potentiated beats (PES) from 12 patients. All but 1 patient had a deceleration of pressure decay after PES. The mean T increased from 51 to 74 ms.

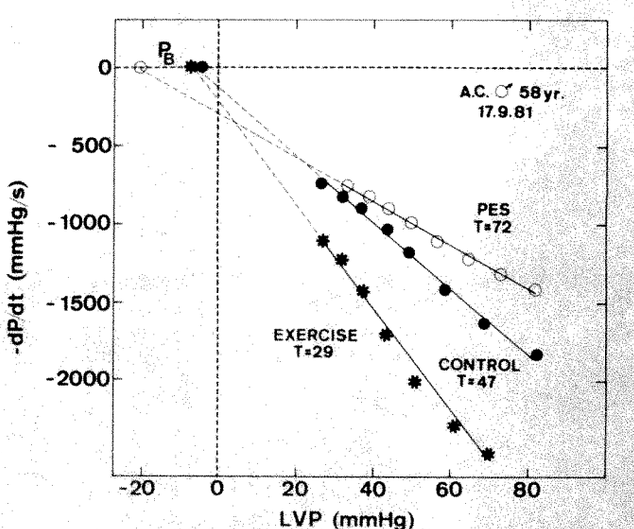



**FIGURE 5.** Left ventricular pressure and negative dP/dt coordinates from the isovolumic relaxation period are shown from the 1 patient who had both postextrasystolic potentiation (PES) and exercise studies. The time constant of relaxation (T) is the negative reciprocal of the slope of the linear regression between pressure and dP/dt coordinates. The **dotted lines** extend the linear regression to the left ventricular pressure axis intercept ($P_B$). During exercise (**asterisks**), T decreased to 29 ms from a control value (**solid circles**) of 47 ms. After PES, T prolonged to 72 ms and $P_B$ became more negative. Exercise and PES have different effects on left ventricular pressure decay despite their similar potentiation of systolic function.

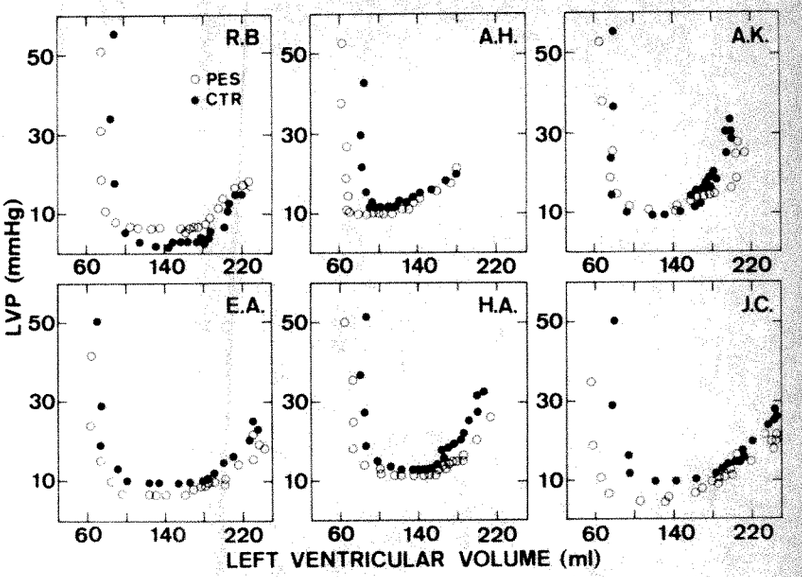



**FIGURE 6.** Six patients had diastolic pressure-volume relations constructed from simultaneous micromanometric left ventricular pressure recordings and biplane angiographic volumes every 20 ms. A control diastole (CTR) (**solid circles**) followed an unpotentiated beat, while the **open circles** represent the diastole immediately after a postextrasystolic potentiated beat (PES). Despite substantially increased T in 5 of the 6 patients, no upward shift of the pressure-volume relation occurred after postextrasystolic potentiation. The 1 patient (J.C.) without an increase in T appeared to have a slight downward shift early in diastole. This probably reflects enhanced elastic recoil from a smaller end-systolic volume. In other patients, the prolonged T apparently balances the enhanced elastic recoil so that pressure-volume relations are not altered.

intraventricular pressures occur in the canine left ventricle if filling is prevented by acute mitral orifice occlusion. Both catecholamines and postextrasystolic potentiation produced smaller end-systolic volumes which relaxed to more negative baseline pressures when filling was prevented. In certain states in humans associated with small end-systolic volumes, negative intraventricular pressures have been reported.[19,20] It appears that negative pressures are not more commonly seen because of the simultaneous occurrence of rapid filling which increases pressure proportional to volume increase. In mitral stenosis, in which rapid early filling is limited, pressure may be negative early in diastole.[19,20] Both during dynamic exercise and after postextrasystolic potentiation we have documented that end-systolic volume decreases. This parameter probably provides a fairly accurate reflection of directional changes in restoring forces. An augmentation of restoring forces could both promote faster relaxation and result in pressure decay to a lower, negative baseline if filling did not occur. Postextrasystolic potentiation is unique in that the rate of pressure decay from the small end-systolic volume is clearly prolonged. The effect of this unusual combination of factors is that filling and pressure-volume relations in the following diastole are unaltered. The significant prolongation of pressure decay may otherwise be expected to reduce early filling and shift upward the pressure-volume relation during early diastole. The lack of such changes suggests that the smaller end-systolic volume counterbalances the effect of delayed pressure decay.

The extrapolated baseline pressure, $P_B$, is derived from isovolumic data and theoretically represents the pressure attained at infinity (when $dP/dt = 0$). Our previous work with exercise-induced ischemia in human subjects revealed an upward shift in $P_B$ paralleling the increase in end-systolic volume and predicting elevated early diastolic pressures.[3] The present study further expands this concept and shows some of its limitations. While postextrasystolic potentiation reduces end-systolic volume and $P_B$ becomes more negative, the normal exercise-induced reduction of end-systolic volume does not produce a more negative $P_B$. In addition, it is apparent that in chronic heart failure with large end-systolic volumes and prolonged time constants, $P_B$ is forced mathematically to an illogical, very negative value (unpublished data). It appears that $P_B$ does not always have the same physiologic meaning as the baseline pressure measured by Hori et al when filling is prevented. $P_B$ does help in characterizing pressure decay which is not adequately described by a time constant alone. During exercise-induced ischemia in human subjects, the time constant did not distinguish those with grossly elevated diastolic pressures from those with normal pressures.[3] In humans, pressure decay cannot be assumed to always decrease to a zero baseline pressure. Quantification of relaxation requires a method allowing for variations in baseline pressure.[21]

Other methods for quantitating pressure decay have subdivided the isovolumic period and calculated several time constants.[22] Rousseau et al[22] showed that these 2 time constants move in the same direction after intracoronary nifedipine.[22] While this method of quantifying relaxation was not completed for our data, it is unlikely that our results would have been affected since postextrasystolic potentiation and exercise produce such directionally opposite effects on pressure decay.

Despite medications being held for the day before catheterization, persistent medication effects are possible. Beta-adrenergic blocking agents may attenuate the heart rate response and do slow pressure decay.[10] We observed no different response to postextrasystolic potentiation in those taking calcium antagonists.

Contrast dye has no known effect on isovolumic relaxation although no specific studies have been reported. Since we analyzed beats occurring early in contrast injection, significant hemodynamic alterations due to contrast were avoided.

The coupling interval for the extrasystole was not systematically altered in this study. In the canine left ventricle, Blaustein et al[7] failed to find a significant effect of coupling interval or compensatory pause on either maximal negative dP/dt or T, even though maximal positive dP/dt was altered. In the present study, the coupling interval was between 400 and 600 ms in all patients but no clear effect of coupling interval on T was noted.

The $P_L$ occurring typically early in diastolic represents a crossover point of 2 major processes: pressure decay from relaxation and pressure rise from filling. After an extrasystolic potentiated beat, pressure decay is slower while filling is unaltered. As predicted, the minimal diastolic pressure is achieved later in diastole. During exercise, pressure decay is accelerated and filling is augmented and the minimal diastolic pressure is earlier in diastole. Maintaining low diastolic pressures with augmented filling should be beneficial during exercise when diastole is significantly abbreviated.

Exercise and postextrasystolic potentiation are commonly occurring events in humans and knowledge regarding their effects on systolic and diastolic dynamics may be useful in several clinical situations. Hypertrophic cardiomyopathy is characterized by a hypercontractile state with an elevated time constant of relaxation.[22,23] The abnormal diastolic mechanics appear to be a consequence not only of the passive properties of the hypertrophied muscle, but also of abnormal relaxation.[22–24] When modifying diastolic function with pharmacologic agents, one must also consider effects on contraction-relaxation. Verapamil may "uncouple" contraction from relaxation since it depresses contractility and decreases the time constant of relaxation in dogs.[25] Thus, it is increasingly apparent that diseases, drugs, and the nature of inotropic stimuli may dissociate diastolic from systolic mechanics.

## References


1. **Weisfeldt ML, Weiss JL, Frederiksen JT, Yin FCP.** Quantification of incomplete left ventricular relaxation: relationship to the time constant of isovolumic pressure fall. Eur Heart J 1980;1(Suppl A):119–129.
2. **Fioretti P, Brower RW, Meester GT, Serruys PW.** Interaction of the left ventricular relaxation and filling during early diastole in human subjects. Am J Cardiol 1980;46:197–203.
3. **Carroll JD, Hess OM, Hirzel HO, Krayenbuehl HP.** Exercise-induced ischemia: does pressure decay influence early diastolic pressures? Circulation 1983; in press.
4. **Mann T, Goldberg S, Mudge GH, Grossman W.** Factors contributing to altered left ventricular diastolic properties during angina pectoris. Circulation 1979;59:14–20.
5. **Mann T, Brodie BR, Grossman W, McLaurin LP.** Effect of angina on the left ventricular diastolic pressure-volume relationship. Circulation 1977;55: 761–766.
6. **Parmley WW, Sonnenblick EH.** Relation between mechanics of contraction and relaxation in mammalian cardiac muscle. Am J Physiol 1969;216: 1084–1091.
7. **Blaustein AS, Gaasch WH, Adam D, Levine HJ.** Myocardial relaxation. V. Postextrasystolic contraction-relaxation in the intact dog heart. Circulation 1981;64:345–351.
8. **Craig WE, Murgo JP.** Evaluation of isovolumic relaxation in normal man during rest, exercise, and isoproterenol infusion (abstr). Circulation 1980;62:Suppl III:III–92.
9. **Karliner JS, Le Winter M, Mahler F, Engler R, O'Rourke RA.** Pharmacologic and hemodynamic influences on the rate of isovolumic left ventricular relaxation in the normal conscious dog. J Clin Invest 1977;60:511–521.
10. **Gaasch WH, Blaustein AS, Andrias CW, Donahue RP, Avital B.** Myocardial relaxation II: hemodynamic determinants of rate of left ventricular isovolumic pressure decline. Am J Physiol 1980;239:H1–H6.
11. **Eichhorn P, Grimm J, Koch R, Hess O, Carroll J, Krayenbuehl HP.** Left ventricular relaxation in patients with left ventricular hypertrophy secondary to aortic valve disease. Circulation 1982;65:1395–1404.
12. **Raff GL, Glantz SA.** Volume loading slows left ventricular isovolumic relaxation rate. Circ Res 1981;48:813–824.
13. **Yellin EL, Sonnenblick EH, Frater RWM.** Dynamic determinants of left ventricular filling. An overview. In: Baan J. Arntzenius AC, Yellin EL, eds. Cardiac Dynamics. The Hague: Martinus Nijhoff, 1980:145–158.
14. **Brutsaert DL, Housmans PR, Goethals MA.** Dual control of relaxation: its role in the ventricular function in the mammalian heart. Circ Res 1980; 47:637–652.
15. **Gaasch WH, Blaustein AS, Adam D.** Myocardial relaxation IV: mechanical determinants of the time course of left ventricular pressure decline during isovolumic relaxation. Eur Heart J 1980;1(Suppl A):111–117.
16. **Goethals MA, Kersschot IE, Claes VA, Hermans CF, Jageneau AH, Brutsaert DL.** Influence of abrupt pressure increments on left ventricular relaxation (abstr). Am J Cardiol 1980;45:392.
17. **Sonnenblick EH.** The structural basis and importance of restoring forces and elastic recoil for the filling of the heart. Eur Heart J 1980;1(Suppl A): 107–110.
18. **Hori M, Yellin EL, Yoran C, Sonnenblick EH, Frater RWM.** Dynamic diastolic negative pressures and pressure-volume relation of the intact nonfilling canine left ventricle (abstr). Circulation 1980;62:Suppl III:III–205.
19. **Sabbah HN, Anbe DT, Stein PD.** Negative intraventricular diastolic pressure in patients with mitral stenosis: evidence of left ventricular diastolic suction. Am J Cardiol 1980;45:562–566.
20. **Grbic M, Sigwart U, Jaeger M, Rivier JL.** Left ventricular filling and contractility in mitral stenosis (abstr). Am J Cardiol 1982;49:990.
21. **Thompson DS, Waldron CB, Juul SM, Naqvi N, Swanton RH, Coltart DJ, Jenkins BS, Webb-Peploe MM.** Analysis of left ventricular pressure during isovolumic relaxation in coronary artery disease. Circulation 1982;65: 690–697.
22. **Rousseau MF, Veriter C, Detry JMR, Brasseur E, Pouleur H.** Impaired early left ventricular relaxation in coronary artery disease: effects of intracoronary nifedipine. Circulation 1980;62:764–772.
23. **Murgo JP, Craig WE.** Relaxation abnormalities in hypertrophic cardiomyopathy (abstr). Circulation 1980;62:Suppl III:III-316.
24. **Lorell BH, Paulus WJ, Grossman W, Wynne J, Cohn PF.** Modification of abnormal left ventricular diastolic properties by nifedipine in patients with hypertrophic cardiomyopathy. Circulation 1982;65:499–507.
25. **Carroll JD, Blaustein AS, Donaldson JT. Gaasch WH, Levine HJ.** Verapamil uncouples contraction-relaxation in the canine left ventricle (abstr). Circulation 1981;64:Suppl IV:IV-211.



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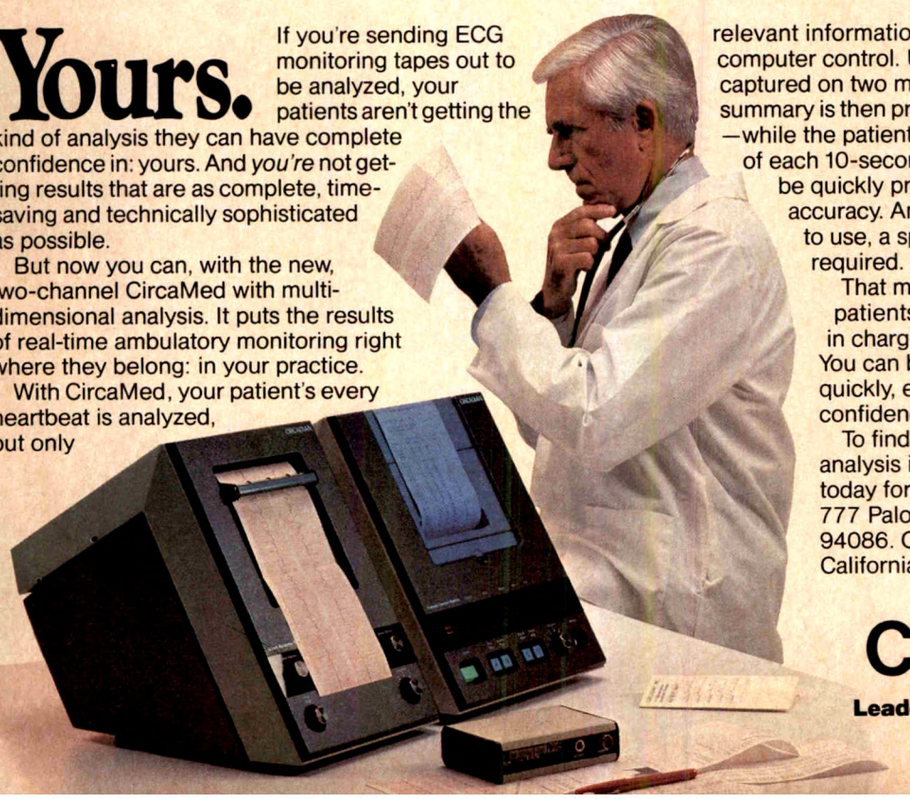
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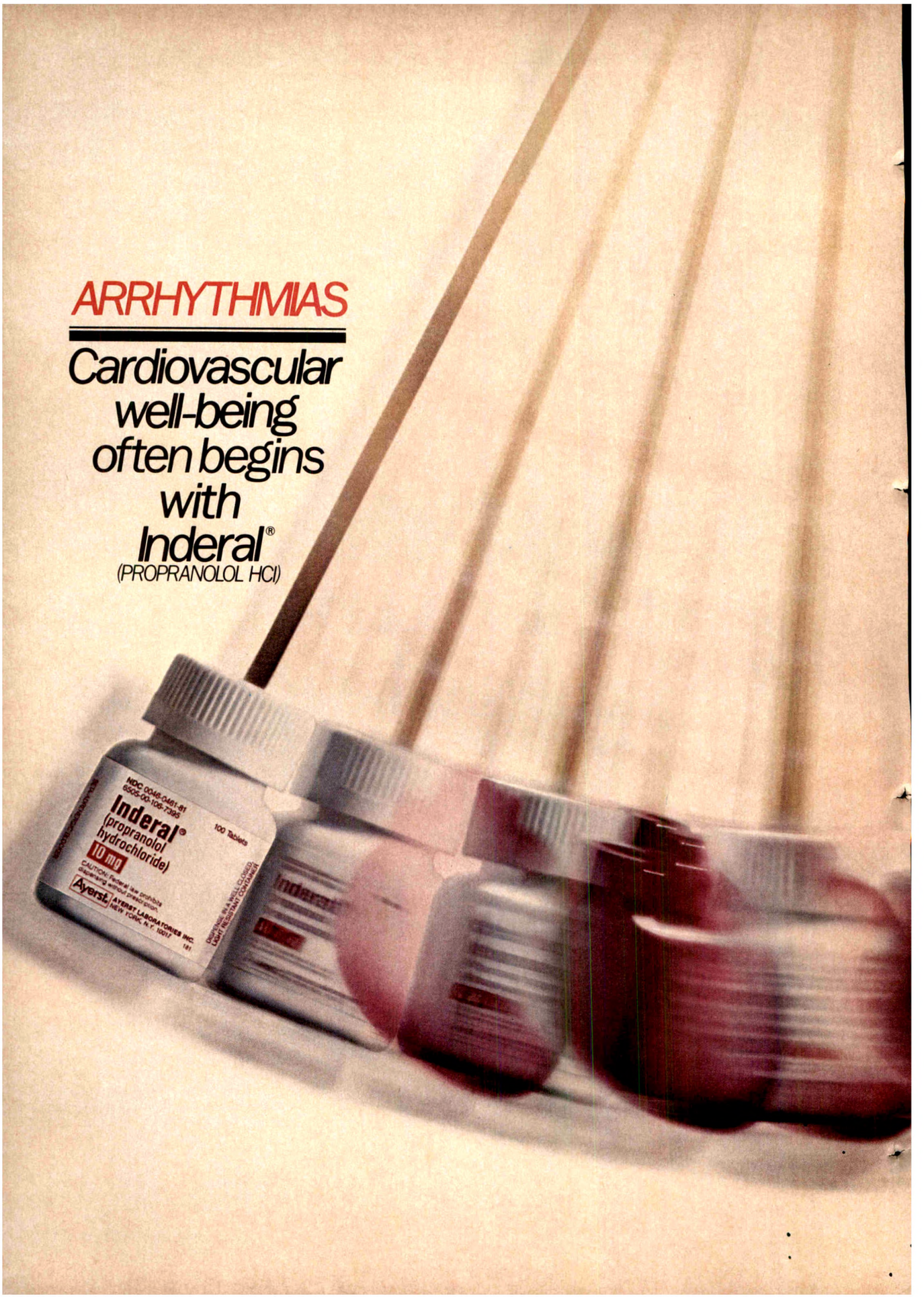
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**Reference:** 1. AMA Department of Drugs: AMA Drug Evaluations, ed. 4. Littleton, Mass., Publishing Sciences Group, Inc., 1980, p. 520.

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*BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
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BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

### CONTRAINDICATIONS

1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless it is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

### WARNINGS

CARDIAC FAILURE: In congestive heart failure, inhibition with beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In patients already receiving digitalis, propranolol may reduce the positive inotropic action of digitalis and may have an additive depressant effect on AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, in rare instances, cardiac failure has developed during propranolol therapy. At the first sign of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. Except in pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery. In case of emergency surgery, the effects of propranolol can be reversed by administration of beta-receptor agonists such as isoproterenol or levarterenol, but such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), administer with caution, since propranolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in patients with labile diabetes. A precipitous elevation of blood pressure may accompany hypoglycemic attacks.

USE IN PREGNANCY: Safe use in human pregnancy not established. Embryotoxic effects have been seen in animals at doses about 10 times the maximum recommended human dose.

### PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if propranolol is administered, since it may occasionally produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

### ADVERSE REACTIONS

*Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease; elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

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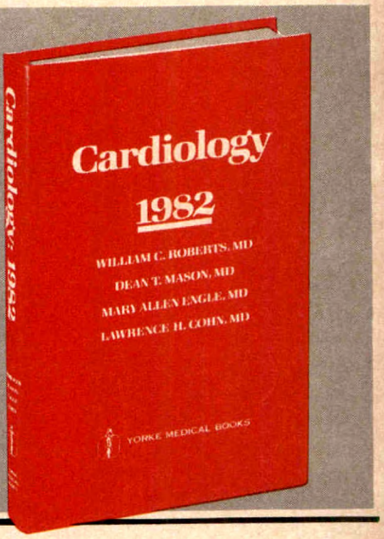
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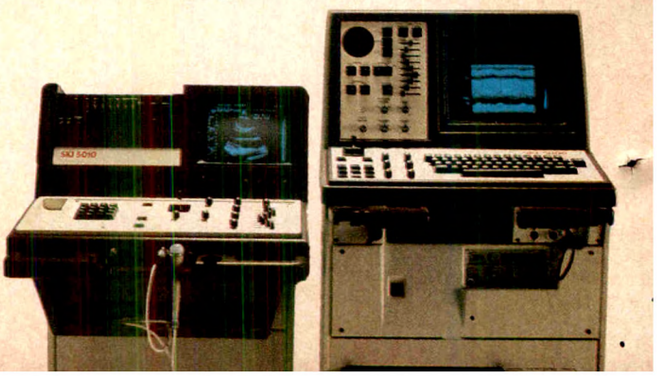
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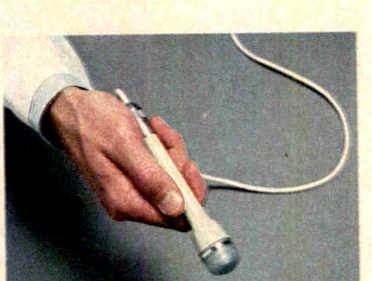


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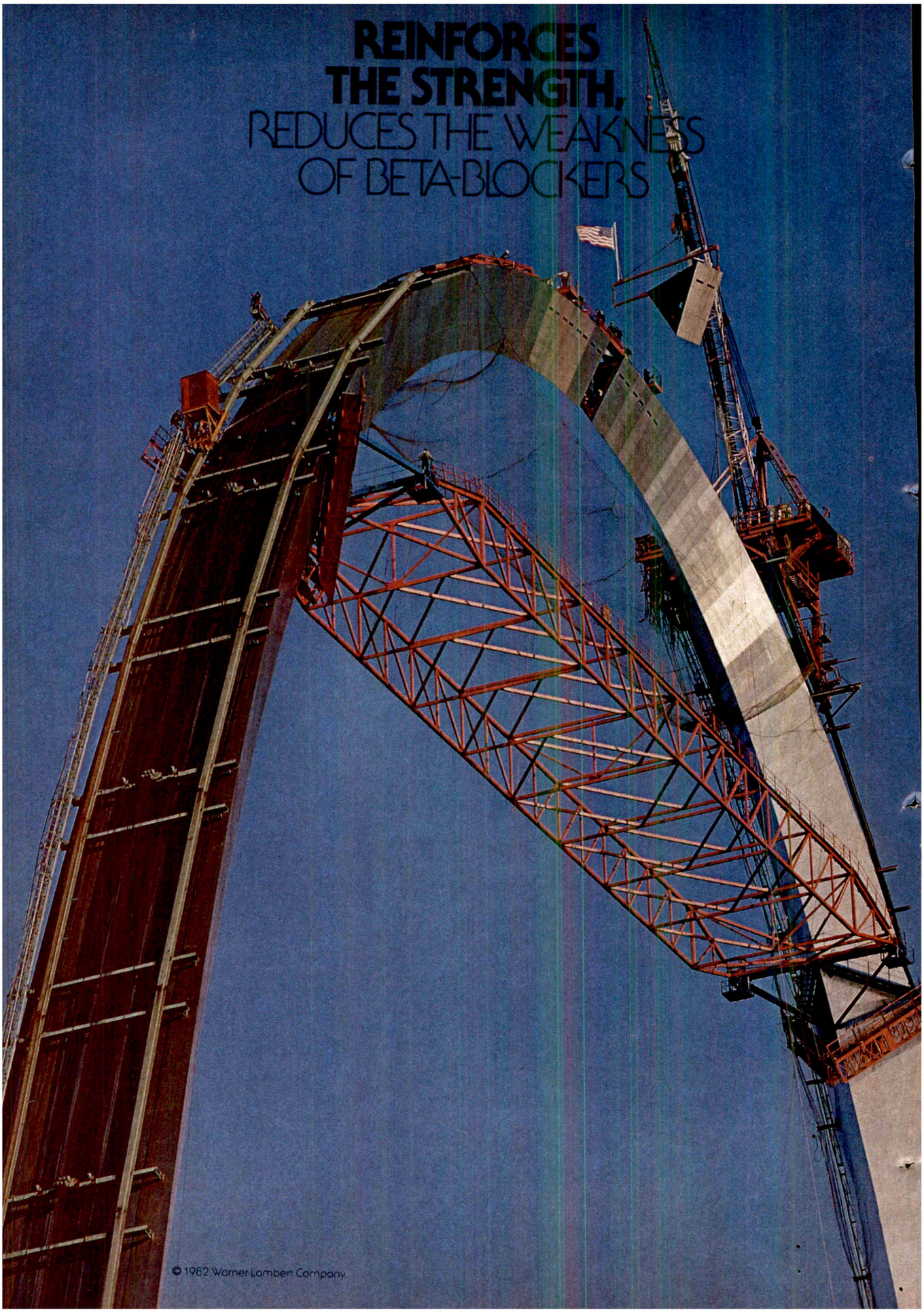
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REFERENCE: 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS and Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833.

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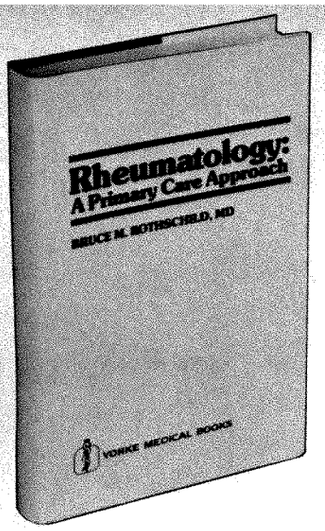
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We know of no other book on rheumatic disease which covers the subject as exhaustively in terms of diagnosis and treatment while avoiding wasting the busy practitioner's time by including information of little interest to the primary care physician. This book emphasizes that information necessary to recognize basic disease processes and their natural history. It provides the reader with the information necessary for making a diagnosis and initiating a plan of treatment. Information on differential diagnosis from the point of view of characteristics which would not fit with a given diagnosis is also provided. It is especially strong on the interpretation of rheumatologic radiology and in its approach to joint examination and assessment of lab results. Rheumatic disease cannot be cured but proper intervention can reduce and sometimes eliminate the attendant disability. This book provides you with the means to diagnose, assess and decide for yourself the necessary intervention.

## From the Preface:

*"More than 15 million individuals in the United States suffer from arthritis, and there are only 3,000 physicians practicing rheumatology. It is evident that the majority of patients receive continuing care from the nonrheumatologist, i.e., the internist, family practitioner, pediatrician and other disciplines in medicine. Therefore, we require concise and authoritative clinical guidelines for the primary care physician. With this as motivation Dr. Bruce Rothschild has skillfully structured a text geared to the particular and immediate needs of the practitioner... This text... is an important contribution to continuing medical education of the clinician. It will be of immediate interest and value to clinicians in a wide variety of specialties and should be of great assistance to the faculties and student bodies of our medical schools. We have long needed this type of approach to primary care of patients with musculoskeletal diseases and we are indebted to the author for his accomplishments."*

**Alfred Soffer, MD**
Chief Editor Archives of Internal Medicine

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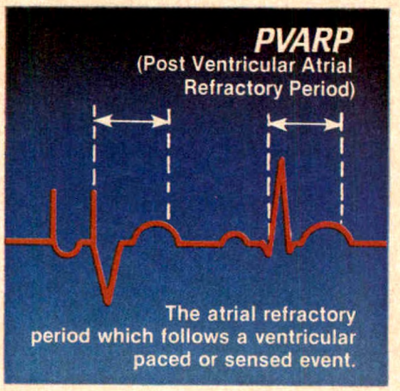
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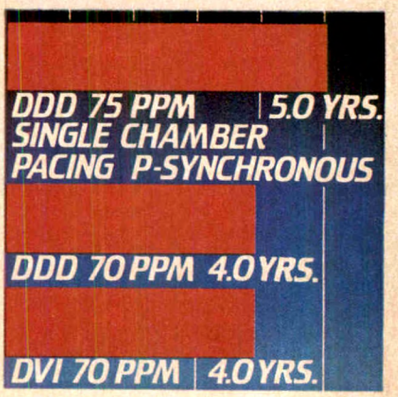
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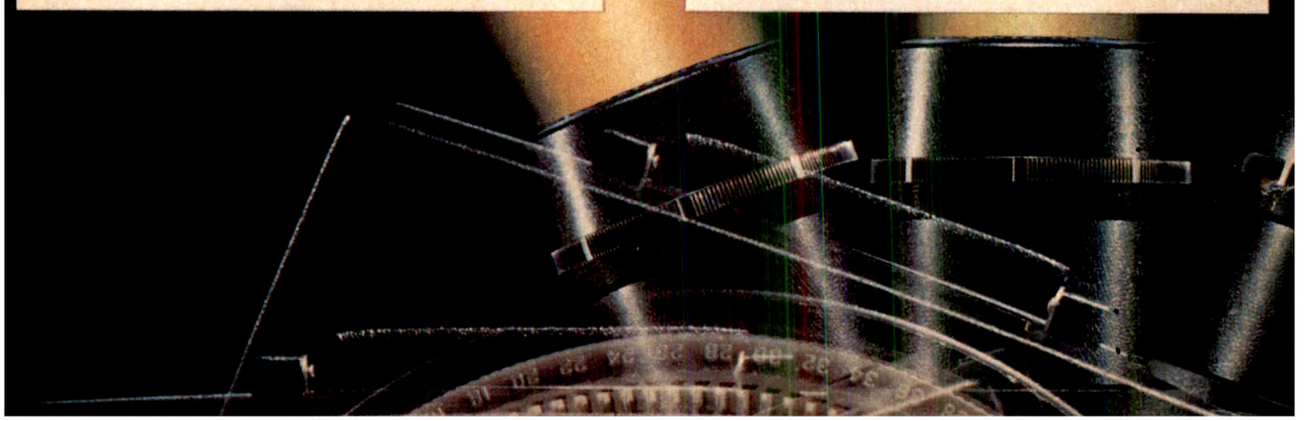



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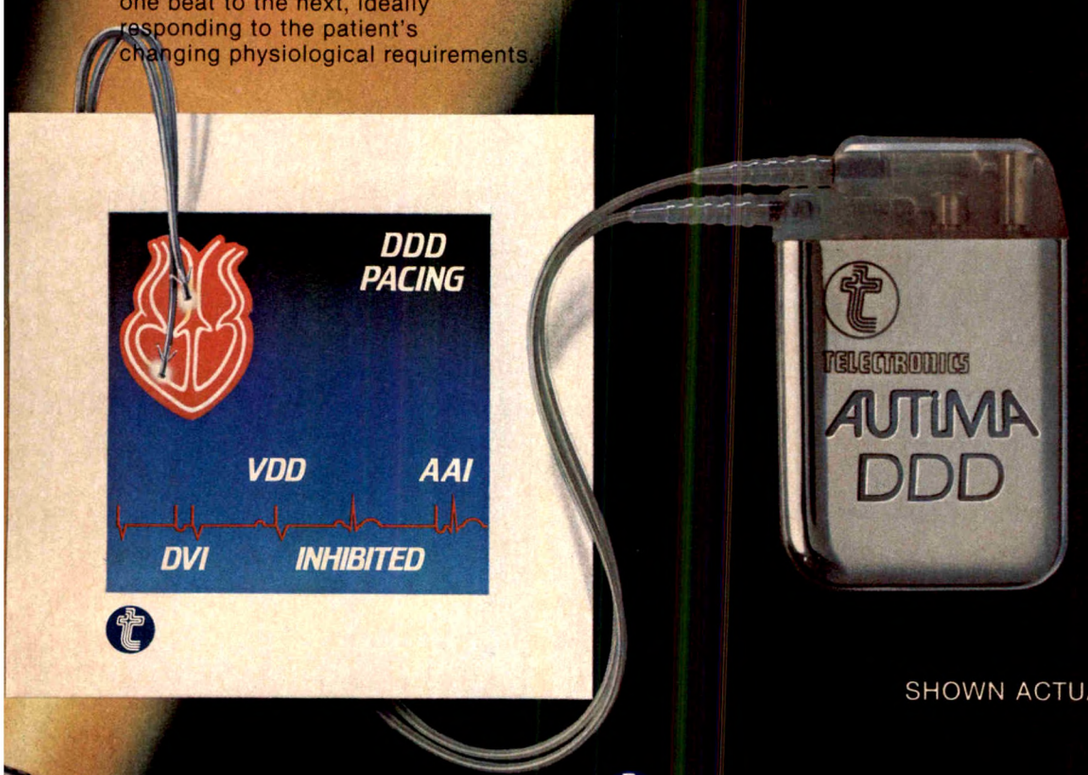


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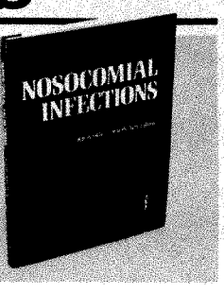


From the American Journal of Medicine

# NOSOCOMIAL INFECTIONS

**edited by**
**Richard E. Dixon, M.D.**

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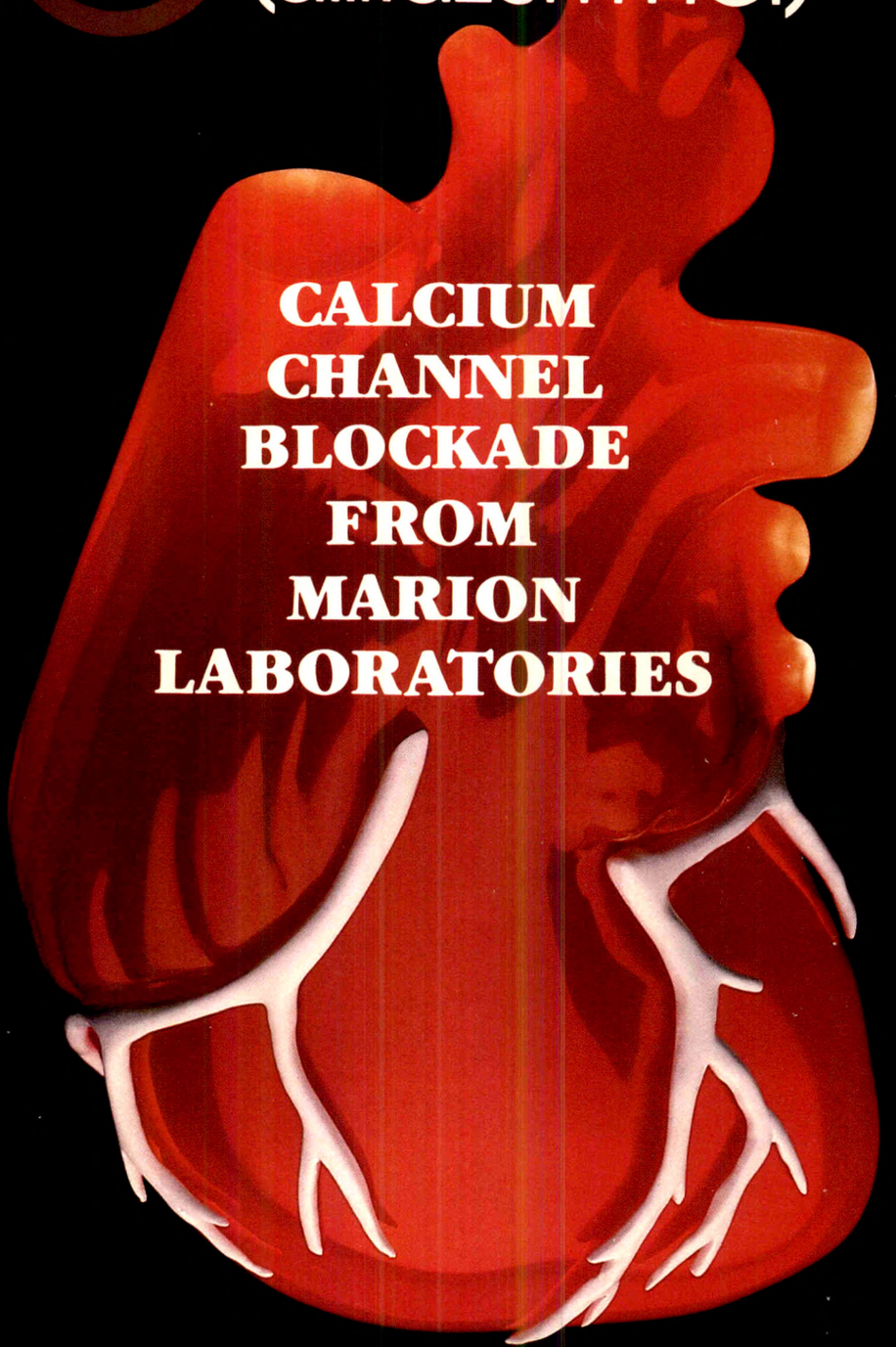
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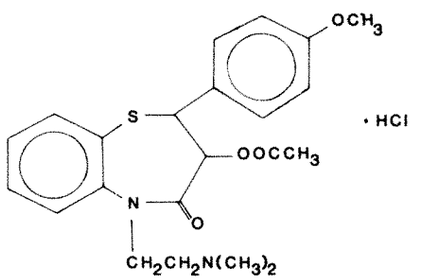
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## ESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagnist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylmino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-.monohydrochloride,(+) -cis-. The chemical structure is:




Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, ethanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or mg diltiazem for oral administration.

## LINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of lcium ions during membrane depolarization of cardiac and vascular smooth muscle.

**Mechanism of Action.** Although precise mechanisms of its antianginal actions are still being delineated, RDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes citation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action tential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small ronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in ronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are companied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

**Hemodynamic and Electrophysiologic Effects.** Like other calcium antagonists, diltiazem decreases sinoatrial d atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients h ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to e, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; diac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly luced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective fractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal unteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV ck. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree rt block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in ne cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR erval, but has not usually produced abnormal prolongation. There were, however, three instances of second-gree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

**Pharmacokinetics and Metabolism.** Diltiazem is absorbed from the tablet formulation to about 80% of a ference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to avenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the hanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma teins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic ncentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single f doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak sma levels 2 to 3 hours after drug administration. The plasma elimination half-life following single or multiple g administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% 0% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood els of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when gle doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

## DICATIONS AND USAGE

**Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).

**Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

here are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of safety of this combination in patients with impaired ventricular function or conduction abnormalities.

## NTRAINDICATIONS

ARDIZEM is contraindicated in 1) patients with sick sinus syndrome except in the presence of a functioning tricular pacemaker, 2) patients with second- or third-degree AV block, and 3) patients with hypotension (less 90 mm Hg systolic).

## RNINGS

**Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.

**Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.

**Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

**Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely and enzymes were nearly of viral hepatitis and received no other drugs but isosorbide dinitrate.

No other similar liver injury has been reported in clinical trials, but marketing experience in Europe ha resulted in a rechallenge confirmed instance of hepatocellular injury. However, it should be noted that ther have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that th relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminas elevation have been reported in Europe, but their relationship to drug is uncertain.

## PRECAUTIONS

**General.** CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with an new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The dru should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog an rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In speci subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes i the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associate with hepatic changes; however, these changes were reversible with continued dosing.

**Drug Interaction.** Pharmacologic studies indicate that there may be additive effects in prolonging AV conductio when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis i usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers o digitalis is currently being investigated in well-controlled studies.

**Carcinogenesis, Mutagenesis, Impairment of Fertility.** A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

**Pregnancy.** Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 5 to 10 times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers.** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

**Pediatric Use.** Safety and effectiveness in children have not been established.

## ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

| | |
|---|---|
| Cardiovascular: | Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart |
| Central Nervous System: | Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations |
| Gastrointestinal: | Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis |
| Dermatologic: | Pruritus, petechiae, urticaria |
| Other: | Photosensitivity, nocturia, thirst, paresthesia, polyuria, osteoarticular pain |

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

## OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

| | |
|---|---|
| Bradycardia | Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. |
| High-Degree AV Block | Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing. |
| Cardiac Failure | Administer inotropic agents (isoproterenol, dopamine or dobutamine) and diuretics. |
| Hypotension | Vasopressors (eg, dopamine or levarterenol bitartrate). |

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral $LD_{50}$'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous $LD_{50}$'s in these species were 60 and 38 mg/kg, respectively. The oral $LD_{50}$ in dogs is considered to be in excess of 50 mg/kg while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

## DOSAGE AND ADMINISTRATION

**Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm.** Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

**Concomitant Use With Other Antianginal Agents.**

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy** — CARDIZEM may be safely co-administered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers** (See WARNINGS and PRECAUTIONS).

## HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 11/82

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EXPERIMENTAL STUDIES

# Comparison of the Antithrombotic Action of Calcium Antagonist Drugs With Dipyridamole in Dogs

CHARLES W. PUMPHREY, DM, MRCP, VALENTIN FUSTER, MD,
MRINAL K. DEWANJEE, PhD, JAMES H. CHESEBRO, MD,
RONALD E. VLIETSTRA, MB, ChB, and MICHAEL P. KAYE, MD,
*With the technical assistance of* JOHN RITTER and JAMES ROSEMARK

**Because platelet activation is associated with fluxes of intracellular calcium, calcium antagonist drugs such as verapamil and nifedipine may have useful platelet inhibitor effects. Accordingly, the effect of these drugs was compared with that of dipyridamole, an established platelet inhibitor, in preventing the deposition of indium-111–labeled autologous platelets and thrombus development in polytetrafluoroethylene (Gore-Tex®) grafts interposed in both femoral arteries in mongrel dogs. Eight dogs received verapamil 7.5 μg/kg/min perioperatively, 8 dogs received nifedipine 4 μg/kg/h perioperatively, 8 dogs received dipyridamole 50 mg orally given twice during the 24 hours before operation, and 16 control dogs received isotonic saline solution perioperatively. After 3 hours of perfusion, the median weight of the grafts and luminal thrombus was less in dogs treated with dipyridamole (465.1 mg), verapamil (453.7 mg), or nifedipine (389.7 mg) than in control dogs (680.2 mg) ($p < 0.001$). In addition, the estimated total platelet deposition along the graft was reduced in dogs treated with dipyridamole (2,073.2 $\times 10^6$) ($p < 0.01$), verapamil (1,898.9 $\times 10^6$) ($p < 0.001$), and nifedipine (1,474.8 $\times 10^6$) ($p < 0.001$) as compared with controls (3,056.2 $\times 10^6$). When the mural thrombus was removed from 14 grafts, a median 73% of the platelets were located in the interface between thrombus and graft. We conclude that all 3 drugs prevent thrombus formation by inhibiting platelet activity in this model, and that the calcium antagonist drugs are as effective as dipyridamole.**

Thrombosis in the high-pressure arterial system is the result of a complex interaction between the vessel wall and blood components. Initially, a primary layer of platelets adhere to the vessel surface; subsequently, platelet-platelet aggregation ensues.[1,2] These platelet aggregates then interact with the coagulation system to form the characteristic red cell-fibrin body of an arterial thrombus.

Three independent biochemical pathways are responsible for the process of platelet activation, namely, cellular release of adenosine diphosphate,[3] the prostaglandin cyclic endoperoxides and thromboxane $A_2$,[4,5] and the platelet aggregating factor pathway.[6,7] The relative importance of these different pathways in arterial thrombosis remains to be established.[8,9] All 3 result in a decrease in cyclic adenosine 5[1]-monophosphate, an increase in cytoplasmic calcium, and a subsequent shape change and release.[10,11] Reduction of this flux of calcium into the cytoplasm might limit or abolish the platelet response, irrespective of the nature of the primary stimulus for activation. Thus, the calcium antagonist drugs nifedipine and verapamil may have a potential role as clinically useful platelet-inhibitor drugs.

In vivo platelet thrombus can now be identified by labeling autologous platelets with indium-111.[12] Therefore, we have developed a model of thrombosis in dogs, using femoral artery grafts, in which we compared the platelet-inhibitor effect of verapamil and nifedipine with that of the established platelet-inhibitor dipyridamole.[13,14]

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## Methods

**The dog model:** Platelet deposition and thrombotic occlusion were studied in bilateral femoral artery grafts in mongrel dogs (weight 20 to 25 kg). After induction of anesthesia with pentobarbital (30 mg/kg), the femoral arteries were

exposed on each side and cross-clamped after a bolus of heparin (100 U/kg Upjohn Beef Lung, Upjohn) had been given intravenously. A 4-cm segment of each femoral artery was then replaced with 5 cm of expanded polytetrafluoroethylene (Gore-Tex, W. L. Gore and Associates), 4 mm in diameter, and running 7-0 Prolene sutures were used at the anastomoses. The longer length of graft used to replace the segment of artery reduced the tension on the anastomotic sites resulting from the intrinsic elasticity of the arteries. By interposing polytetrafluoroethylene grafts bilaterally, any thrombus formation that might have resulted from unilateral errors in surgical technique rather than differences in antithrombotic therapy could be recognized.

Three hours after blood flow was resumed through the grafts, the dogs were killed with an overdose of pentobarbital and the grafts were removed. By this time no effect of circulating heparin on the partial thromboplastin time was demonstrable.

**Treatment groups:** Forty animals were studied; 8 received intravenous verapamil (7.5 μg/kg/min), 8 received intravenous nifedipine (4 μg/kg/min), 8 received oral dipyridamole (100 mg in the 24 hours before the study), and 16 served as controls.

The dosage regimens were selected on the basis of published reports.[15–17] Both verapamil and nifedipine were given in isotonic saline solution immediately after induction of anesthesia before operation was begun, and the infusion was continued until the grafts were removed. Verapamil plasma levels were determined by a modification of the high pressure liquid chromatographic method of Harapat et al.[18] The median verapamil concentration was 174.5 ± 33.4 ng/ml (mean ± standard deviation) at 3 hours; this regimen caused a 7.8 ± 3.2% increase in femoral artery blood flow measured by a 2 channel electromagnetic flow meter (Carolina Medical Electronics), a 14.2 ± 2.7% increase in heart rate, and no alteration in mean aortic pressure. No plasma nifedipine levels were measured, but the dosage regimens used caused a 7.6 ± 4.5% increase in femoral artery blood flow, a 17.3 ± 6.7% increase in heart rate, and a 5.6 ± 1.8% decrease in mean aortic pressure. Because of the photosensitivity of nifedipine in solution, a light-free system of administration was used.

Dipyridamole was given orally in 2 doses during the 24 hours before the study. The second dose, given 1 to 2 hours before operation, resulted in a median plasma dipyridamole concentration of 370 ng/ml (range 235 to 550) at 3 hours. No hemodynamic measurements were made and, as with the control dogs, isotonic saline solution (100 ml/h) was given intravenously during the study to these dogs. This volume of saline solution was similar to that given to the dogs treated with verapamil and nifedipine.

**Indium-111 labeling of platelets:** Eighteen to 24 hours before operation, 43 ml of blood was withdrawn from the dog into 7 ml of acid-citrate-dextrose anticoagulant and labeled with indium-111 tropolone according to the method of Dewanjee et al.[19] Two hours later, the platelets, resuspended in plasma, were injected in doses of 300 to 500 μCi.

**Processing of grafts:** After the grafts were removed, they were gently perfused with isotonic saline solution and any blood was cleaned off the exterior surface. The grafts were then sectioned into 5 pieces in order to assess thrombus formation in different parts of the graft. Each anastomotic section consisted of 2 mm of native artery and 2 mm of polytetrafluoroethylene. The middle sections consisted of 3 equal lengths of polytetrafluoroethylene.

The effect of the drugs was assessed in 2 ways:

1. *Thrombus formation:* Formation of thrombus was estimated from the weights of the graft section; because the dry weight of each 5-cm length of polytetrafluoroethylene was found to be almost the same (257 to 264 mg), the increased weight of the graft sections represented thrombus formation. Before the sections were weighed, care was taken to ensure that no saline solution remained in these graft sections.
2. *Platelet deposition:* The radioactive counts arising from platelets deposited on the graft wall were measured in a gamma counter (Beckman Gamma 8000). The gamma-ray spectrometer was adjusted to include the 174, 247, and 421 (sum peak) keV of indium-111 radionuclide. The activities of 3 5-ml samples of blood, taken from each animal at the time the grafts were removed, were also counted. From the platelet count (measured on a sample taken before heparinization), the number of platelets deposited/centimeter length of graft could be estimated.

**Platelet distribution in thrombus:** To assess the relation between weight and platelet count, 14 grafts underwent further analysis. After weighing the graft and thrombus together, the body of each thrombus was removed and weighed separately. From the radioactivity of each graft and that of the thrombus removed from it (corrected for weight), the number of platelets located at the graft-thrombus interface and within the body of the thrombus could be measured.

**Analysis of data:** The results of thrombus weight and platelet deposition from the 2 grafts in each dog were averaged and the average values were analyzed.

For statistical analysis the Mann-Whitney U test for differences between independent samples was used.

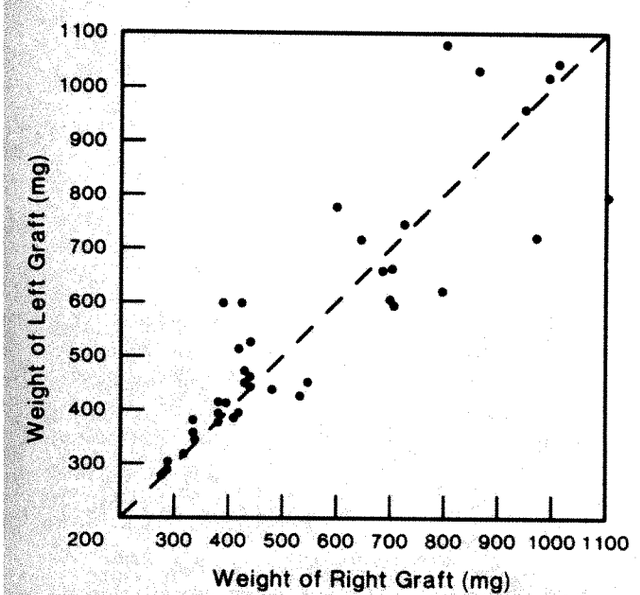



**FIGURE 1.** Comparison of total weights of right and left polytetrafluoroethylene grafts (including thrombus) after 3 hours of perfusion in control (n = 16) and treated (n = 8) dogs for each group.

## Results

The degree of occlusion observed in the grafts varied; there was usually either a white lining layer of platelets streaked with red cells, or partial occlusion of the graft by protruding red thrombus extending along its length. In 6 control dogs and in 2 dogs from each treatment group, however, the grafts were occluded.

**Thrombus weight:** For each dog studied a close correlation existed ($r = 0.88$, $p < 0.001$) between the

**TABLE I Total Weight of Thrombus and Graft* After 3 Hours of Perfusion**

| | n | Median (mg) | Range (mg) | p Value Versus Control |
|---|---|---|---|---|
| Control | 16 | 680.2 | 401.9–1032.6 | . . . |
| Dipyridamole | 8 | 465.1 | 387.5–863.9 | <0.001 |
| Verapamil | 8 | 453.7 | 302.4–742.9 | <0.001 |
| Nifedipine | 8 | 389.7 | 355.0–837.0 | <0.001 |

* Includes 2 mm of native artery at each anastomosis.

**TABLE II Total Platelet Deposition Within the Graft* After 3 Hours of Perfusion**

| | n | Median Platelet Count $\times 10^6$ | Range | p Value Versus Control |
|---|---|---|---|---|
| Control | 16 | 3,056.2 | 1,040.9–7,764.6 | . . . |
| Dipyridamole | 8 | 2,073.2 | 812.1–8,261.8 | <0.01 |
| Verapamil | 8 | 1,898.9 | 360.5–5,631.8 | <0.001 |
| Nifedipine | 8 | 1,474.8 | 885.2–8,972.9 | <0.001 |

* Includes 2 mm of native artery at each anastomosis.

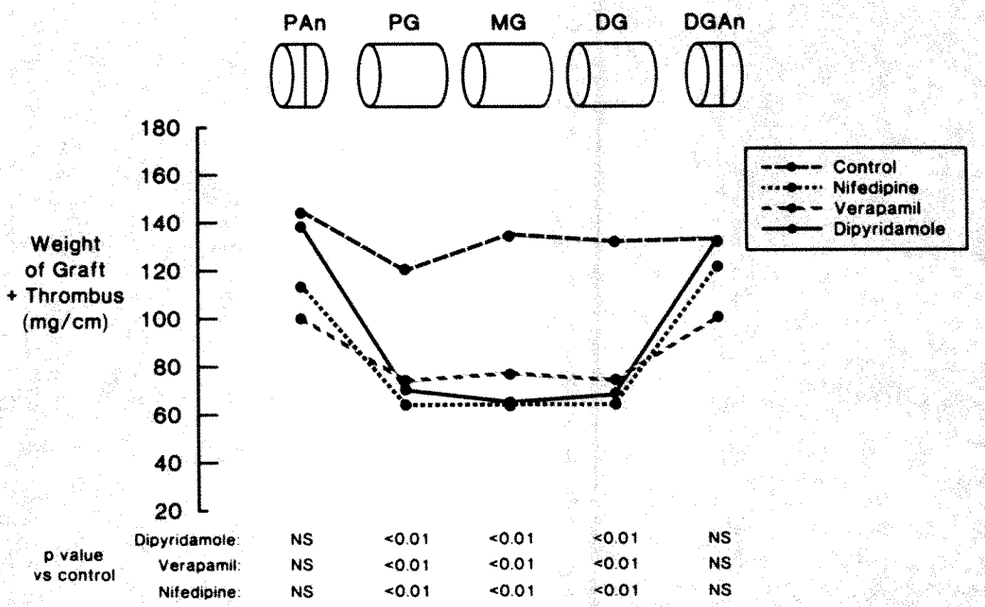



**FIGURE 2.** Distribution of thrombus formation in polytetrafluoroethylene grafts after 3 hours of perfusion (median values, mg/cm) in control (n = 16) and treated (n = 8) dogs for each group. (The weights of the anastomoses have been standardized to 1.0 cm for comparison with the rest of the graft sections.) DG = distal graft section; DGAn = distal anastomosis; MG = middle graft section; PAn = proximal anastomosis; PG = proximal graft section.

weight of the thrombus deposited in each of the 2 grafts (Fig. 1). The median weight of the grafts from the treated dogs was significantly lower than the median weight of those from the control dogs (Table I). No difference in median weights was observed among the various treatment groups.

The reduction in weight occurred along all 3 middle sections of the grafts, but not at the anastomoses (Fig. 2).

**Platelet deposition:** For each of the dogs studied, a close correlation existed ($r = 0.89$, $p < 0.001$) between the number of platelets deposited in each of the 2 grafts (Fig. 3). Overall, significantly fewer platelets were deposited in the grafts of the treated dogs than in those of the control group (Table II). In the latter group, platelet accumulation was greatest at the distal anastomosis and diminished proximally; the platelet accumulation at the proximal anastomosis was only half that at the distal anastomosis (Fig. 4). The effect of the drugs was most significant on the 3 middle sections and although all of the drugs had an effect at the distal anastomosis, only verapamil reduced platelet accumulation at the proximal anastomosis.

**Platelet distribution in thrombus:** The median radioactivity of thrombus removed from 14 grafts was 27% (range 5 to 49) of that of the total graft. Thus, most platelets in the thrombosed grafts were located at the graft thrombus interface and few platelets were present in the body of the thrombus. This pattern of distribution of platelets within the thrombus indicated that the notable decrease in platelet deposition observed in the treated dogs was not merely caused by a reduction in the amount of mural thrombus, but also by an actual decrease in platelets deposited along the graft surface.

## Discussion

This in vivo model of thrombosis in a high-pressure, high-flow system has advantages over in vitro tests; that is, there is no unphysiologic separation of the sequence of events which take place during thrombosis, and calcium-chelating anticoagulants are not used. Although

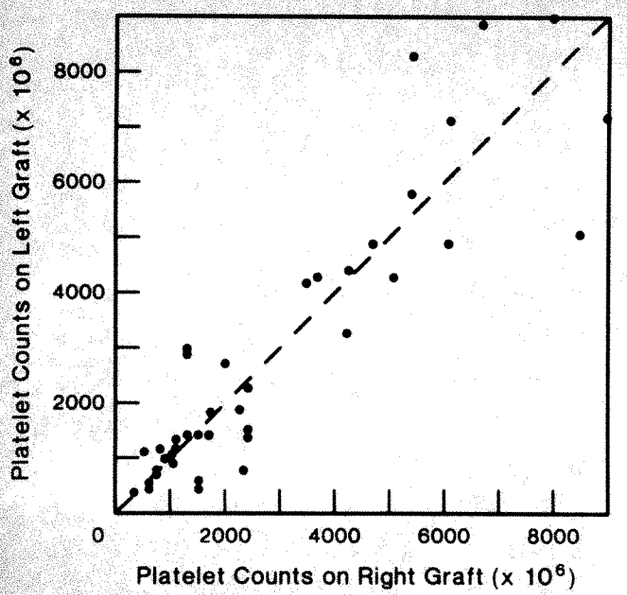


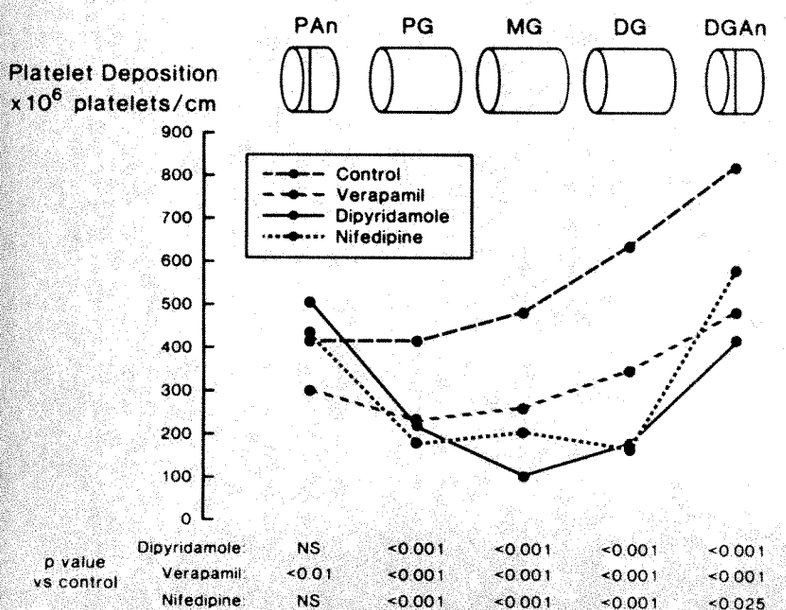

**FIGURE 3.** Comparison of total number of platelets deposited on right and left polytetrafluoroethylene grafts after 3 hours of perfusion in control (n = 16) and treated (n = 8) dogs for each group.

the contribution of circulating prostacyclin in preventing thrombosis is uncertain, the grafts do not have the protection of the prostaglandin and fibrinolytic systems located in the natural vascular endothelium. It therefore remains an artificial system in which the possible counterbalancing effect of drug treatment on these natural antithrombotic mechanisms cannot be totally assessed.

In this model, dipyridamole, verapamil, and nifedipine all had effective antithrombotic actions in the doses administered and this action seemed to be mediated through platelet inhibition. The activity of dog platelets is very variable and 6 control dogs and 2 dogs from each treated group developed occlusions in both grafts; however, no other tests of platelet function were performed which might have shown that these dogs had more active platelets. Frequently, only a lining white layer of platelets streaked with red cells was observed in the grafts of the treated animals. It is possible that a threshold number of platelets has to accumulate on the graft surface to trigger the formation of the red cell fibrin network of which the bulk of mural thrombi are made. The drugs may reduce this platelet accumulation and thereby prevent thrombus formation.

All 3 drugs are known to alter circulatory hemodynamics. Such changes might have contributed to the reduced thrombus formation observed in the treated dogs. However, only a small increase (<8%) in femoral artery blood flow was observed; this is unlikely to be a critical change. Furthermore, no relation was observed between femoral artery blood flow and thrombus formation.

The anastomotic sites of the grafts are important foci for thrombogenesis. Both the presence of sutures and difference in compliance of the artery and the graft result in turbulence which leads to thrombus formation. The effect of the drugs on these sites was less clear. The number of platelets on the anastomoses included those plugging the suture line and those trapped in extravascular thrombus adherent to the sutures; this is difficult to remove completely during the preparation of the graft for analysis, which may account for the lack of demonstrable effect of any of the drugs on thrombus weight at either anastomosis. Furthermore, in the control dogs, platelet deposition at the distal anastomosis was twice that at the proximal anastomosis, suggesting that thrombus formation begins distally. All 3 drugs reduced platelet deposition at the distal anastomosis, but only verapamil was effective at the proxi-




| p value vs control | PAn | PG | MG | DG | DGAn |
|---|---|---|---|---|---|
| Dipyridamole | NS | <0.001 | <0.001 | <0.001 | <0.001 |
| Verapamil | <0.01 | <0.001 | <0.001 | <0.001 | <0.001 |
| Nifedipine | NS | <0.001 | <0.001 | <0.001 | <0.025 |

**FIGURE 4.** Distribution of platelet deposition on polytetrafluoroethylene grafts after 3 hours of perfusion (median values, platelet count × $10^6$/cm). Abbreviations as in Figure 2.

mal anastomosis. This may indicate that verapamil is a more effective platelet inhibitor than either dipyridamole or nifedipine.

**Dipyridamole:** This drug is often prescribed as a platelet inhibitor, particularly in combination with aspirin.[20] It appears that by blocking the platelet phosphodiesterase enzyme,[13,21] dipyridamole potentiates the increase in cyclic adenosine 5′ monophosphate and platelet inhibition caused by the vessel wall prostacyclin. The platelet-inhibition action of this drug was well demonstrated in this dog model and gives a point of reference against which other drugs may be compared.

**Nifedipine and verapamil:** Nifedipine and verapamil have different structural, electrophysiologic, and pharmacologic properties.[22] In this study, their antithrombotic effect was found to be similar and equivalent to that of dipyridamole. The plasma levels of verapamil and dipyridamole were in the range encountered in clinical practice[23,24]; the plasma level of nifedipine was not measured but produced hemodynamic changes similar to those of verapamil. Other investigators have differed about whether verapamil has a significant platelet inhibiting action at therapeutic plasma levels,[25,26] but in contrast to this study, their conclusions were based mainly on in vitro platelet function tests.

The mechanism by which these calcium antagonists inhibit platelets is uncertain. They may prevent internal release of calcium from the tubular system into the cytoplasm; alternately they may reduce calcium flux across the plasma membrane, a process that is known to occur during platelet activation, and which may be the stimulus for the mobilization of intracellular calcium.[27,28] Regardless of their specific action, however, the final effect may be equivalent to that of dipyridamole in that they inhibit the final stages of the biochemical pathways involved in platelet activation.

*In conclusion*, this study has demonstrated that in this model both nifedipine and verapamil have a platelet-inhibitor function equivalent to that of dipyridamole and both can reduce the development of thrombus on prosthetic material. The well-recognized species variability of platelet behavior prevents any direct comparisons between the findings in this study and the likely platelet inhibitory effect of these drugs in humans. Preliminary reports by other investigators,[27,28] however, suggest that human platelets can be inhibited by verapamil. If so, our findings may indicate another useful feature of 2 calcium antagonist drugs already of proven value in the management of cardiovascular disease.

## References


1. **Fuster V, Chesebro JH.** Antithrombotic therapy: role of platelet inhibitor drugs. Current concepts of thrombogenesis. Role of platelets. Mayo Clinic Proc 1981;56:102–112.
2. **Fuster V, Bowie EJW, Lewis JC, Fass DN, Owen CA Jr.** Resistance to arteriosclerosis in pigs with von Willebrand's disease. Spontaneous and high cholesterol diet induced arteriosclerosis. J Clin Invest 1980;61: 722–730.
3. **Packham MA, Mustard JF.** Clinical pharmacology of platelets. Blood 1977;50:555–573.
4. **Marcus AJ.** The role of lipids in platelet function, with particular reference to the arachidonic acid pathway. J Lipid Res 1978;19:793–826.
5. **Moncada S, Vane JR.** Unstable metabolites of arachidonic acid and their role in haemostasis and thrombosis. Br Med Bull 1978;34:129–136.
6. **Chignard M, Tence M, LeCovedic JP, Vargaftig BB, Benveniste J.** Is platelet aggregating factor the mediator for the third pathway for platelet aggregation? (abstr). Fed Proc 1979;38:1342.
7. **Tence M, Polonsky J, LeCovedic JP, Benveniste J.** Release purification and characterization of platelet aggregating factor. Biochimie 1980;62: 251–259.
8. **Kinlough-Rathbone RL, Packham MA, Reimers HJ, Cazenave JP, Mustard JF.** Mechanisms of platelet shape change, aggregation and release induced by collagen, thrombin, or A23187. J Lab Clin Med 1977;90:707–719.
9. **Packham MA, Guccione MA, Greenberg JP, Kinlough-Rathbone RL, Mustard JF.** Release of $^{14}$C-Serotonin during initial platelet changes induced by thrombin, collagen, or A23187. Blood 1977;50:916–926.
10. **Owen NE, LeBreton GC.** The involvement of calcium in epinephrine or ADP potentiation of human platelet aggregation. Thromb Res 1980;17:855–863.
11. **Charo IF, Feinman RD, DeTwiler TC.** Inhibition of platelet secretion by an antagonist of intracellular calcium. Biochem Biophys Res Commun 1974;72:1462–1467.
12. **Fuster V, Dewanjee MK, Kaye MP, Josa M, Metke MP, Chesebro JH.** Noninvasive radioisotopic technique for detection of platelet deposition in coronary artery bypass grafts in dogs and its reduction with platelet inhibitors. Circulation 1979;60:1508–1512.
13. **Moncada S, Korbut R.** Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. Lancet 1978;1:1286–1289.
14. **Harker LA, Slichter SJ.** Platelet and fibrinogen consumption in man. N. Engl J Med 1972;287:999–1005.
15. **Mangiardi LM, Hariman RJ, McAllister RG, Bhargava V, Surawicz B, Shabetai R.** Electrophysiologic and haemodynamic effects of verapamil. Correlation with plasma drug concentrations. Circulation 1978;57:366–372.
16. **McAllister RG, Bourne DWA, Dittert LW.** The pharmacology of verapamil. 1. Elimination kinetics in dogs and correlation of plasma levels with effect on the electrocardiogram. J Pharmacol Exp Ther 1977;202:38–44.
17. **Henry PD, Schuchleib R, Borda LJ, Roberts R, Williamson JR, Sobel BE.** Effects of nifedipine on myocardial perfusion and ischemic injury in dogs. Circ Res 1978;43:372–380.
18. **Harapat SR, Kates RE.** Rapid high-pressure liquid chromatographic analysis of verapamil in blood and plasma. J Chromatogr 1979;170:385–390.
19. **Dewanjee MK, Rao SA, Didisheim P.** Indium-111 tropolone, a new high affinity platelet label: preparation and evaluation of labeling parameters. J Nucl Med 1981;22:981–987.
20. **Fuster V, Chesebro JH.** Antithrombotic therapy: role of platelet-inhibitor drugs. Mayo Clin Proc 1981;56:266–273.
21. **Mills DCB, Smith JB.** The influence on platelet aggregation of drugs that affect the accumulation of adenosine 3$^1$:5$^1$-cyclic monophosphate in platelets. Biochem J 1971;121:185–196.
22. **Henry PD.** Comparative pharmacology of calcium antagonists: nifedipine, verapamil, and diltiazem. Am J Cardiol 1980;46:1047–1058.
23. **Shand DG, Hammill SC, Aanson L, Pritchett ELC.** Reduced verapamil clearance during long-term oral administration. Clin Pharmacol Ther 1981;30:701–703.
24. **Tyce GM, Fuster V, Owen CA:** Dipyridamole levels in plasma of man and other species. Res Commun Chem Pathol Pharmacol 1979;26:495–508.
25. **Davenport N, Goldstein RE, Rossing DR, Leon M, Jordan J, Shulman NR.** Platelet response of patients on verapamil (abstr). Circulation 1981;64:Suppl IV:IV-56.
26. **Chierchia S, Crea F, Bernini W, Gensini G, Parodi O, DeCaterina R, Maseri A.** Antiplatelet effects of verapamil in man (abstr). Am J Cardiol 1981;47: 399.
27. **Heptinstall S, Taylor PM.** The effect of citrate and extracellular calcium ions on the platelet release reaction induced by adenosine diphosphate and collagen. Thromb Haemost 1979;42:778–793.
28. **Massini P, Luscher EF.** On the significance of the influx of calcium ions into stimulated human blood platelets. Biochimi Biophys Acta 1976;436: 652–663.

# Influence of Intracoronary Platelet Aggregation on Ventricular Electrical Properties During Partial Coronary Artery Stenosis

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**Several clinical studies suggest that drugs which interfere with platelet function may protect persons at risk for sudden death. However, there is no direct evidence that intracoronary platelet aggregation produces cardiac arrhythmias. Induction of fixed partial coronary stenoses in dogs resulted in spontaneous cyclical reductions in coronary blood flow of 21 to 81% ($p < 0.01$). These changes are known to be associated with the formation and distal embolization of platelet aggregates. These reductions in coronary blood flow were accompanied by significant decreases in the repetitive extrasystole (−40%) and ventricular fibrillation (−38%) thresholds. Prostacyclin ($PGI_2$), a potent vasodilator and inhibitor of platelet activation, in increasing doses of from 25 to 100 ng/kg/min caused a stepwise decrease in the frequency and magnitude of coronary blood flow fluctuations and restored the vulnerable period thresholds to control levels. Indomethacin (5 mg/kg), an inhibitor of cyclo-oxygenase activation and platelet thromboxane $A_2$ production, produced similar results. The mechanism of coronary blood flow reduction appears to be mechanical blockade of the vessel lumen by platelet thrombi and production of myocardial ischemia. These results suggest that intracoronary platelet aggregation contributes to electrical destabilization of the myocardium and may predispose to ventricular fibrillation. A model is thus available for further investigating the role of platelets and antiplatelet drugs in modulating ventricular electrical stability.**

The problem of sudden cardiac death compels increasing attention because of the inordinate magnitude of fatality as well as the growing realization that the problem is reversible as well as preventable.[1] Although death is caused by ventricular fibrillation, the precipitating mechanisms of the lethal arrhythmia remain undefined. Since in most sudden death victims acute cardiac morphologic lesions are lacking, the possibility of a transient ischemic process needs to be considered. Intravascular platelet aggregates may contribute to the ischemic process. The induction of platelet aggregation in animals with adenosine diphosphate causes both myocardial infarction and lethal arrhythmias.[2,3] Pathologic studies on patients who have died suddenly have shown platelet microthrombi and platelet aggregates in numbers far greater than in those whose death was not sudden.[4–6] In a recent epidemiologic study involving patients who had recovered from acute myocardial infarction, the antiplatelet drug sulfinpyrazone decreased the occurrence of sudden death.[7]

While platelet aggregation may contribute to the pathophysiology of sudden death, there are no studies defining the effect of platelet aggregation on the electrical stability of the myocardium. A major methodologic advance has been provided by Uchida,[8] Folts,[9] and their co-workers, who developed a model of partial coronary stenosis in which cyclical reductions in coronary blood flow occur. These changes in coronary flow result from intermittent intracoronary platelet aggregation.[10]

The objectives of the present study were (1) to determine whether alterations in coronary flow brought about by intracoronary platelet aggregation result in

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significant changes in the vulnerable period threshold, and (2) to define mechanisms involved in the observed effects.

## Methods

**General procedures:** Twenty-six healthy mongrel dogs of either sex, weighing 12 to 22 kg, were used in this study. Anesthesia was induced with intravenous alpha-chloralose, 100 mg/kg (Sigma Chemical, 10% weight/volume). Additional alpha-chloralose, 50 mg/kg, was given to maintain the level of anesthesia during the course of experiments. The animals were ventilated with a mixture of room air and 100% oxygen given through a cuffed endotracheal tube, using a Harvard respirator. The mixture contained approximately 40% oxygen and was adjusted, together with respiratory rate, to maintain arterial oxygen tension of 80 to 100 mm Hg and arterial pH of 7.35 to 7.45. A polyethylene catheter was inserted into a femoral artery to sample arterial blood and monitor systemic blood pressure. Mean pressures were obtained by electrically integrating the pulsatile output of the transducer. A femoral vein was cannulated for drug administration. Defibrillation was accomplished within 5 seconds of initiation of ventricular fibrillation, utilizing a direct current capacitor discharge from a Lown cardioverter. A 10 to 40 W second shock was delivered by means of 2 electrode paddles applied directly to the heart.

A left thoracotomy was performed through the fifth left intercostal space and the heart exposed after pericardiotomy. The left circumflex coronary artery was dissected about 1 cm from its origin and a 1.5 to 2.2 mm electromagnetic flow probe placed around it, proximal to any side branches. Coronary blood flow measurements were performed, using a Gould Statham Blood Flowmeter, model SP2202. Pulsatile and mean coronary artery blood flow were recorded throughout the experiment, together with aortic blood pressure, on a multichannel polygraph recorder.

**Cardiac testing:** Testing stimuli of variable duration were employed, using electrically isolated Grass S44 and S88 square wave pulse generators. A Kepco operational power supply (type OPS-100) provided constant current stimuli (2% accuracy). The current output was directly verified by means of a Tektronix P6021 alternating current probe attached to a Tektronix P6120N oscilloscope. Timing of stimuli was controlled, using a BRS digital timer with a crystal-controlled time base (±0.01% accuracy) and was synchronized from the peak of the QRS complex. The pulse generator was equipped with appropriate circuitry to shut off the pacemaker output for up to 3 seconds after delivery of the test stimuli. Ventricular fibrillation thresholds were determined using the single stimulus method.[11]

**Single stimulus method:** Two bipolar catheters were used. The first (Medtronic 5818 platinum electrodes with an interelectrode distance of 1.5 cm and a pole width of 3 mm) was placed in the right ventricular apex by way of a jugular vein. This catheter served to deliver test stimuli. The second catheter (U.S. Catheter Corporation, semifloating 003992 4F) was bound to the pacing catheter by silk ligatures and terminated 20 mm proximal to the tip of the pacing catheter. This catheter was used to record the intracavitary electrocardiogram. Heart rate was controlled using a variable rate pacemaker that delivered constant current rectangular stimuli with a duration of 2 ms. The current of the pacemaker was set at twice the diastolic threshold. Atrial pacing was carried out, using 2 Grass needle electrodes applied directly to the left atrial appendage. During cardiac testing, the heart rate was maintained at a constant level of 210 beats/min.

The duration of the test stimulus was set at 10 ms and the initial current at 4 mA. Electrical diastole was then scanned in 10 ms intervals beginning at the boundary of the effective refractory period and terminating beyond the T wave. The current was then increased in 2 mA steps and scanning was continued. The lowest stimulus intensity that elicited ventricular fibrillation was taken as the ventricular fibrillation threshold (VFT). The lowest stimulus provoking a single undriven extrasystole was taken as the repetitive extrasystole threshold (RET).

**Technique of partial coronary stenosis:** Partial coronary stenosis was produced using methods described by Folts et al.[9,10] Plastic cylinders 2.5 mm long and of variable internal diameter (1.3 to 1.8 mm) were placed around the left circumflex coronary artery distal to the coronary flow probe. Care was taken to leave no patent coronary branches between the flow probe and occluder. In each case, occluders of progressively smaller diameters were applied to the coronary vessel until no reactive hyperemic response could be elicited after a 20 second total coronary occlusion. When the proper cylinder had been selected, blood flow, heart rate, blood pressure, and intracavitary electrogram were monitored continuously for 1 hour. As soon as cyclical changes in coronary blood flow had been demonstrated to be a consistent phenomenon (3 cycles in a 30 minute period was the minimal requirement), determinations of the threshold current for ventricular fibrillation and repetitive extrasystole were made during control or high flow periods and during maximal observed reductions in coronary blood flow.

**Platelet aggregation studies:** After the partial obstruction was produced, a 5 ml blood sample was collected from the femoral artery catheter and discarded and a second 10 ml sample withdrawn into a plastic syringe containing 1 part of 3.8% sodium citrate for each 9 parts of blood. In all studies, samples for aggregation testing were collected before electrical testing and debrillation. Platelet-rich plasma was obtained by centrifuging this mixture at 800 rpm for 8 minutes at room temperature. After the platelet-rich plasma was withdrawn, platelet poor plasma was prepared by centrifuging the remaining mixture at 2,000 rpm for 15 minutes. Aggregation studies were performed by a modification of the method of Born[12] using a Chrono-Log Platelet Aggregometer model 330 (Chrono-Log Corporation, Broomall, Pennsylvania). Fourtenth ml platelet-rich plasma was placed at 37° in a siliconized cuvette in the aggregometer with a siliconized stirring bar. The aggregometer was adjusted to give 10 and 90% light transmission readings on a strip chart recorder with platelet-rich and platelet-poor plasma, respectively. Doses of 2.9 to 9.6 $\mu M$ adenosine diphosphate were used as the aggregating agent. The minimal concentrations of adenosine diphosphate that resulted in maximal platelet aggregation was then used in all subsequent phases of the experiment.

**Baroreceptor denervation:** Prostacyclin has been shown to cause significant systemic hypotension, which results from peripheral arterial vasodilation. The hypotension in turn causes an increase in reflex sympathetic tone[13] resulting in enhanced vulnerability to ventricular fibrillation. Baroreceptor denervation was therefore performed before the infusion of prostacyclin. The aortic arch was denervated by sectioning the cervical vagi bilaterally. This procedure completely eliminates the afferent fibers from the aortic arch pressor receptors.[14] To denervate the carotid sinus receptors, a dissection was performed bilaterally in the neck, midway between the mandibular angle and thyroid cartilage. The bifurcation of the internal and external carotid artery was located and the carotid sinus identified. By careful dissection, the sinus nerve was exposed and sectioned. To ensure completeness of denervation, the adventitia was stripped from the carotid vessels in the region of the sinuses. Successful denervation of the carotid sinus was always associated with a distinct heart rate

increase of 20 to 60 beats/min and an increase in blood pressure of 30 to 60 mm Hg.

**Balloon catheter placement:** In order to restrict coronary flow to a predetermined level, an occlusive balloon catheter (Brunswick, Quincy, Massachusetts) was used. A thoracotomy was performed through the fifth intercostal space and the catheter placed around the left circumflex coronary artery at the level of the left atrial appendage, distal to the coronary flow probe. The balloon was gradually inflated over 5 to 7 minutes to that point at which coronary blood flow was reduced by 50 to 80% of control values. Balloon inflation was continuously adjusted to keep coronary blood flow constant. When coronary blood flow was stabilized at the reduced value, and within 60 seconds of the occlusion, RET and VFT determinations were made. The balloon was deflated upon onset of ventricular fibrillation and remained deflated while defibrillation was performed.

**Prostaglandin infusion:** One to 5 mg of powdered prostacyclin (supplied in powder form by Upjohn Pharmaceutical) was dissolved in 1 to 5 ml of absolute ethanol to yield a stock solution concentration of 1 mg/ml. The stock solution was then diluted in a carbonate/bicarbonate buffer (0.01*M*/0.02*M*) with a pH of 10.0, and this solution was made isotonic by the addition of sodium chloride. Concentrations of the drug were prepared to allow for infusion volumes of 0.2 to 1.2 ml/min, using a Harvard infusion pump. Solutions were kept cool using a crushed ice bath. Conduit tubing from syringe to animal measured <10 cm to prevent inadvertant warming of the solution during infusion. The prostaglandin was infused into the femoral vein catheter in all experiments.

A solution of indomethacin (supplied in powder form by Merck, Sharp and Dohme) (3.6 mg/ml) was prepared by adding warm (50°C) sodium bicarbonate 300 mg in 30 ml 0.9% sodium chloride to 150 mg of indomethacin dissolved in 10 ml of 90% ethanol. Doses of 5 mg/kg were drawn up into a plastic syringe and infused into the femoral venous catheter over a 10 minute period using a Harvard infusion apparatus.

**Statistics and calculations:** Statistical analysis of the data was performed using the paired Student's *t* test wherein differences were considered significant when $p < 0.05$. All values in text and figures are expressed as mean ± standard error of the mean.

Percent decrease in coronary blood flow was calculated as follows: [(Control flow − reduced flow)/control flow] ×100.

**Experimental groups:** *Prostaglandin treatment:* Eleven animals underwent baroreceptor denervation and had an appropriately sized plastic cylinder affixed. Seven of the animals manifested cyclical changes in coronary blood flow; 4 animals had no demonstrable flow alterations. Control values for mean arterial blood pressure, coronary blood flow, platelet aggregation, RET, and VFT were obtained. Prostacyclin was infused at a constant dose of 25, 50, and 100 ng/kg/min in each animal. Each infusion lasted approximately 20 minutes, during which time coronary blood flow, and electrocardiographic mean arterial blood pressure, and electrocardiographic readings, were continually recorded and values for RET and VFT obtained. At each dose level, the number of cyclical changes in coronary blood flow together with the duration of each were noted. Before the termination of each prostacyclin infusion and before commencing electrical testing, arterial blood was sampled for a platelet aggregation study.

*Indomethacin treatment:* Indomethacin (5 mg/kg) was used in a group of 10 animals, 6 of which had reproducible cyclical blood flow changes. Baseline measurement of blood pressure, coronary blood flow, platelet aggregation, and ventricular vulnerability were made. Indomethacin was administered over a 10-minute period, after which all of the determinations were repeated.

*Balloon catheter coronary occlusion:* In 5 animals, coronary blood flow was interrupted using the externally applied balloon occluder to reduce coronary blood flow by 50 to 80%. Application of a balloon occluder was not accompanied by cyclical flow changes. Cardiac electrical testing was carried out before and after inflation of the balloon. After a recovery time of 30 minutes, indomethacin was administered (5 mg/kg), and the effect on platelet aggregation was determined. Determinations of the RET and VFT were again made before and during reduction in coronary blood flow.

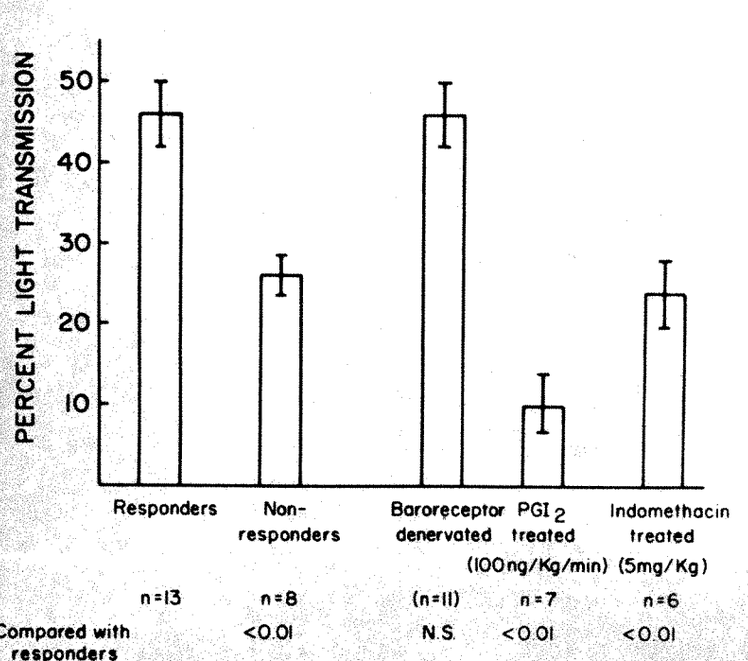



**FIGURE 1.** Adenosine diphosphate-mediated platelet aggregation in control animals before and after baroreceptor denervation, and after treatment with high-dose prostacyclin ($PGI_2$) and indomethacin.

**TABLE I Changes in Coronary Blood Flow (CBF), Repetitive Extrasystole Threshold (RET), Ventricular Fibrillation Threshold (VFT), and S-T Segments in 13 Animals Demonstrating Cyclical CBF Reductions After Application of the Plastic Cylinder**

| | CBF (ml/min) | | RET (mA) | | VFT (mA) | | S-T Deviation |
|---|---|---|---|---|---|---|---|
| Animal | C | R | C | R | C | R | |
| 1 | 45 | 24 | 6 | . . . | 14 | 10 | ↑ |
| 2 | 21 | 9 | 22 | 12 | 30 | 18 | ↔ |
| 3 | 34 | 19 | 14 | 12 | 16 | 14 | ↓ |
| 4 | 48 | 25 | 20 | 12 | 24 | 18 | ↓ |
| 5 | 35 | 22 | 24 | 14 | 40 | 20 | ↑ |
| 6 | 23 | 10 | 12 | 8 | 20 | 16 | ↔ |
| 7 | 38 | 15 | 18 | 10 | 22 | 18 | ↔ |
| 8 | 40 | 17 | 12 | 10 | 20 | 16 | ↓ |
| 9 | 36 | 14 | 14 | 8 | 30 | 16 | ↑ |
| 10 | 45 | 20 | 20 | 12 | 36 | 22 | ↑ |
| 11 | 44 | 21 | 16 | 8 | 18 | 12 | ↔ |
| 12 | 35 | 20 | 14 | 12 | 18 | 14 | ↑ |
| 13 | 60 | 23 | 8 | . . . | 18 | 12 | ↓ |
| Mean | 38 | 18 | 15 | 9 | 23 | 16 | 5↑ |
| ± SEM | ± 3 | ± 2 | ±2 | ± 1 | ± 2 | ± 1 | 4↓ |
| | | | | | | | 4↔ |

Measurement of RET and VFT were made at control (C) and reduced (R) coronary blood flow. SEM = standard error of the mean.

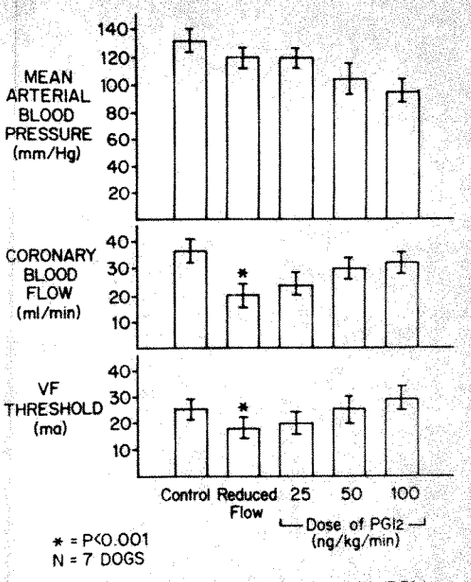



**FIGURE 2.** Influence of varying doses of prostacyclin ($PGI_2$) on coronary artery blood flow and ventricular vulnerability during partial coronary stenosis. VF = ventricular fibrillation.

## Results

**Effect of cyclical flow changes on VFT:** Thirteen of the 21 animals (62%) had cyclical reductions in coronary blood flow after induction of coronary stenosis. The platelet aggregation in response to adenosine diphosphate in these 13 responder animals is displayed in Figure 1. In the remaining 8 dogs, no cyclical flow changes could be elicited, despite the production of sufficient stenosis to abolish the hyperemic response, and no changes in the VFT or in the S-T segments were observed. Platelet aggregation in the 8 nonresponders was significantly less than that of responder animals despite the use of the same dose of adenosine diphosphate (Fig. 1). There was no statistical difference between the 2 groups of animals in baseline coronary blood flow or MABP and these measurements did not correlate with the extent of coronary blood flow reduction. Once cyclical flow changes were established, they continued for the remainder of the experiment or until a drug intervention was performed. The flow reduction cycles averaged 11/hour and the degree of reduction in coronary blood flow ranged from 21 to 80%. Each cyclical flow reduction was followed by an abrupt return of flow to control values which, in the majority of instances, occurred spontaneously. However, approximately 25 to 30% of these cycles were not self-terminating, and the vessel was tapped gently to dislodge thrombi and restore flow.

Determination of the RET and VFT were made at the following points: (1) when coronary blood blow was maximal (control flow), (2) when coronary blood flow was reduced by at least 30 but no more than 60% below control flow, and (3) immediately upon coronary reperfusion.

Nine of the 13 animals that had flow changes also manifested recurrent S-T segment alterations during flow reduction, consisting of S-T elevation or depression of from 1 to 3 mV (Table I). Such evidence of myocardial ischemia was noted during those sequences in which coronary flow fell to <50% of control. Five dogs had S-T segment elevation and 4 had S-T segment depression. There was no difference in extent or frequency of flow reduction in those animals with S-T segment elevation or depression. The S-T segment changes were accentuated with progressive decreases in coronary blood flow. S-T segments were restored to normal within 3 to 5 seconds of flow recovery.

Arterial blood pressure did not decrease during the cyclical coronary flow changes, unless coronary blood flow was reduced below 70% of control values when mean arterial blood pressure was lowered by 10 to 15 mm Hg. This blood pressure change was immediately reversed upon restitution of flow.

Reductions in coronary blood flow produced a significant decrease in both RET (15 ± 2 to 9 ± 1 mA) and VFT (23 ± 2 to 16 ± 1 mA) ($p < 0.001$) (Table I). Upon reperfusion, coronary blood flow increased to levels greater than control (hyperemic response) and VFT decreased to 11 ± 3 mA. Repetitive extrasystoles could not be consistently elicited without antecedent ventricular fibrillation during the reperfusion phase.

**Effects of prostacyclin:** Baroreceptor denervation was performed before prostacyclin infusion. In 11 animals tested, baroreceptor denervation did not cause a significant change in platelet aggregation to adenosine diphosphate (Fig. 1). Furthermore, control mean arterial blood pressure, coronary blood flow, RET, and VFT values were obtained after baroreceptor denervation.

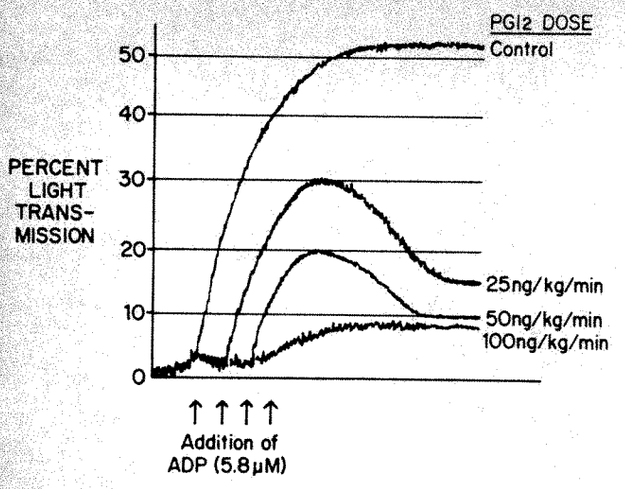



**FIGURE 3.** Effects of varying doses of prostacyclin ($PGI_2$) on adenosine diphosphate (ADP)-mediated platelet aggregation.

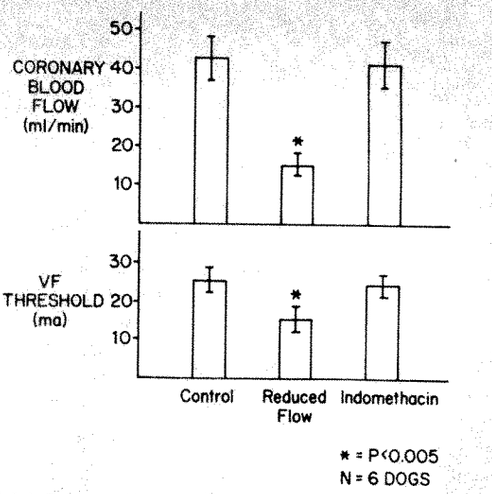



**FIGURE 4.** Influence of indomethacin (5 mg/kg) on coronary blood flow and ventricular vulnerability during partial coronary stenosis. VF = ventricular fibrillation.

Prostacyclin caused a progressive decrease in mean arterial blood pressure as a function of increasing dose. Prostacyclin also caused a decrease in the frequency and rapidity of coronary blood flow cycles, decreasing from 11/hour to 7/hour using 25 ng/kg/min and to 3/hour using doses of 50 ng/kg/min. Cyclical flow changes were completely abolished during an infusion rate of 100 ng/kg/min and coronary blood flow returned to control values (Fig. 2). Prostacyclin progressively inhibited platelet function and was most effective at the highest infusion rate (Fig. 1). The aggregation results from a single animal study are shown in Figure 3.

Four animals which exhibited no cyclical flow reductions underwent baroreceptor denervation and prostacyclin infusion. Although the hemodynamic responses to prostacyclin (100 ng/kg/min) were similar to those observed in dogs which manifested cyclical flow changes, no significant change in either the RET (18 ± 1 mA to 17 ± 2 mA) or VFT (27 ± 3 mA to 24 ± 3 mA) was observed in these 4 nonresponder animals.

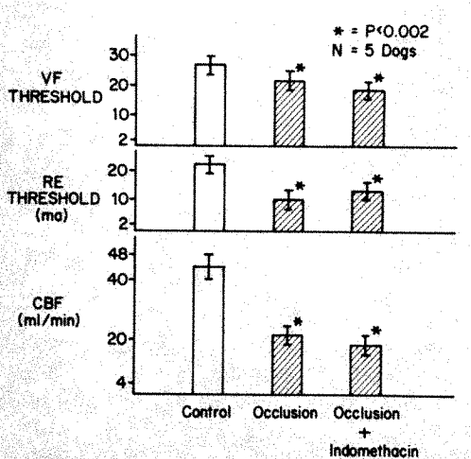



**FIGURE 5.** Effect of nonthrombotic coronary occlusion induced by a balloon catheter on ventricular fibrillation (VF) threshold and coronary blood flow (CBF) before and after treatment with indomethacin (5 mg/kg). RE = repetitive extrasystole.

**Effects of indomethacin:** Indomethacin (5 mg/kg) reduced platelet aggregation in response to adenosine diphosphate from 50 to 6 to 24 ± 4%, $p < 0.01$ (Fig. 1), and completely inhibited the second phase of aggregation to adenosine diphosphate in 6 animals manifesting cyclical changes in coronary blood flow. This effect on platelet aggregation was accompanied by a prompt (within 5 minutes) cessation of cyclical coronary blood flow changes and a return of the VFT to control values (Fig. 4). Indomethacin exerted no significant effect on VFT (23 ± 2 ± 1 mA) when administered in 4 animals that had no spontaneous cyclical flow changes.

**Effect of balloon catheter coronary occlusion and treatment with indomethacin:** In 5 animals, coronary occlusion was carried out with an external balloon catheter and coronary blood flow held at a level approximately 60% less than control values (44 ± 4 to 21 ± 3 ml/min). Reductions were observed in both the RET (−45%) and VFT (−28%). After treatment with indomethacin, RET and VFT remained unaltered (Fig. 5).

## Discussion

The role of intracoronary platelet aggregation in the genesis of malignant cardiac arrhythmias is an issue of significant clinical interest. The evidence implicating thrombus formation in sudden death, however, has been indirect, based on autopsy and epidemiologic data.[4–7] The studies of Uchida,[8,15] Folts,[9,10] Aiken,[16] and their co-workers have provided a new biologic model for investigating the effects of intracoronary platelet aggregation on myocardial ischemia. Specifically, Folts et al[9,10] demonstrated that application of a plastic cylinder around a major coronary artery causes platelets to adhere to adjacent coronary endothelium, resulting in cyclical reductions in coronary blood flow. Thus, it is

possible to stimulate and monitor spontaneous changes in intracoronary platelet aggregation and thereby induce myocardial ischemia. The present study examined the effects of platelet aggregation on ventricular electrical properties as assessed by the RET and VFT. These indexes were selected because they have been shown to provide accurate and reproducible measurements of myocardial electrical stability.[11,17]

This investigation demonstrates that with the onset of myocardial ischemia, there are marked reductions in RET and VFT. Our results also indicate that there is a significant increase in vulnerability to ventricular fibrillation during reperfusion which occurs as a result of platelet dislodgment. This phenomenon is in accord with that observed during reperfusion produced by abrupt deflation of a balloon occluder. The changes in vulnerability observed during decreased flow and reperfusion are completely abolished within 30 seconds of restoration of coronary blood flow.

**Effects of prostacyclin:** Prostacyclin is an effective agent for evaluating the role of platelet aggregation in the generation of both cyclical flow reduction[16] and ventricular electrical changes. First, this substance is devoid of any direct cardiac electrophysiologic effects. Changes in ventricular vulnerability may, however, be brought about by baroreceptor reflex activation.[13] Baroreceptor denervation was thus performed in the present study to preclude an indirect effect on RET and VFT. Second, prostacyclin is a most potent platelet inhibitor. It exerts its effects by binding to specific receptors and increasing platelet cyclic adenosine monophosphate levels.[18] These effects occur in a dose-dependent fashion, so that inhibition of platelet aggregation is related to the dose of prostacyclin.[19] Third, prostacyclin is produced by vascular endothelium and may inhibit platelet aggregation and thrombus formation on exposed subendothelium.[20] Human subjects have received prostacyclin in doses up to 50 ng/kg/min without adverse effects.[21] In fact, significantly smaller doses have eliminated the ischemic pain resulting from arteriosclerosis obliterans.[22] However, whether this agent will become useful in the clinical setting in the treatment of coronary disease is uncertain since the doses required for these purposes are quite high.

**Relation of platelet aggregation to cyclical flow changes:** Indomethacin caused an abrupt and long-lasting cessation of cyclical flow changes which correlated with inhibition of platelet aggregation and abolition of electrical changes. Indomethacin is an inhibitor of thromboxane $A_2$ synthesis. Therefore, the protective effect of indomethacin in this model suggests that thromboxane generation may be an important factor in the production of the myocardial ischemia and electrical instability that occurs during cyclical flow alterations. There was no significant change in the VFT with indomethacin in animals without cyclical blood flow changes. This suggests that changes in coronary vascular resistance seen with indomethacin in patients with coronary artery disease[23] do not influence ventricular vulnerability in the nonischemic canine heart. Indomethacin completely restored coronary blood flow in animals with partial stenosis, indicating that changes in coronary vascular resistance with indomethacin in this particular model of myocardial ischemia is not a significant factor.

There was a strong correlation between platelet sensitivity to adenosine diphosphate and the frequency and magnitude of cyclical flow changes. Animals which were less sensitive to adenosine diphosphate generally failed to manifest coronary flow alterations. While we did not specifically investigate the reason for intrinsic variability in platelet aggregability, interanimal differences in arachidonic acid metabolism may provide an explanation.[24,25] Furthermore, as platelets were progressively inhibited with increasing doses of prostacyclin, there was a corresponding restitution of coronary flow and abolition of electrical changes. Our findings of a correlation between reduced VFT, coronary blood flow, and the extent of platelet aggregation indicates a central role of platelet function in coronary perfusion changes when coronary flow is substantially restricted.

**Mechanisms for alteration of vulnerability:** We sought to determine whether changes in ventricular vulnerability during partial coronary stenosis are contributed to by impedance of flow by platelet plugs or are due to release of platelet factors. To shed light on this question, we utilized the balloon catheter to produce degrees of flow reduction comparable to those observed when cyclical flow reduction occurred during fixed partial stenosis. Reduction in flow produced nonthrombotically by balloon obstruction significantly decreased the vulnerable period threshold as previously reported.[26–28] These changes, moreover, were comparable to those observed during intracoronary platelet aggregation induced using the plastic cylinder. Use of the balloon occluder was not associated with a further gradual decrease in coronary flow attributable to intracoronary platelet aggregation. The reason for this difference is not clear but may have been due to a greater extent of endothelial disruption with a rigid cylinder. In any case, with nonthrombotic occlusion induced by means of the balloon catheter, platelet inhibition by indomethacin administration did not prevent the vulnerable period threshold changes associated with coronary obstruction. These results suggest that alterations in cardiac vulnerability noted during partial stenosis are due, at least in part, to the mechanical impairment of flow through the stenotic site.

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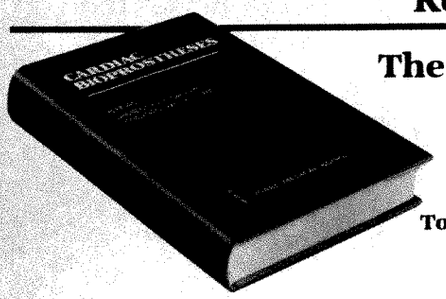
## References

1. **Lown B, Wolf M.** Approaches to sudden death from coronary heart disease. Circulation 1971;44:130–142.
2. **Jorgensen L, Rowsell H, Hovig T, Glynn M, Mustard J.** Adenosine diphosphate-induced platelet aggregation and myocardial infarction in swine. Lab Invest 1967;17:616–644.
3. **Haft J, Gershengorn K, Kranz P, Oestreicher R.** Protection against epinephrine-induced myocardial necrosis by drugs that inhibit platelet aggregation. Am J Cardiol 1972;30:838–843.
4. **Schwartz C, Gerrity R.** Anatomical pathology of sudden unexpected cardiac

death. Circulation 1975;52:Suppl III:III-18–III-26.
5. **Jorgenson L, Haerem J, Chandler A.** The pathology of acute coronary death. Acta Anaesthesiol Scand [Suppl] 1968;29:193–209.
6. **Haerem J.** Platelet aggregates and mural microthrombi in early stages of acute, fatal coronary disease. Thromb Res 1974;5:243–249.
7. The Anturane Reinfarction Trial Research Group. Sulfinpyrazone in the prevention of cardiac death after myocardial infarction. N Engl J Med 1978;298:289–295.
8. **Uchida Y, Yoshimoto N, Murao S.** Cyclic changes in peripheral pressure and flow of partially constricted coronary artery. J Jpn Col Angiol 1974; 14:383–390.
9. **Folts J, Gallagher K, Rowe G.** Phasic coronary blood flow changes with partial coronary artery obstruction. Physiologist 1974;17:223–229.
10. **Folts J, Crowell E, Rowe G.** Platelet aggregation in partially obstructed vessels and its elimination with aspirin. Circulation 1976;54:365–372.
11. **Matta R, Verrier RL, Lown B.** Repetitive extrasystole as an index of vulnerability to ventricular fibrillation. Am J Physiol 1976;230:1469–1473.
12. **Born GVR.** Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature 1962; 194:927–929.
13. **Kowey P, Verrier R, Lown B.** Effects of prostacyclin ($PGI_2$) on vulnerability to ventricular fibrillation in the normal heart and ischemic canine heart. Eur J Pharmacol 1982;80:83–91.
14. **Nonidez J.** Distribution of the aortic nerve fibers and the epitheloid bodies (supracardial "paranganglia") in the dog. Anat Rec 1937;69:299–313.
15. **Uchida Y, Yoshimoto N, Murao S.** Cyclic fluctuations in coronary blood pressure and flow induced by partial constriction of coronary artery. Jpn Heart J 1975;16:454–462.
16. **Aiken J, Gormon R, Shebuski R.** Prevention of blockage of partially obstructed coronary arteries with prostacyclin correlates with inhibition of platelet aggregation. Prostaglandins 1979;17:483–494.
17. **Kowey P, Verrier RL, Lown B.** The repetitive extrasystole threshold as an index of vulnerability to ventricular fibrillation during myocardial ischemia (abstr). Am J Cardiol 1981;47:391.
18. **Higgs E, Moncada S, Vane J.** Effect of prostacyclin ($PGI_2$) on platelet adhesion to rabbit arterial subendothelium. Prostaglandins 1978;16:17–22.
19. **Whittle B, Moncada S, Vane J.** Comparison of the effects of prostacyclin ($PGI_2$), prostaglandin E, and $D_2$ on platelet aggregation in different species. Prostaglandins 1978;16:373–388.
20. **Weis H, Turitto V.** Prostacyclin (prostaglandin $I_2$, $PGI_2$) inhibits platelet adhesion and thrombus formation of subendothelium. Blood 1979;53:244–250.
21. **Szczeklik A, Gryglewski R, Nizankowski R, Musial J, Pieton R, Mruk J.** Circulatory and antiplatelet effects of intravenous prostacyclin in healthy men. Pharmacol Res Commun 1978;10:545–549.
22. **Szczedlik A, Scawinski S, Gluszko P.** Successful therapy of advanced arteriosclerosis obliterans with prostacyclin. Lancet 1979;I:1111–1114.
23. **Friedman P, Brown E, Gunther S, Alexander R, Barry W, Mudge G, Grossman W.** Coronary vasoconstrictor effect of indomethacin in patients with coronary artery disease. N Engl J Med 1981; 305:1171–1175.
24. **Johnson GJ, Leis LA, Raw GHR, White JG.** Arachidonic acid-induced platelet aggregation in the dog. Thromb Res 1979;14:147–157.
25. **Johnson GJ, Raw GHR, Leis LA, White JG.** Effect of agents that alter cAMP on arachidonic acid-induced platelet aggregation in the dog. Blood 1980; 55:722–729.
26. **Lambert P, Frank H, Bellman S, Williams J.** Electrical excitability of ventricular myocardium in relationship to graded changes in coronary inflow. J Surg Res 1961;1:251–259.
27. **Dixon M, Trank J, Dobell A.** Ventricular fibrillation threshold: variation with coronary flow and its value in assessing experimental myocardial revascularization. J Thorac Cardiovasc Surg 1964;47:620–627.
28. **Gorza D, While F, Hall R, Bloor C.** Effect of coronary collateral development on ventricular fibrillation threshold. Basic Res Cardiol 1974;69:371–379.

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# Cordis Sequicor Technical Information.

## Sequicor, Model 233D Programmable Parameters

| | |
|---|---|
| Modes | DDD, DVI, DAD, VDD, VAT, VVI, DOO, VOO |
| Minimum Pacing Rate, (Interval) | 50 (1200), 60 (1000), 70 (857), 80 (750) |
| Maximum Pacing Rate (Interval) | 100 (600), 130 (461), 160 (375), 180 (333) |
| Atrial Sensitivity, (mV) | 0.8, 1.5, 7.0, OFF |
| Ventricular Sensitivity, (mV) | 0.8, 1.5, 2.5, OFF |
| Atrial Output Pulse Duration, (ms) | OFF, 0.5, 1.0, 1.5, |
| Ventricular Output Pulse Duration, (ms) | 0.5, 1.0, 1.5, 2.0, |
| A/V Delay (ms) | 80, 120, 165, 250 |
| Atrial Tachycardia Response | Fall Back, 2:1 Block |
| Fall Back Rate (Interval) | 55 (1.090), 65 (932), 75 (800), 85 (706) |

## Sequicor Refractory Periods

| Atrial Tachycardia Response | Maximum Rate | Total Atrial Refractory | Total Ventricular Refractory | A/V Programmed Delay | Total Atrial Refractory Following the Ventricle Pulse |
|---|---|---|---|---|---|
| 2:1 Block | 100 ppm | 600 ms | 302 ms | 80 ms | 520 ms |
| | | | | 120 | 480 |
| | | | | 165 | 435 |
| | | | | 250 | 350 |
| | 130 ppm | 461 ms | 302 ms | 80 ms | 381 ms |
| | | | | 120 | 341 |
| | | | | 165 | 296 |
| | | | | 250 | 211 |
| | 160 ppm | 375 ms | 302 ms | 80 ms | 295 ms |
| | | | | 120 | 255 |
| | | | | 165 | 210 |
| | | | | 250 | 125 |
| | 180 ppm | 333 ms | 302 ms | 80 ms | 253 ms |
| | | | | 120 | 213 |
| | | | | 165 | 168 |
| | | | | 250 | 83 |
| Any Fall Back Rate | Any Maximum Rate | 305 ms | 302 ms | 80 ms | 225 ms |
| | | | | 120 | 185 |
| | | | | 165 | 140 |
| | | | | 250 | 55 |

## Important Information—Sequicor, Models 233D and 233E

**Indications and Contraindications**
The medical literature describes currently accepted indications for various pacing modes. The physician's clinical experience and judgment must ultimately be the guide in selecting the pacing mode best suited to the patient's needs. *The physician should be thoroughly familiar with the pacing mode chosen.*

Pacing of the ventricles (VVI) is indicated for control of heart rate in patients with A-V block or sick sinus syndrome. *Asynchronous pacing is contraindicated when inherent activity is present or is likely to be present in the chamber being paced.* There are no other known contraindications for ventricular pacing to control heart rate.

Atrial-synchronized ventricular pacing (VDD) is indicated for permanent or intermittent complete heart block with normal atrial rhythm. A-V sequential (DVI) pacing is indicated for permanent sinus bradycardia with or without heart block. Automatic dual-chamber demand pacing (DDD) is indicated when there is an A-V conduction disturbance and/or sinus mode dysfunction (sinus bradycardia with A-V block or bradytachy syndrome). These atrial pacing modes are intended for patients who would benefit from the restoration of atrial contribution to cardiac output.

*Atrial-synchronized ventricular pacing and automatic dual-chamber demand pacing modes are contraindicated for use in the presence of persistent atrial flutter or atrial fibrillation.* VVI mode is recommended for these conditions.

**Precautions**
Cordis Sequicor pacers may respond to programmers of other manufacturers. Because of the unknown nature of such response, use only the Cordis Omnicor Programmer, Model 222C (with the 222C-8 control panel card), the Cordis Programmer III, Model 225A or the Cordis Interactive Programmer, Model 256A for reprogramming.

**Warnings**
None

**Adverse Effects**
The following list includes a number of complications related to pacer therapy that have been reported in the medical literature. Noninvasive techniques for assessing and managing such complications are available to the physician. Malfunctions occur randomly and may occur at any time after implant. Complications associated with pacer therapy are listed below.

*Pacer*—battery depletion, component malfunction, electromagnetic interference, decreased sensitivity.

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*Patient*—reaction, infection/erosion, increase in stimulation threshold.

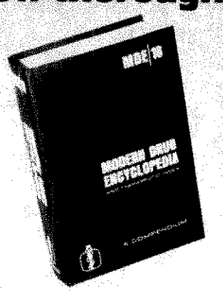
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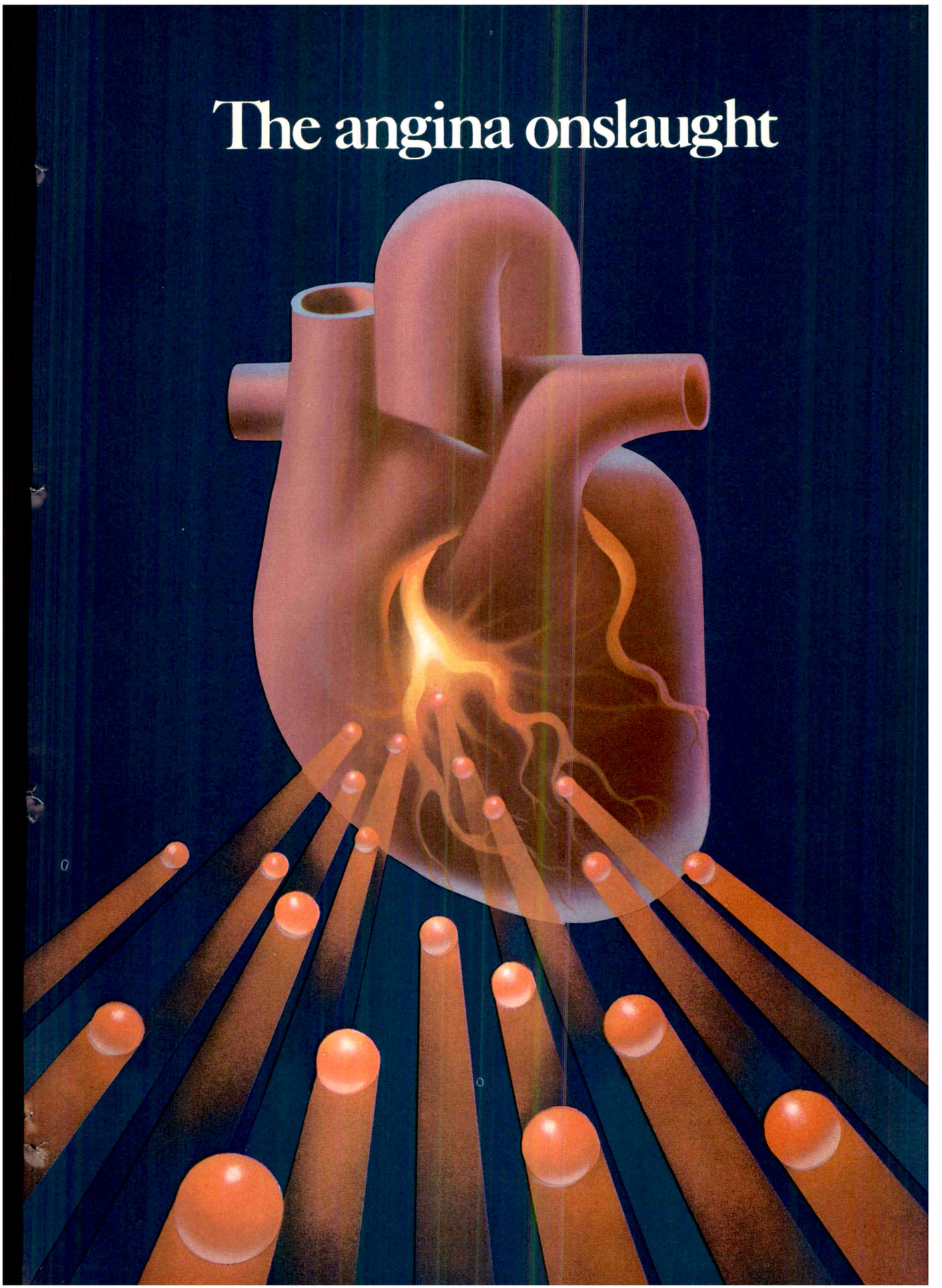
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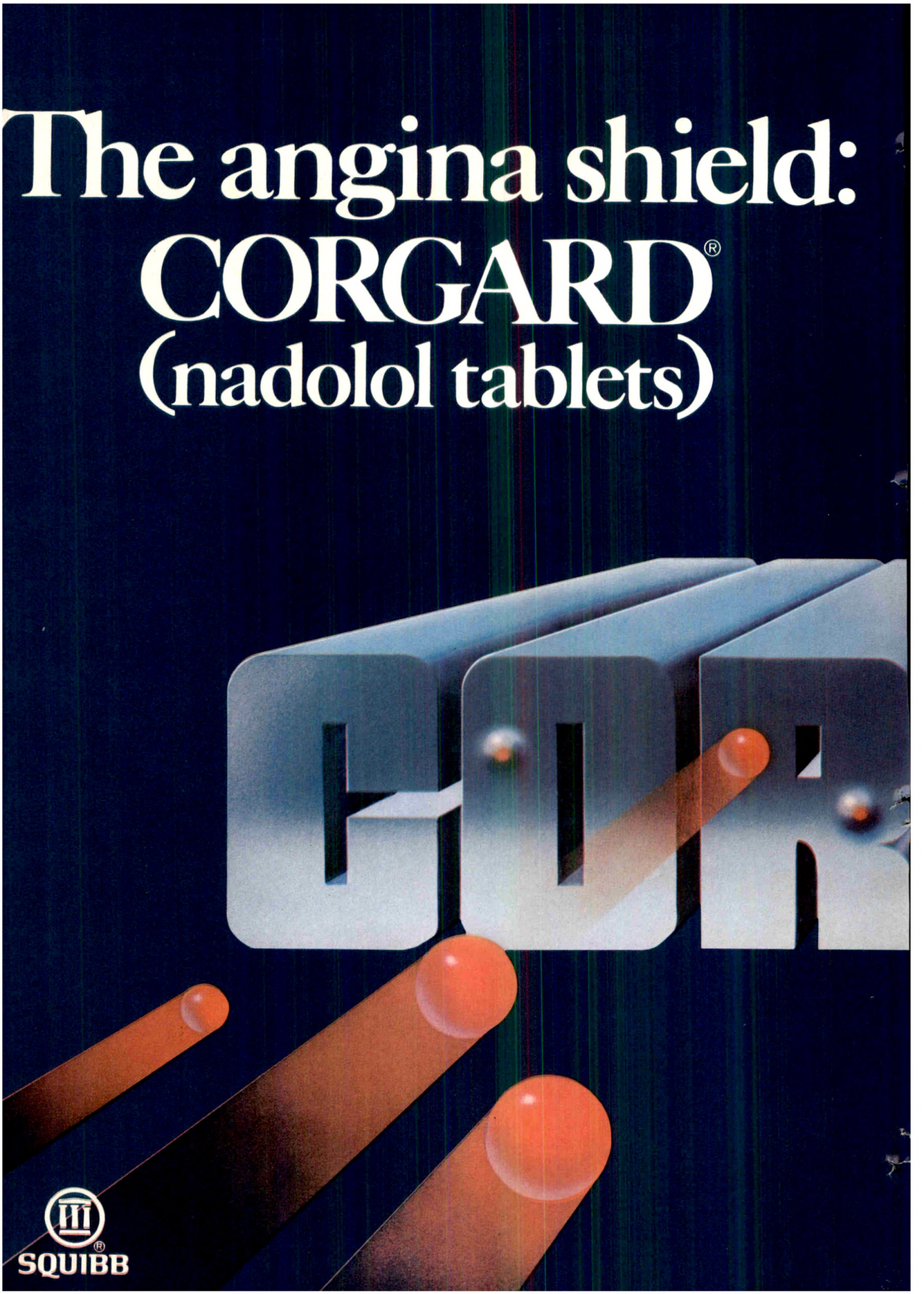
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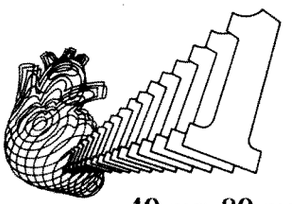
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**DESCRIPTION:** Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

**CONTRAINDICATIONS:** Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

**WARNINGS: Cardiac Failure** — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal** — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)** — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

**Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

**Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

**Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

**PRECAUTIONS: Impaired Hepatic or Renal Function** — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

**Information for Patients** — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

**Drug Interactions** — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

**Carcinogenesis, Mutagenesis, Impairment of Fertility** — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

**Pregnancy** — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

**Nursing Mothers** — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

**Pediatric Use** — Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

**Cardiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

**Potential Adverse Effects:** Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

**OVERDOSAGE:** Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

**Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

**Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

**Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

**Bronchospasm** — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

**DOSAGE:** For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

**HOW SUPPLIED:** In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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EDITORIAL

# Congestive Heart Failure: A Propitious Time For Intensified Research

EUGENE BRAUNWALD, MD, MICHAEL M. MOCK, MD, and JOHN T. WATSON, PhD

Chronic congestive heart failure is one of the most common serious illnesses, affecting an estimated 3 to 4 million Americans. Because the prognosis in most patients with heart failure is poor, life expectancy being measured in months or a few years, not only the prevalence but also the incidence of this condition is high. Heart failure causes great personal suffering and places enormous economic burdens on the patient, the family, and society at large.

Cognizant of the importance of congestive heart failure as a medical problem, the Cardiology Program of the Division of Heart and Vascular Diseases of the National Heart, Lung and Blood Institute sponsored a Workshop on Congestive Heart Failure in Bethesda, Maryland in April 1981. The objective of the Workshop was to review important recent advances and to identify opportunities for research in this field.

The Workshop was divided into 6 sections: Section I, Clinical Definitions and Current Clinical Studies, chaired by Jay N. Cohn, MD; Section II, Diagnostic Procedures for Evaluating Heart Failure, chaired by Arthur J. Moss, MD; Section III, Etiology, Biochemical, and Structural Changes in Heart Failure, chaired by L. Maximilian Buja, MD; Section IV, Research on the Physiology of Congestive Heart Failure, chaired by A. Clifford Barger, MD; Section V, Assessment of Clinical Treatment, Monitoring, and Surgical Intervention in Advanced Congestive Heart Failure, chaired by Benedict R. Lucchesi, MD; Section VI, Future of Clinical Investigation in Evaluating Treatment of Congestive Heart Failure, chaired by Michael B. Mock, MD. Although the proceedings of this Workshop were recently published,[1] it was considered desirable to summarize some of the major points that emerged.

From the Department of Medicine, Harvard Medical School, and the Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received December 9, 1982, accepted January 13, 1982.

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It was noted during the Workshop that in the past 2 decades conspicuous advances have been made in our understanding of the pathophysiologic aspects of heart failure, in the ability to assess normal and impaired left ventricular function, in research on drugs that improve cardiac contraction, and in operations designed to treat valvular and coronary heart disease (2 of the most common causes of congestive heart failure). In addition, there have been encouraging developments in the use of mechanical devices to replace the failing heart and in cardiac transplantation in the treatment of irreversible heart failure. Among many important gaps in the field that were identified, several stand out as being particularly ripe for further advances.

**Development of heart failure:** It is well established that many forms of heart failure are the consequence of a deterioration in the ventricle's response to a hemodynamic burden, rather than of an aggravation in the severity of that burden. The ventricle is capable of sustaining an excessive load while its function remains normal for many months (in experimental animals such as the genetically hypertensive rat) or for years (in patients). However, at some point, ventricular function becomes impaired and the chronically stressed ventricle begins to fail. What is responsible for this deterioration of ventricular function? Although there have been many investigations of the biochemical, physiologic, and pathologic changes that occur in the myocardium shortly after the imposition of the stress and in the very late stages of congestive heart failure, far less is known about the conversion of normal ventricular function to early ventricular dysfunction in the hypertrophied heart. The progression from hypertrophy to heart failure should be amenable to precise characterization by combining anatomic, biochemical, physiologic, and pathologic techniques, first in animal models and then in selected clinical situations.

**Animal models of heart failure:** Although a great deal of information has already been obtained from

animal modes of heart disease, this field now appears poised for further important advances. The response of myocardium to identical stress may vary. For example, the left ventricle of some patients with aortic stenosis is capable of sustaining this burden for many years without dilatation or reduction of cardiac output, whereas the left ventricle in others with an identically sized orifice exhibits excessive hypertrophy and dilatation. Similar examples can be cited in the case of other mechanical loads placed on the heart, such as those imposed by regurgitant valvular lesions, systemic hypertension, and congenital pulmonary stenosis. The basis for these widely differing responses is not clear, but carefully controlled studies in animal models of cardiac overload may well provide useful information. Thus, there are great interspecies and interindividual variations in the response to hemodynamic stress in animals with naturally occurring or artificially induced mechanical overloading. Elucidation of the genetic basis for these differences in the myocardium's response to stress appears to offer a particularly fruitful area for research.

**Characterization of the heart's functional reserve:** Although gross dysfunction of the left ventricle can readily be described by both invasive and noninvasive techniques, formidable problems remain in the characterization of early or mild impairment of left ventricular function and in the assessment and even the definition of the functional reserve of the heart. A number of opportunities exist in this field. A variety of methods have been employed, but their precise value is unclear. Thus, 1 group of investigators, a relatively small number in the United States but a larger number in Europe, particularly in Scandinavian countries, assess cardiac function by determining the maximal total body oxygen consumption during exercise ($\dot{V}O_2max$). It is not yet clear whether a reduction of $\dot{V}O_2max$ can serve as a sensitive indicator of mildly impaired function and be useful prognostically in patients with heart disease. The study of exercise tolerance and the measurement of $\dot{V}O_2max$ in patients with cardiovascular disease to identify early dysfunction is indicated.

**"Profiling" patients with heart failure:** The function of a variety of organ systems and control systems is clearly altered in heart failure. These systems include both limbs of the autonomic nervous sytem, that is, the sympathetic, including the adrenal medulla, as well as the parasympathetic; the renin-angiotensin-aldosterone axis, and the posterior pituitary gland, to name only the most obvious. Differences in the extent of activation of these neurohumoral mechanisms result in many differences in the clinical manifestations of heart failure observed among different patients. For example, elevations in systemic vascular resistance induced by adrenergic vasoconstriction are responsible for the maintenance of arterial pressure in the presence of reduced cardiac output, sometimes to the further detriment of the cardiac output; activation of the renin-angiotensin-aldosterone system and renal vasoconstriction result in retention of extracellular fluid and therefore in the symptoms resulting from pulmonary congestion, as well as in hepatomegaly and edema. Abnormalities in function of the sympathetic and parasympathetic systems are responsible for the relatively fixed heart rate characteristic of advanced heart failure.

A variety of agents that can block these various compensatory mechanisms are now available: atropine for blocking the parasympathetic nervous system, beta-adrenergic blocking agents for the cardiac adrenergic receptors, alpha-adrenergic blocking agents for peripheral adrenergic receptors, saralasin for the effects of angiotensin II, a family of converting enzyme inhibitors for blocking the production of angiotensin II, and spironolactone for aldosterone. Examining the responses of these blockades, measurement of circulating renin, angiotensin, and catecholamines and measurement of beta-adrenergic receptor density on circulating white blood cells and sometimes even on cardiac tissue, could be used to "profile" patients with congestive heart failure in an attempt to clarify the existing pathophysiologic abnormalities and to establish the most appropriate therapy.

**Newer inotropic agents:** The treatment of congestive heart failure has become stereotyped; often it commences with diuretics, includes cardiac glycosides, and finally vasodilators are added sequentially. It is not clear whether this treatment is optimal for all or even most patients. It is important to determine whether some modification, such as the treatment with afterload-reducing agents *before* the development of symptoms, could delay the development of congestive heart failure. Although the effectiveness of a number of orally active nonglycoside-positive inotropic agents, including amrinone, and several orally active beta-adrenergic agonists on hemodynamics has been demonstrated, the effect, if any, of these drugs on the survival of patients with heart failure has yet to be established.

**Epidemiology of heart failure:** Surprisingly little is known about the epidemiology of congestive heart failure. The only data available on prevalence are "soft" and come from analysis of the use of cardiac glycosides. In terms of the natural history of heart failure, available information comes from the Framingham data, most of which are now 20 years old. It was of interest how much information on the natural history of heart failure has come from Specialized Centers of Research (SCORs) in Ischemic Heart Disease, underscoring the importance of National Heart, Lung, and Blood Institute support in adding to the body of knowledge about ischemic heart failure. Although information on this subgroup of patients with heart failure is extremely useful, its applicability is obviously limited to patients with this particular cause of heart failure. Extensive prospective surveys of different populations for the incidence and natural history of congestive heart failure are sorely needed. Such studies should examine the influence of sex, age, race, and geographic, social, and regional differences. Also, these surveys should be carried out at regular intervals as diagnostic and therapeutic developments occur (such as the successful treatment of

hypertension and rheumatic valvular heart disease and the prolongation of life in patients with coronary artery disease).

*Conclusions:* It was concluded in the Workshop that great gaps exist in our understanding of the congestive heart failure state, ranging from an elucidation of the most fundamental molecular mechanisms of heart failure to a characterization of the epidemiologic aspects of this condition. Despite the acknowledged importance of congestive heart failure as a clinical problem, and despite its recognition in the national program plan of the National Heart, Lung, and Blood Institute, there is no program of support by the Institute dedicated to the study of this condition. However, the scientific underpinnings for important advances in this field have been established and the research community is now in a good position to capitalize on the wealth of fundamental and clinical observations in heart failure made during the past 2 decades. Thus, the time appears to be propitious for focusing increasing attention on this condition and indeed for launching a major investigative effort in this area.

**Acknowledgment:** The helpful cooperation of the section chairmen listed in the editorial in preparing lucid reviews of their sections of the workshop were invaluable in the preparation of this summary.

## Reference

1. **Braunwald E, Mock MM, Watson JT, eds.** Congestive Heart Failure: Current Research and Clinical Application. New York: Grune & Stratton, 1982.

# A More Meaningful Scoring System for Determining the Severity of Coronary Heart Disease

GOFFREDO G. GENSINI, MD

Selzer[1] in a recent editorial criticized the classification of the severity of coronary artery disease (CAD) which is currently used in all randomized trials on the surgical versus medical therapy of CAD. He pointed out that the classification of single-, double-, triple-vessel and main left (SDTML) coronary artery disease allows the inclusion in each subgroup of a mixture of patients with both a favorable and an unfavorable prognosis and provides, at best, only marginal differentiation of medically and surgically treated patients. He further suggested that patients with CAD should be identified on the basis of severity of narrowings, cardiac performance, effectiveness of coronary collateral circulation, amount of myocardium jeopardized by ischemia, and possibly other factors as well.

I wholeheartedly share these views, as described in my book in 1975.[2] An updated version of this scoring and stratifying method and a critique of the SDTML disease classification appeared in 1980.[3] There I stated: "A method that assigns a different severity score depending on the degree of luminal narrowing and the geographical importance of its location would be desirable. . . . Several years ago, recognizing these shortcomings, I devised a system that takes into consideration the geometrically increasing severity of lesions, the cumulative effects of multiple obstructions, the significance of their locations, the modifying influence of the collaterals, the size and quality of the distal vessels, and the importance of the status of myocardial function [Fig. 1]. . . . The fundamental concept forming the basis of this system is the hypothesis that the severity of coronary artery disease must be regarded as a consequence of the functional significance of the vascular narrowing and the extent of the area perfused by the involved vessel or vessels; the presence of an effective collateral situation may, on the other hand, modify the functional significance of a severe obstruction or occlusion. . . . Although this method may not be ideal, it provides more useful information than the simple division of patients into single-, double-, and triple-vessel disease. The advantages of this scoring method are as follows: (1) it provides an accurate stratification of patients according to the functional significance of their disease; (2) it lends itself to computer elaboration, storage, retrieval, and analysis; (3) it provides an opportunity to match patients with similar degrees of coronary artery disease who are receiving different forms of treatment; and (4) it allows for continuous, microprocessor-assisted studies of interobserved and intraobserver variability. Computer hardware and software to elaborate and store this type of information are readily available and are inexpensive."

Thus, the challenge of Selzer had already been met several years ago by a classification of patients with CAD, but this classification has not been utilized by others. It is time for cardiologists to adopt a more meaningful measurement of the severity of CAD.

From Msgr. Toomey Cardiovascular Laboratory, St. Joseph's Hospital Health Center, Syracuse, New York.

## References

1. **Selzer A.** On the limitation of therapeutic intervention trials in ischemic heart disease: a clinician's viewpoint. Am J Cardiol 1982;49:252–255.
2. **Gensini GG.** Coronary arteriography. Mt. Kisco, NY: Futura, 1975:488.
3. **Gensini GG.** Coronary arteriography. In: Heart Disease. Braunwald E, ed. Philadelphia: WB Saunders, 1980:352–353.

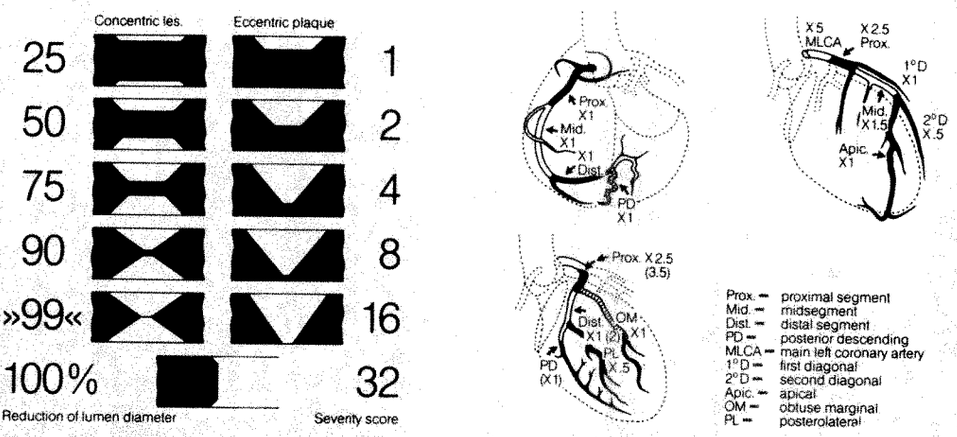



**FIGURE 1. Left panel,** roentgenographic appearance of concentric lesions and eccentric plaques resulting in, respectively, 25, 50, 75, 90, and 99% obstruction as well as complete occlusion (100%). The right column in this panel indicates the relative severity of these lesions using a score of 1 for 25% obstruction and doubling that number as the severity of the obstructions progresses according to the indicated reduction of lumen diameter (left column). **Right panel,** the principal vascular segments of (from left to right) the right coronary artery, the left anterior descending, and the circumflex. Each segment is followed by a multiplying factor such as X1, X2.5, and so on, depending on the functional significance of the area supplied by that segment.

# Pericardial Windows Are Suboptimal

DAVID H. SPODICK, MD, DSc

Experience with pericardial disease indicates that pericardial "windows" tend to close.[1] For a patient who can tolerate reasonably extensive thoracotomy, as much parietal pericardium as possible should always be resected, particularly in patients with continuing pathologic processes. Even then, pericardial remnants occasionally produce potentially constrictive fibrous tissue or bands of calcium, making the widest excision desirable. The pericardial window therefore has served as a palliative procedure mainly for systemically ill patients, such as those with malignant neoplasms or renal failure, who might not tolerate a more extensive procedure. Subxiphoid pericardiotomy[2] can be done if necessary under local anesthesia and permits the creation of a pericardial window, the resected tissue representing a generous biopsy. It also permits digital and endoscopic inspection of the pericardium, thus avoiding immediate thoracotomy without precluding near-total pericardectomy when the patient is in better condition.

From the Department of Medicine, University of Massachusetts Medical School and the Division of Cardiology, St. Vincent Hospital, Worcester, Massachusetts.

## References

1. **Spodick DH.** The normal and diseased pericardium. J Am Coll Cardiol 1983;1 (in press).
2. **Prager RL, Wilson CH, Bender HW.** The subxiphoid approach to pericardial disease. Ann Thorac Surg 1982;34:6–9.

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**Journal:** Vismara LA, Vera Z, Miller RR, Mason DT. Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. Am J Cardiol 1977; 39:1027–1034.

**Chapter in Book:** Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. Heart Disease in Infants, Children and Adolescents. Baltimore: Williams & Wilkins, 1968: 134–139.

**Book:** Berne E. Principles of Group Treatment. New York: Oxford University Press, 1966:26.

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*Equivalent to dobutamine

# Sites of Action of Positive Inotropic Catecholamines[1-5]

| Drug | Heart | | | |
|---|---|---|---|---|
| | $\beta_1$ Receptors | | | |
| | S-A Node (Heart Rate) | Specialized Conduction Fibers (Potential for Arrhythmia) | Myocardial Muscle Contractility | Adrenergic Nerve Fiber (Causes Release of Norepinephrine) |
| **Dobutamine/Dobutrex®** Dobutamine HCl | + | + | ++++ | 0 |
| Dopamine Hydrochloride† | ++ | ++ | ++++ | ++++ |
| Isoproterenol Hydrochloride | ++++ | ++++ | ++++ | 0 |
| Norepinephrine Bitartrate† | ++++ | ++++ | ++++ | ++++ |

| Drug | Blood Vessels | | |
|---|---|---|---|
| | α Receptors | $\beta_2$ Receptors | "Dopaminergic" Receptors |
| | Peripheral Vasoconstriction | Peripheral Vasodilation | Dilates Renal Vasculature |
| **Dobutamine/Dobutrex®** Dobutamine HCl | 0 to + | ++ | 0 |
| Dopamine Hydrochloride† | 0 to +++++ | ++ | Yes |
| Isoproterenol Hydrochloride | 0 | +++++ | 0 |
| Norepinephrine Bitartrate† | +++++ | 0 | 0 |


1. Tuttle, R. R., and Mills, J.: Dobutamine: Development of a New Catecholamine to Selectively Increase Cardiac Contractility, Circ. Res., *36*:185, 1975.

2. Goldberg, L. I., Hsieh, Y.-Y., and Resnekov, L.: Newer Catecholamines for Treatment of Heart Failure and Shock: An Update on Dopamine and a First Look at Dobutamine, Prog. Cardiovasc. Dis., *19*:327, 1977.

3. Robie, N. W., Nutter, D. O., Moody, C., and McNay, J. L.: In Vivo Analysis of Adrenergic Receptor Activity of Dobutamine, Circ. Res., *34*:663, 1974.

4. Goldberg, L. I.: Cardiovascular and Renal Actions of Dopamine: Potential Clinical Applications, Pharmacol. Rev., *24*:1, 1972.

5. Innes, I. R., and Nickerson, M.: Norepinephrine, Epinephrine, and the Sympathomimetic Amines, in The Pharmacological Basis of Therapeutics, Ed. 5 (edited by L. S. Goodman and A. Gilman), p. 477. New York: Macmillan Publishing Co., Inc., 1975.


†Action on adrenergic nerve fibers causes release of norepinephrine.

+ = Degree of stimulation
0 = No stimulation

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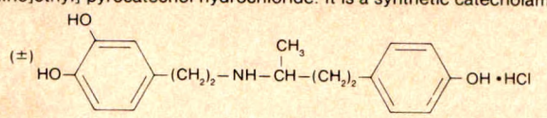
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Molecular Formula: $C_{18}H_{23}NO_3 \cdot HCl$ Molecular Weight: 337.84

The clinical formulation is supplied in a sterile lyophilized form for intravenous use only. Each vial contains 250 mg of dobutamine and 250 mg of mannitol. Hydrochloric acid is used to adjust the *p*H. The *p*H of the reconstituted solution is between 2.5 and 5.5.

**Clinical Pharmacology:** Dobutrex is a direct-acting inotropic agent whose primary activity results from stimulation of the beta receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short-term—up to several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas the output of others returned toward base-line values.

The onset of action of Dobutrex is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is two minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

**Indications and Usage:** Dobutrex is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutrex.

**Contraindication:** Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

**Warnings:** 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

**Precautions: 1. During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

*Usage Following Acute Myocardial Infarction*—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

*Usage in Pregnancy*—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

*Pediatric Use*—The safety and effectiveness of Dobutrex for use in children have not been studied.

*Drug Interactions*—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

**Adverse Reactions:** *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

*Miscellaneous Uncommon Effects*—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

*Longer-Term Safety*—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

**Overdosage:** In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

**Administration and Dosage:** *Reconstitution and Stability*—Dobutrex is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add another 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstitution time periods stated above.

*Recommended Dosage*—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

| Drug Delivery Rate (mcg/kg/min) | Infusion Delivery Rate | | |
|---|---|---|---|
| | 250 mcg/ml* (ml/kg/min) | 500 mcg/ml† (ml/kg/min) | 1000 mcg/ml‡ (ml/kg/min) |
| 2.5 | 0.01 | 0.005 | 0.0025 |
| 5 | 0.02 | 0.01 | 0.005 |
| 7.5 | 0.03 | 0.015 | 0.0075 |
| 10 | 0.04 | 0.02 | 0.01 |
| 12.5 | 0.05 | 0.025 | 0.0125 |
| 15 | 0.06 | 0.03 | 0.015 |

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

**How Supplied:** Vials Dobutrex® (dobutamine hydrochloride, Lilly), for Injection (lyophilized), equivalent to 250 mg dobutamine, 20-ml size, rubber-stoppered, in packages of 1. [121979]

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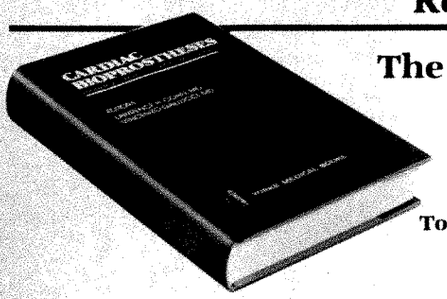
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**Lawrence H. Cohn, MD,** is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

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# Ventricular Flutter During Treatment With Amiodarone

GUANGGENG CUI, MD, WEIMIN HUANG, MD, and FERDINAND URTHALER, MD

Amiodarone is a widely used antiarrhythmic drug with long-lasting efficacy, minimal side effects, and few contraindications. However, amiodarone is not absolutely safe because it can itself trigger ventricular tachyarrhythmias[1,2] or cause sinus arrest,[3] as demonstrated in the patient to be described.

*A 48-year-old woman with known rheumatic mitral valve disease and recent onset of atrial fibrillation (Fig. 1-1) was started on digoxin (0.25 mg daily) and amiodarone (600 mg daily) on December 17, 1980. On January 5, 1981, the ventricular rate was about 80 beats/min and the dose of digoxin was decreased to 0.125 mg/day. Because of persisting atrial fibrillation, the dosage of amiodarone was increased to 800 mg/day on January 12, 1981. Ten days later sinus rhythm was restored, but the Q-T interval was prolonged to 0.48 second (Fig. 1-2). Digoxin was withdrawn and the dosage of amiodarone was reduced to 400 mg/day. The following day, Stokes-Adams attacks occurred. The electrocardiogram showed an atrioventricular (AV) junctional rhythm with ventricular bigeminy (Fig. 1-3), followed a few moments later by ventricular flutter (VF) (200 beats/min) (Fig. 1-4). At the time, the plasma level of digoxin, determined by radioimmunologic assay, was 0.92 ng/ml. Serum potassium, measured twice, was 3.5 and 4.0 mEq/liter, respectively. Lidocaine (200 mg) given intravenously was ineffective. Direct current shock with 100 W-s converted the VF to a slow[4] (Fig. 1-5) and then to a normal AV junctional rhythm[4] (Fig. 1-6) before restoring sinus rhythm with giant U wave alternans (Fig. 1-7). The next day VF recurred but was stopped by cardioversion, and by February 3 the electrocardiogram was normal (Fig. 1-8) and remained so for at least 6 months.*

Amiodarone prolongs the duration of the action potential in both atrial and ventricular cells.[5,6] It is not known whether amiodarone selectively inhibits potassium ion conductance or increases the slow inward current inactivation time constant, or both.[6] However, it is likely that a generalized prolongation of the action potentials will be reflected in a lengthening of the Q-T interval. Our patient had a prolonged Q-T interval that returned to normal 11 days after amiodarone therapy was discontinued. Others have made the same observation, but few adverse effects have been associated with amiodarone-induced lengthening of the Q-T interval.

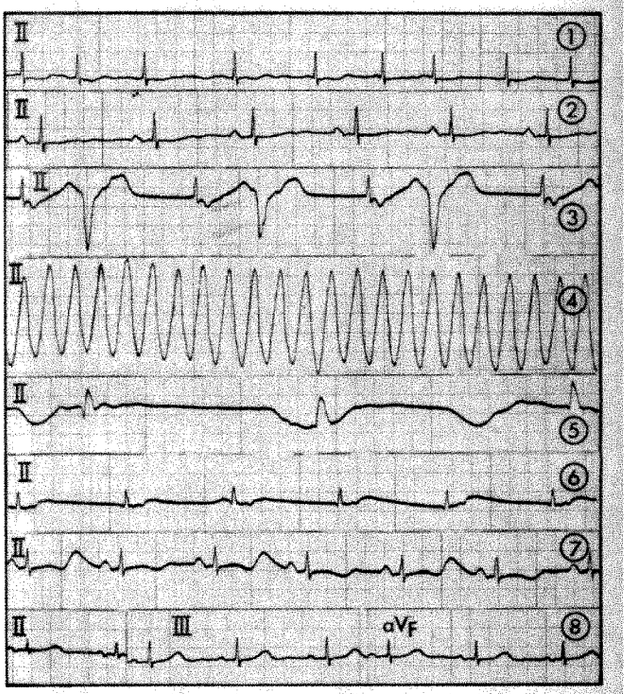



**FIGURE 1.** Lead II electrocardiograms (except for bottom strip with leads II, III, and aVF) illustrating episodes of (1) atrial fibrillation, (2) sinus rhythm, (3) AV junctional rhythm with retrograde atrial capture and ventricular premature beats (bigeminy), (4) ventricular flutter, (5) slow AV junctional rhythm, and (6) normal AV junctional rhythm. Paper speed 25 mm/s.

Our patient had a transient sinus arrest immediately before and after electroconversion of VF; however, in contrast to 2 cases of a previous report[3] in which the automaticity of the escape foci also was depressed, our patient had a normal substitute AV junctional escape rhythm.[4] Such depressions of automaticity could be due to an amiodarone-induced inhibition of the slow channel. Calcium entry blocking drugs are more effective in depressing sinus node automaticity than AV junctional automaticity.[7]

A profound decrease in heart rate coupled with an amiodarone-induced rate-independent prolongation of the Q-T interval will enhance the temporal dispersion of the refractory period[8] and favor the development of ventricular premature beats. Our patient had several

From the Shanghai Sixth People's Hospital, Shanghai, People's Republic of China; and the Department of Medicine, University of Alabama Medical Center, Birmingham, Alabama. This study was supported by the National Heart, Lung, and Blood Institute (Program Project Grant HL 11310 and SCOR on Ischemic Heart Disease HL 17667) and was conducted while Dr. Huang was on sabbatical leave in Birmingham, Alabama. Manuscript received September 1, 1982, accepted September 16, 1982.

premature beats immediately before the onset of VF. Although digitalis levels reportedly increase after administration of amiodarone,[9] our patient's digoxin level was normal. Thus, amiodarone can elicit dysrhythmias, and the simultaneous occurrence of depressed automaticity, a prolonged Q-T interval, and ventricular premature beats is an ominous premonitory sign.

### References


1. **McComb JM, Logan KR, Khan MM, Geddes JS, Adgey AAJ.** Amiodarone-induced ventricular fibrillation. Eur J Cardiol 1980;11:381–385.
2. **Keren A, Tzivoni D, Gottlieb S, Benhorin J, Stern S.** Atypical ventricular tachycardia (torsade de pointes) induced by amiodarone. Chest 1982;81: 384–386.
3. **McGovern B, Garan H, Ruskin JN.** Sinus arrest during treatment with amiodarone. Br Med J 1982;284:160–161.
4. **Urthaler F, Katholi CR, Macy J Jr, James TN.** Electrophysiological and mathematical characteristics of the escape rhythm during complete AV block. Cardiovasc Res 1974;8:173–186.
5. **Singh BN, Vaughan-Williams EM.** The effect of amiodarone, a new anti-anginal drug, on cardiac muscle. Br J Pharmacol 1970;39:657–667.
6. **Goupil N, Lenfant J.** The effects of amiodarone on the sinus node activity of the rabbit heart. Eur J Pharmacol 1976;39:23–31.
7. **Urthaler F, James TN.** Experimental studies on the pathogenesis of asystole after verapamil in the dog. Am J Cardiol 1979;44:651–656.
8. **Han J, Millet D, Chizzonitti G, Moe GK.** Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate. Am Heart J 1966;71:481–487.
9. **Nademanee K, Kannon R, Hendrickson J, Burnam H, Kay I, Singh B.** Amiodarone-digoxin interaction during treatment of resistant cardiac arrhythmias (abstr). Am J Cardiol 1982;49:1026.


# Myocardial Ischemia in Anomalous Origin of the Right Coronary Artery From the Pulmonary Trunk

## Proof of a Coronary Steal

GARY S. MINTZ, MD, ABDULMASSIH S. ISKANDRIAN, MD, CHARLES E. BEMIS, MD, ELDRED D. MUNDTH, MD, and JOHN S. OWENS, MD

Anomalous origin of the right coronary artery from the pulmonary artery is considered a benign entity. At least 22 patients with this condition have been reported. Two patients, both young, died suddenly.[1,2] This report describes another consequence of an anomalous right coronary artery.

*A 47-year-old man presented after having angina pectoris for 2 months. Findings on physicial examination, resting electrocardiography and chest roentgenography were normal. A multistage, graded treadmill exercise test was performed. After 9 minutes of exercise (at a heart rate of 160 beats/min), the patient described angina, and the electrocardiographic monitor showed 3 mm downsloping S-T segment depression in the anterior precordial leads (Fig. 1). A thallium-201 myocardial perfusion scan showed a decrease in perfusion of the anterior surface during exercise with normal perfusion in the 4-hour delayed study. On selective coronary arteriography the left anterior descending and left circumflex coronary arteries were normal. The right coronary artery (RCA) originated from the pulmonary trunk; it filled retrogradely by way of collaterals from the left coronary artery and emptied into the pulmonary trunk (Fig. 2). Myocardial perfusion scintigraphy using intracoronary injection of labelled particles was performed after coronary arteriography. Three mCi of technetium-99m human albumin microspheres were injected selectively into the left coronary artery. Total lung counts were 19,314 (84%); heart counts were 3,963 (16%) (Fig. 3).*

*The coronary artery anomaly was operatively corrected. The RCA was isolated; its origin was excised from the anterior surface of the pulmonary trunk and reimplanted into the aorta. Before excision, blood flow through the anomalous artery was 1,200 to 1,400 ml/min toward the pulmonary artery. After reimplantation, blood flow into the RCA was normal in direction. The postoperative course was uneventful. Findings were normal on exercise thallium-201 myocardial scintigraphy 3 months after operation. Arteriography showed that anastomosis of the RCA was normal.*

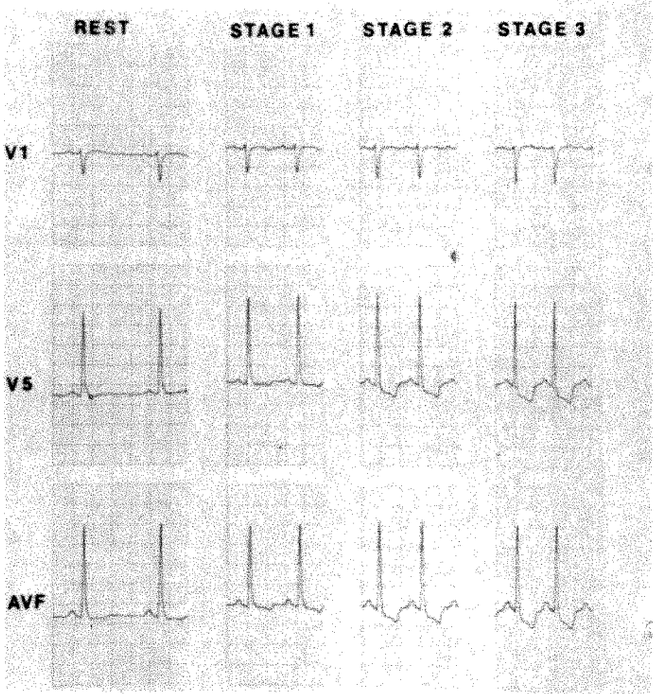



**FIGURE 1.** At stage 3 of the Bruce protocol, the treadmill exercise tests shows 3 mm downsloping S-T depression in the anterior precordial ($V_5$) and inferior (aVF) leads.

Coronary arterial steal may result from shunting of blood from 1 coronary artery to another (*intercoronary*), from 1 location in a coronary to another in the

From the Likoff Cardiovascular Institute, Hahnemann University and Hospital, Philadelphia, Pennsylvania. Manuscript received July 15, 1982; revised manuscript received August 10, 1982; accepted August 13, 1982.

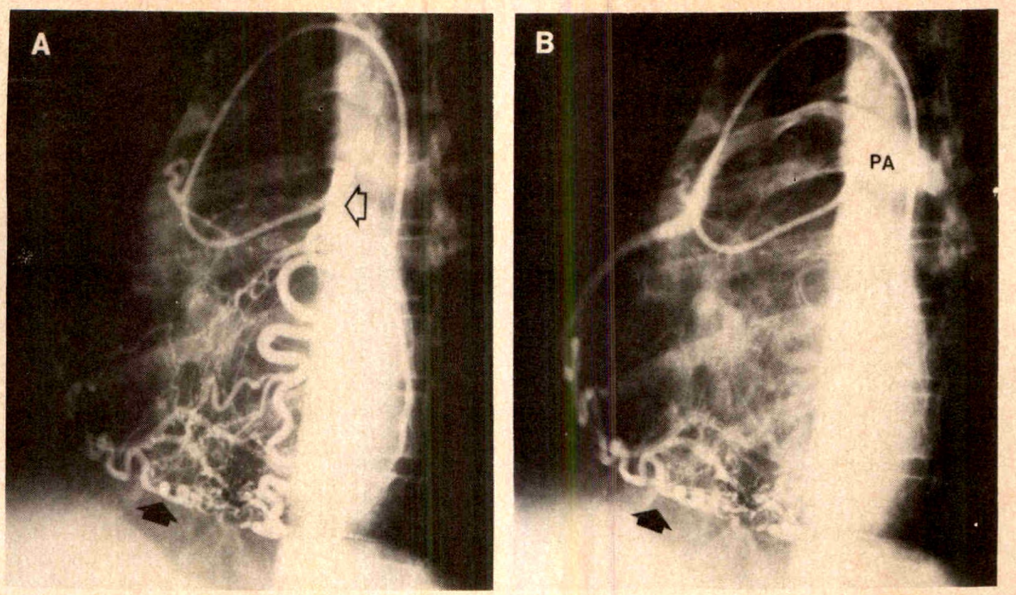



**FIGURE 2.** Selective coronary arteriograms demonstrating the anomalous origin of the right coronary artery from the pulmonary artery. **A**, contrast material is injected into the left coronary artery (**open arrow**); the right coronary artery (**solid arrow**) begins to opacify faintly. **B**, a later frame from the same injection shows denser opacification of the right coronary artery (**solid arrow**) as well as visualization of the anomalous artery originating from the pulmonary artery (PA).

same coronary through collateral flow (*intracoronary*), and from a coronary artery to a venous connection (*arteriovenous*). There are 3 potential causes: congenital or acquired anatomic malformations, obstructive coronary artery disease, and vasoactive pharmacologic interventions.

The most common congenital cause of a coronary steal is anomalous origin of the left coronary artery from the pulmonary trunk. After birth, the pulmonary arterial pressure falls, and survival depends on the acute development of collateral blood flow from the right to the left coronary artery. The collateral flow causes a large arteriovenous shunt, and the coronary steal embarasses left ventricular myocardial function.[3,4] It has been postulated that intercoronary shunting may exist in patients with obstructive coronary artery disease. Blood may be "stolen" from the less diseased artery by way of collateral flow to the more diseased artery.[5] Pharmacologic experiments have shown that vasodilators can cause "shunting" of blood from ischemic to nonischemic (or from subendocardial to subepicardial) myocardium. Alpha-adrenergic stimulation and vasoconstriction will reverse this phenomenon. It can be argued that these changes do not represent a true coronary steal, but rather a decrease in the effective perfusion pressure needed to maintain maximal collateral blood flow to the ischemic zone.[6,7]

Our patient with an anomalous origin of the RCA has an unusual proof of a true coronary artery steal. Of the technetium-99m labeled microspheres injected into the left coronary artery, 84% passed through the collaterals to the RCA to lodge in the pulmonary artery; thus, there was a 5 to 1, resting left-to-right shunt through the collateral circulation of the coronary vascular bed. (Because approximately 95% of these microspheres are

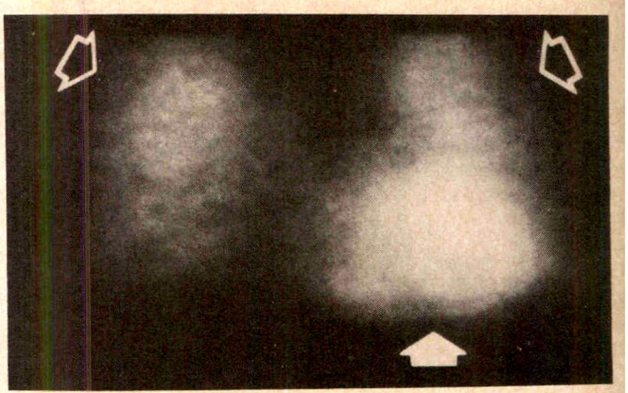


**FIGURE 3.** Three mCi of technetium-99m human albumin microspheres were injected selectively into the left coronary artery. Scintigraphic images of the heart and lungs show total lung counts of 19,314 (**open arrows**) and total heart counts of 3,963 (**solid arrows**). The left-to-right shunt through the coronary circulation is approximately 5 to 1.

10 to 30 $\mu$m in diameter, their presence in the lungs in such magnitude indicates large diameter collateral vessels.) During exercise, angina developed; myocardial scintigraphy showed decreased anterior wall perfusion; and the exercise electrocardiogram showed marked anterior precordial S-T segment depression. After reimplantation of the anomalous RCA, the patient became asymptomatic; and both the exercise scintigraphic and electrocardiographic results became normal.

Two explanations are possible. First, intercoronary steal from the anterior myocardial circulation caused anterior ischemia. Second, because the coronary circulation was maximally dilated, there was no ability to

increase blood flow to the anterior myocardium to meet the increased demand of exercise. Because the zone of ischemic myocardium was in the distribution of the left anterior descending artery, a steal was likely.

At surgery, coronary blood flow was 1,200 to 1,400 ml/min toward the pulmonary artery. Thus (by inference from the 5 to 1 intercoronary shunt), total anterograde left coronary blood flow was 1,440 to 1,680 ml/min, but only 240 to 280 ml/min supplied myocardium. Normal myocardial blood flow is approximately 85 ml/min/100 g of left ventricular myocardium at rest.[8,9] During maximal exercise, myocardial blood flow increased 4 times; during maximal pharmacologic coronary vasodilatation with dipyrimadole, myocardial blood flow increases 5 times. In our patient at rest before surgery, anterograde left coronary blood flow was greater than the maximal expected flow after maximal coronary vasodilatation. The ability to augment total flow during exercise was limited. A steal and myocardial ischemia resulted.

Thus, anomalous origin of the RCA is not benign. A coronary steal may cause exercise-induced myocardial ischemia. This may be the mechanism of sudden death reported in this disorder. If exercise-induced myocardial scintigraphy documents a steal, surgical correction appears warranted.

### References


1. **Wald S, Stonecipher K, Baldwin BJ, Nutter DO.** Anomalous origin of the right coronary artery from the pulmonary artery. Am J Cardiol 1971;127:677–681.
2. **Bregman D, Brennan FJ, Singer A, Vinci J, Parodi EN, Cassarella WJ, Edie RN.** Anomalous origin of the right coronary artery from the pulmonary artery. J Thorac Cardiovasc Surg 1976;72:626–630.
3. **Wright NL, Baue AE, Baum S, Blakemore WS, Zinsser HF.** Coronary artery steal due to an anomalous left coronary artery originating from the pulmonary artery. J Thorac Cardiovasc Surg 1970;59:461–467.
4. **Ihekwaba FN, Davidson KG, Ogilvie B, Caves PK.** Anomalous origin of the left coronary artery from the pulmonary artery steal in adults. Thorax 1976;31:337–345.
5. **Robertson P, Kostuk WJ, Ahuja SP.** The localization of coronary artery stenoses by 12 lead ECG response to graded exercise test—support for intercoronary steal. Am Heart J 1976;91:437–444.
6. **Becker LC.** Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 1978;57:1103–1110.
7. **Flameng W, Wusten B, Schaper W.** On the distribution of myocardial blood flow. II. Effects of arterial stenosis and vasodilatation. Basic Res Cardiol 1972;69:435–446.
8. **Jorgesen CR, Gobel FL, Taylor HL, Yang W.** Myocardial blood flow and oxygen consumption during exercise. Ann NY Acad Sci 1977;301:213–223.
9. **Kitamura K, Jorgensen CR, Gobel FL, Taylor HL, Yang W.** Hemodynamic correlates of myocardial oxygen consumption during upright exercise. J Appl Physiol 1972;32:516–522.


# Blood Cyst of the Papillary Muscle

## Clinical, Echocardiographic and Anatomic Observations

ANDREW M. HAUSER, MD, KAMALSINGH RATHOD, MD, JANET McGILL, MD, BARBARA F. ROSENBERG, MD, SEYMOUR GORDON, MD, and GERALD C. TIMMIS, MD

We describe the echocardiographic and anatomic features of an intraventricular cardiac blood cyst which was diagnosed after an embolic stroke.

*A 27-year-old man was admitted with acute right-sided hemiparesis and expressive aphasia. The cardiac sounds were normal and a grade 1/6 apical systolic murmur was heard. Findings on chest radiography, electrocardiography, and brain scan were normal. The hemiparesis and aphasia disappeared in 48 hours. A 2-dimensional echocardiogram (Fig. 1) demonstrated mild left atrial enlargement and systolic mitral valve prolapse. A 2.5 cm echolucent mass attached to the tip of the anterolateral papillary muscle moved in synchrony with adjacent chordae tendineae. In systole, anterior motion of the mass toward the left ventricular outflow tract was observed.*

From the Noninvasive Laboratory, the Division of Cardiovascular Diseases, the Department of Internal Medicine, the Department of Anatomic Pathology, the Division of Cardiovascular Diseases, and the Cardiac Laboratories, William Beaumont Hospital, Royal Oak, Michigan. Manuscript received September 3, 1982; revised manuscript received September 14, 1982, accepted September 17, 1982.

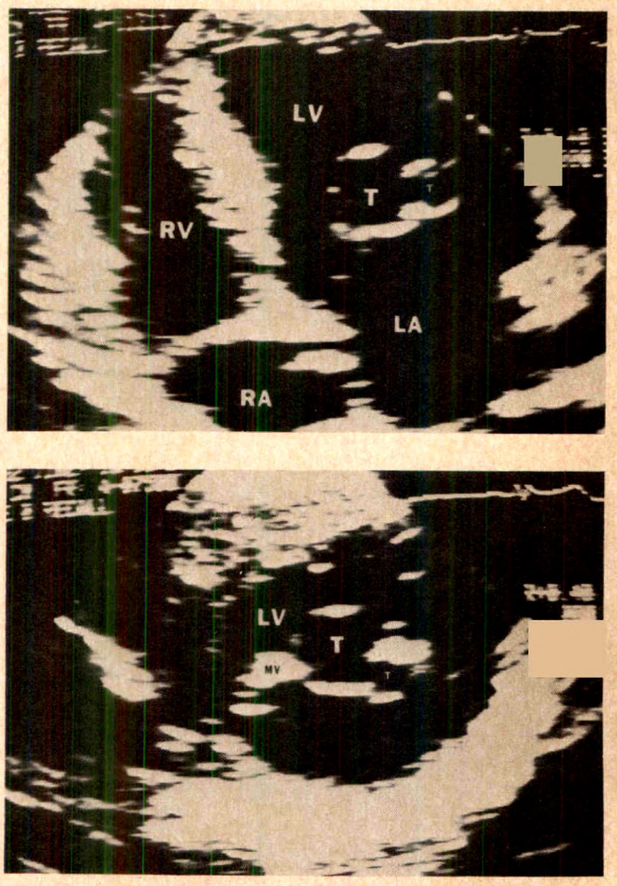



**FIGURE 1.** Apical 4-chamber view (**top**) and parasternal short-axis view (**bottom**) demonstrating the bilobed and cystic appearance of a mobile mass attached to the tip of the anterolateral papillary muscle and adjacent chordae tendineae. The left atrium (LA) is mildly enlarged. LV = left ventricle; RA = right atrium; RV = right ventricle; T = tumor.

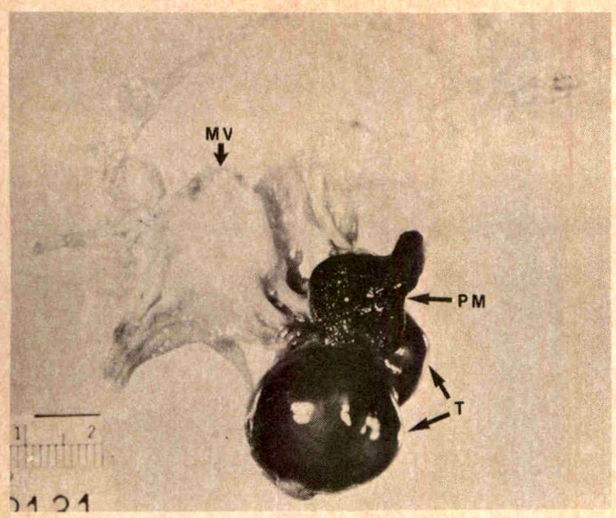



**FIGURE 2.** The 2.5 cm bilobed cyst attached to the papillary muscle. MV = normal mitral valve; PM = papillary muscle; T = tumor.

*Through a left atrial incision, a bilobed 2.5 cm cystic mass was found attached to the anterolateral papillary muscle and adjacent chordae tendineae. Complete removal necessitated replacement of the mitral valve also. The mass was formed of 2 contiguous cysts with trabeculated inner linings and contained dark red blood (Fig. 2). The cyst wall extended from the tip of the papillary muscle, adhered to adjacent chordae tendineae, and consisted of relatively dense collagenous fibrous tissue containing elastic fibers, lymphocytes, and a few plasma cells and eosinophils. The cyst was lined by endothelial-like cells. The mitral leaflets were normal.*

Since cystic cardiac masses are rare, there have been few echocardiographic descriptions. Farooki et al[1] noted an echo-free appearance on M-mode examination of an intramural fluid-filled hydatid cyst in a child with echinococcosis. The angiographic and pathologic appearance of a nonendothelialized cyst involving the mitral valve has been described by Leatherman et al.[2] Blood-filled cysts also may involve the pulmonic valve and can result in obstruction.[3–5] Our case differs from these in several respects: papilllary muscle attachment is unique, and to date, it is the only blood cyst detected by echocardiography. The echocardiogram provided the only clinical clue to the etiology of our patient's embolic event and obviated the need for cardiac catheterization.

### References

1. **Farooki ZQ, Adelman S, Green EW.** Echocardiographic differentiation of a cystic and a solid tumor of the heart. Am J Cardiol 1977;39:107–111.
2. **Leatherman L, Leachman RD, Hallman GL, Cooley DA.** Cyst of mitral valve. Am J Cardiol 1968;21:428–430.
3. **Jimenez-Martinez M, Franco-Vazquez S, Anglo-Hernandez O, Reta-Villalobos A.** Blood cysts of the pulmonary valve producing pulmonic stenosis. J Thorac Cardiovasc Surg 1968;56:165–169.
4. **Cumming GR, Ferguson CC.** An elusive tumor of the pulmonary valve associated with coronary arteriovenous fistula. J Thorac Cardiovasc Surg 1965;50:715–720.
5. **Liese GJ, Brainard SC, Goto U.** Giant blood cyst of the pulmonary valve. N Engl J Med 1963;269:465–467.

# Transmural Ischemia During Preexercise Hyperventilation

BERNHARD H. LISKER, MD and
SANFORD E. LEFF, MD

Hyperventilation is performed in many laboratories as an adjunct to stress testing. Its purpose is to identify an abnormal electrocardiographic response that may occur from the hyperventilation associated with exercise rather than the exercise itself. There have been no reported complications of this procedure. We were recently involved in the care of a patient in whom profound myocardial ischemia developed during routine hyperventilation.

*The patient (LW) was a 69-year-old white man with systemic hypertension and exertional angina. His medications were hydrochlorothiazide and captopril. The 12-lead electrocardiogram, heart rate, and blood pressure were recorded supine, standing, and after 30 seconds of hyperventilation. With hyperventilation the heart rate increased from 76 to 122 beats/min and the blood pressure increased from 180/80 to 200/110 mm Hg. S-T segment elevations of 3 mm appeared in leads I and aVL and S-T segment depressions of 2 mm in the inferior leads (Fig. 1). The patient was dyspneic but without chest pain. The electrocardiogram returned to baseline after several minutes (Fig. 2). The patient was hospitalized. Serial cardiac enzyme levels were normal, but the electrocardiogram evolved T-wave inversions across the precordium lasting 4 days, consistent with nontransmural injury. Cardiac catheterization revealed 90% diameter narrowing of the left main coronary artery and multiple high grade narrowings in the proximal and mid right and left coronary arteries. The patient was treated with long-acting nitrates in addition to the antihypertensive medications and was referred for coronary bypass surgery.*

From the Division of Cardiology, Department of Medicine, Jewish Hospital and Medical Center of Brooklyn, Brooklyn, New York. Manuscript received September 27, 1982, accepted October 16, 1982.

Patients with angiographically proven normal coronary arteries have a propensity to electrocardiographic changes induced by hyperventilation. It has been suggested that subjects be routinely studied with at least 25 seconds of hyperventilation before exercise testing to rule out false-positive results.[1] However, there are reports that hyperventilation may induce changes in patients with angiographically proven coronary artery disease, demonstrating that these entities do coexist.[2] During hyperventilation a 20 to 30% increase in resting heart rate is expected, possibly because of stimulation of sympathetic activity.[3] Additionally, an analysis of coronary vascular dynamics after 6 minutes of hyper-

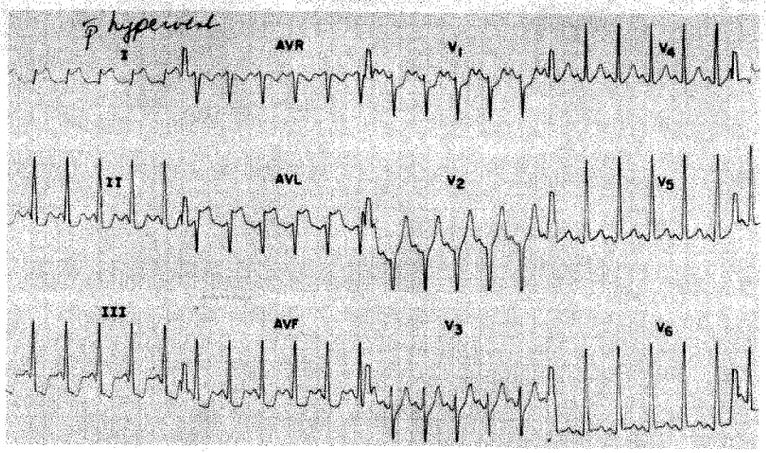



**FIGURE 1.** Electrocardiogram of patient LW immediately after hyperventilation, showing S-T segment elevations and depressions and pseudonormalization of T waves.

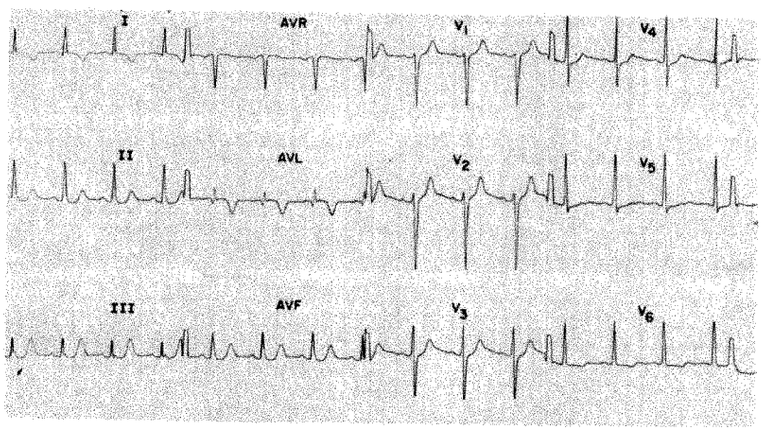



**FIGURE 2.** Three minutes after hyperventilation the electrocardiogram had returned to baseline.

ventilation showed an increase in myocardial oxygen uptake independent of the rate-pressure product, without reduction in coronary sinus blood flow, suggesting that hyperventilation can increase myocardial oxygen extraction but does not cause significant coronary vasoconstriction.[4] Coronary spasm has been elicited by respiratory alkalosis in a patient known to have variant angina[5] and in a recent series of 10 patients also with variant angina.[6] However, in all cases, more than 4 minutes of hyperventilation was required; the onset of electrocardiographic changes was usually delayed by several minutes; S-T segment elevations were rarely more than 1 mV.

Our patient had transmural ischemia that could be explained by a doubling of the rate-pressure product and a possible secondary or independent increase in myocardial oxygen extraction in a high risk setting. We cannot exclude spasm, but it is unlikely to have been provoked by such brief hyperventilation; we chose not to challenge with ergonovine during catheterization in view of the recent injury and severe obstructive coronary disease. The response to hyperventilation that we encountered, regardless of the exact cause, confirms that the responses to hyperventilation are complex, and the routine use of this procedure before exercise testing may yield unpredictable information that is not necessarily false-positive.

## References

1. **McHenry PL, Richmond HW, Weisenberger BL, Rodway JS, Perry GF, Jordan JW.** Evaluation of abnormal exercise electrocardiogram in apparently healthy subjects: labile repolarization (ST-T) abnormalities as a cause of false positive responses. Am J Cardiol 1981;47:1152–1160.
2. **Joy M, Trump DW.** Significance of minor ST segment and T wave changes in the resting electrocardiogram of asymptomatic subjects. Br Heart J 1981;45:48–55.
3. **Greenberg PS, Cooke BM Jr, Bible M, Ellestad MH.** Use of heart rate response to standing and hyperventilation at rest to detect coronary artery disease: correlation with the S-T response to exercise. J Electrocardiol 1980;13:373–378.
4. **Wilson JR, Goldberg S, Hirshfeld JW, Harken AH.** Effects of respiratory alkalosis on coronary vascular dynamics and myocardial energetics in patients with coronary artery disease. Am Heart J 1981;102:202–205.
5. **Mortensen SA, Vilhelmsen R, Sandie E.** Prinzmetal's variant angina. Circadian variation in response to hyperventilation. Acta Med Scand (Suppl) 1981;644:38–41.
6. **Girotti LA, Crosatto JR, Messuti H, Kaski JC, Dyszel E, Rivas CA, Araujo LI, Vetulli HD, Rosenbaum MB.** The hyperventilation test as a method for developing successful therapy in Prinzmetal's angina. Am J Cardiol 1982; 49:834–841.

# Two-Dimensional Echocardiographic Detection of Right Atrial Thrombi

BRUNO V. MANNO, MD, IOANNIS P. PANIDIS, MD, MORRIS N. KOTLER, MD, GARY S. MINTZ, MD, and JOHN ROSS, RCPT

Right atrial thrombi are rarely diagnosed antemortem.[1,2] We describe 2 cases of right atrial thrombi detected by 2-dimensional echocardiography. A 62-year-old man with amyloid heart disease and congestive heart failure underwent 2-dimensional echocardiography, which revealed 4-chamber enlargement, especially of the right atrium. A dense echogenic band was reproducibly visualized coursing the right atrium only in an off-axis apical view while not seen in standard views (Fig. 1). This was confirmed as thrombus in the right atrial appendage at autopsy. A 34-year-old man underwent uneventful repair of a secundum atrial septal defect. Echocardiography performed postoperatively revealed an enlarged right atrium and ventricle. An irregular, immobile speckled mass was visualized posterolaterally in the right atrium in apical 4-chamber, right ventricular inflow, and right-sided apical 2-chamber views (Fig. 2). Angiography later confirmed this mass as thrombus.

Right atrial thrombus formation is uncommon; it is found in patients with an enlarged right atrium, reduced cardiac output, and relative stasis of blood, such as congestive cardiomyopathy,[3] idiopathic dilation of the right atrium[4] with foreign bodies,[5] or after endocardial damage.[6] Several of these factors were present in both of our cases.

The typical 2-dimensional echocardiographic appearance of atrial thrombus is a nonhomogeneous, immobile mass with a broad base of attachment to the atrial wall and a distinct intracavitary margin, as seen in our second patient (Fig. 2). However, the other pathologically confirmed thrombus was visualized as a curvilinear echodense band with a distal echo-free area seen only in an off-axis view (Fig. 1). The distal echo-free zone may be explained pathologically by the lack of organization or fibrosis; the band represented the interface between the blood and the thrombus. A previous report emphasized the necessity of visualizing right atrial masses in multiple standard planes to eliminate artifactual echoes.[1] The reproducibility and persistence of the band with varying transducer angulation and gain settings make artifact an unlikely cause. This suggests that nonstandard views may be necessary to detect right atrial thrombi, especially those in the right atrial appendage, and that thrombus may have an atypical echocardiographic appearance. Right atrial thrombus must be differentiated from other causes of a right atrial mass such as myxomas, sarcomas, and other neoplasms, primary or secondary. Secondary neoplasms can extend into the right atrium by way of the inferior vena cava, especially in patients with hypernephromas.[1,2] Differentiation from thrombus may be difficult; however, the site of attachment of the mass is useful. In myxomas, the site of attachment is the atrial septum, and in secondary tumors extension from the inferior vena may assist in the differentiation of right atrial masses. Triscuspid valve vegetation also may present as a right atrial mass; however, the attachment to the tricuspid leaflet and mobility during the cardiac cycle often help in the differentiation from thrombus. Several intrinsic right atrial structures such as Chiari network, aneurysm of the atrial septum, and Eustachian valves may appear as atrial masses. However, their location and mobility again help differentiate these structures from thrombus.

From the Likoff Cardiovascular Institute, Hahnemann University, Philadelphia, Pennsylvania. Manuscript received October 14, 1982; revised manuscript received October 24, 1982, accepted October 27, 1982.

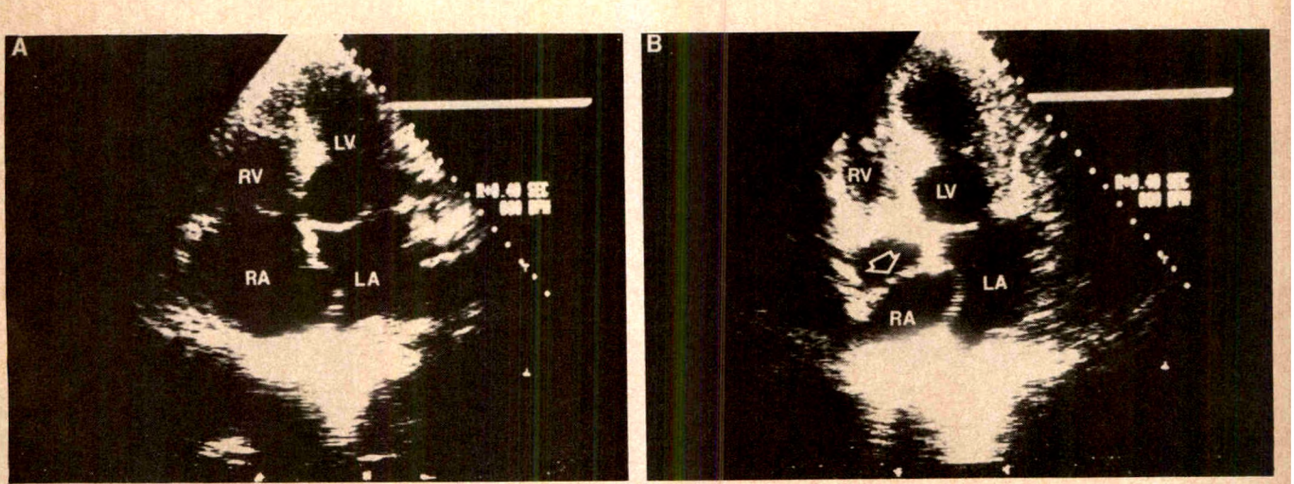



**FIGURE 1. A,** a 2-dimensional 4-chamber apical view. The right atrium (RA) is enlarged. No thrombus is seen. **B,** off-axis apical 4-chamber view. An echodense band is seen coursing the right atrium (**arrow**). LA = left atrium; LV = left ventricle; RV = right ventricle.

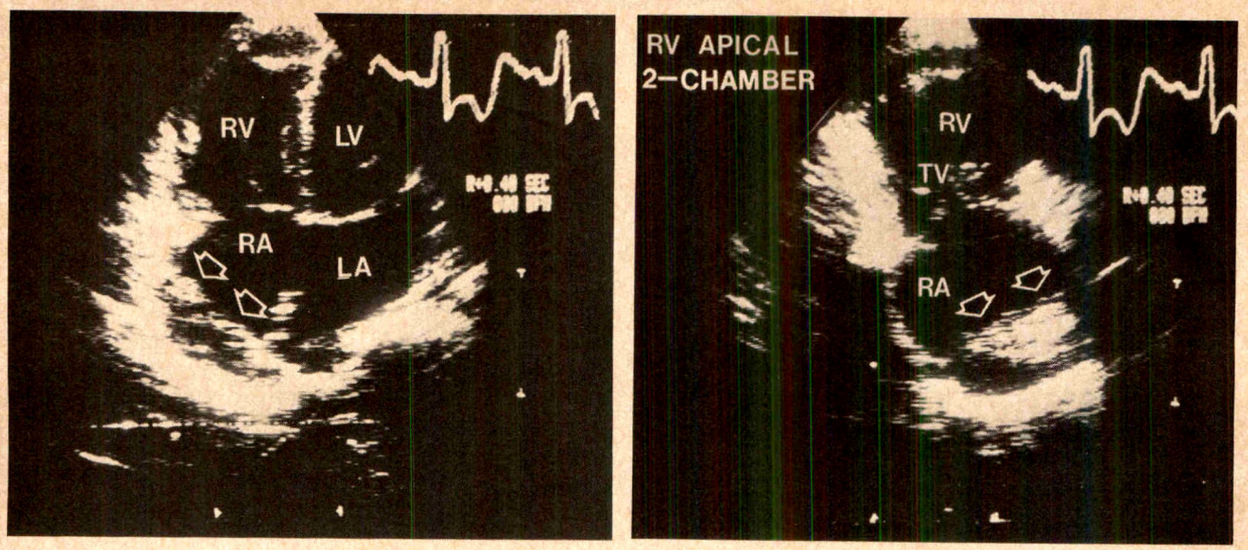



**FIGURE 2. Left,** 2-dimensional 4-chamber apical view demonstrating thrombus in posterolateral right atrium (RA) (**arrows**). **Right,** right ventricular apical 2-chamber view again demonstrates thrombus in right atrium (**arrow**). LA = left atrium; LV = left ventricle; RV = right ventricle; TV = tricuspid valve.

*In conclusion*, right atrial thrombus, although an uncommon finding, can be reliably diagnosed and differentiated from other atrial masses using 2-dimensional echocardiography. Use of off-axis as well as standard views may be necessary to visualize the thrombus.

## References

1. **Riggs T, Paul MH, DeLeon S, Ilbawi M.** Two-dimensional echocardiography in evaluation of right atrial masses: five cases in pediatric patients. Am J Cardiol 1981;48:961–966.
2. **Seward JB, Gura GM, Hagler DJ, Tajik AJ.** Evaluation of M-mode echocardiography and wide-angle two-dimensional sector echocardiography in the diagnosis in intracardiac masses (abstr). Circulation 1978;58:Suppl II:II–234.
3. **Roberts WC, Ferrans VJ.** Pathologic anatomy of the cardiomyopathies; idiopathic dilated and hypertrophic types, infiltrative types and endomyocardial disease with and without eosinophilia. Hum Pathol 1975;6:287–342.
4. **Sheldon WC, Johnson CD, Favaloro RG.** Idiopathic enlargement of the right atrium. Am J Cardiol 1970;23;278–284.
5. **Prozan GB, Shipley RE, Madding GF, Kennedy PA.** Pulmonary thromboembolism in the presence of an endocardial pacing catheter. JAMA 1968; 206:1564–1565.
6. **Salyir WR, Page DL, Hutchins GM.** The development of cardiac myxomas and papillary endocardial lesions from mural thrombus. Am Heart J 1975; 89:4–17.

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### Step 3: Nitrates and calcium antagonists

Calcium antagonists have special usefulness in controlling cases where the myocardial oxygen supply is diminished by coronary vasospasm; their use in combination with nitrates is recommended if Step 2 therapy is unsatisfactory (or if the patient has variant or vasospastic angina).

Consensus of the Symposium

**Nitrates are basic in step-care therapy for ischemic heart disease**

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**Step 2**
If not controlled: Nitrates + beta blockers

**Step 3**
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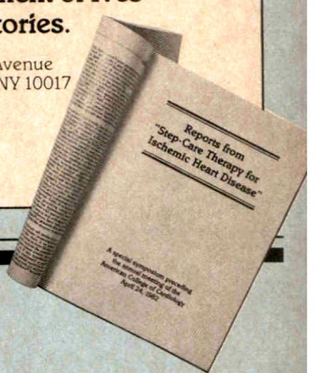
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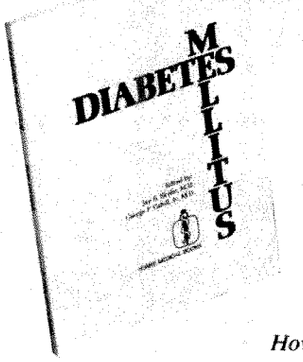
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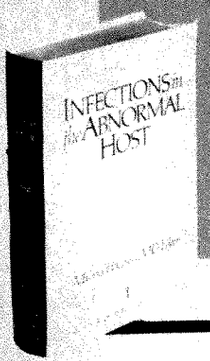
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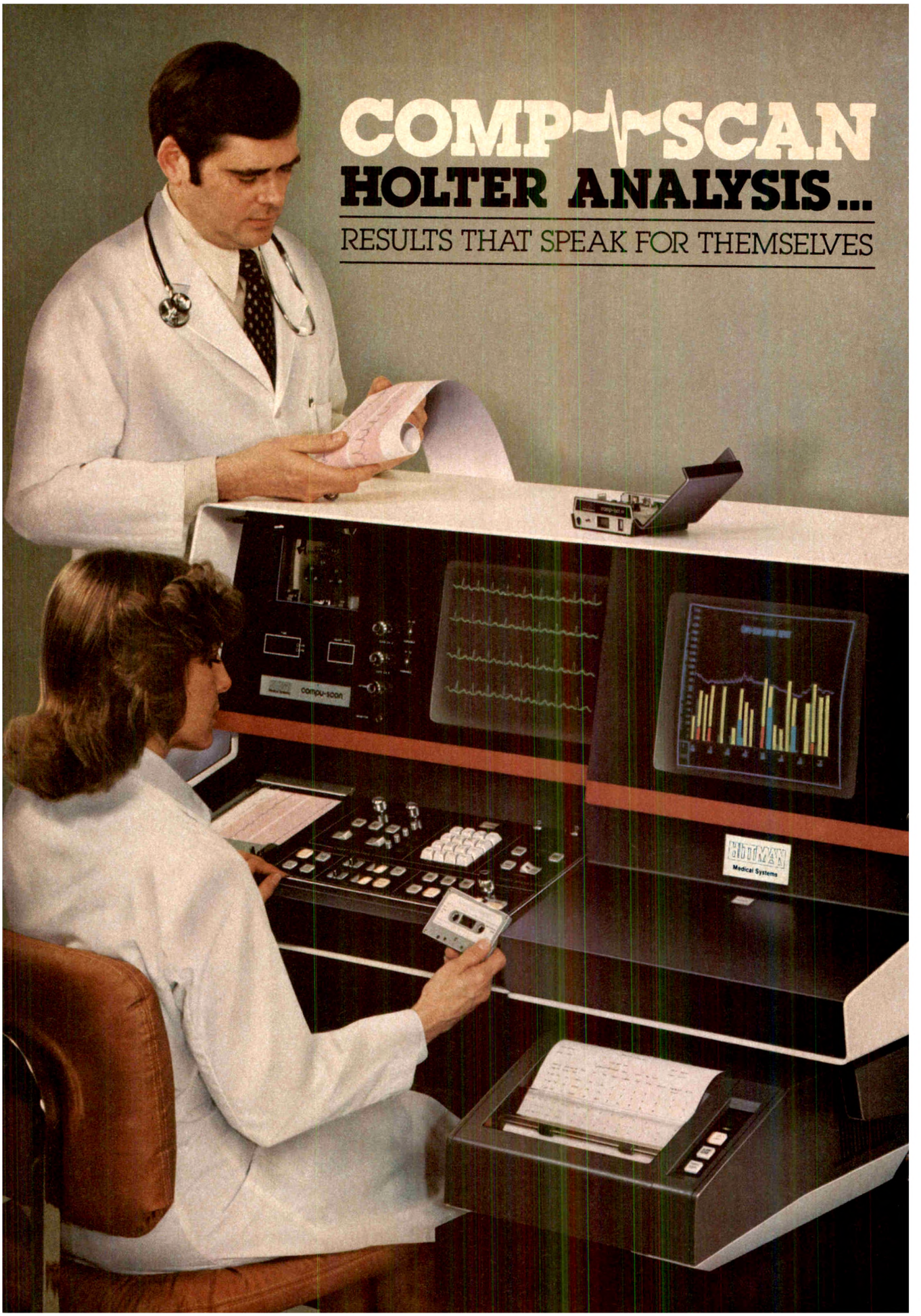
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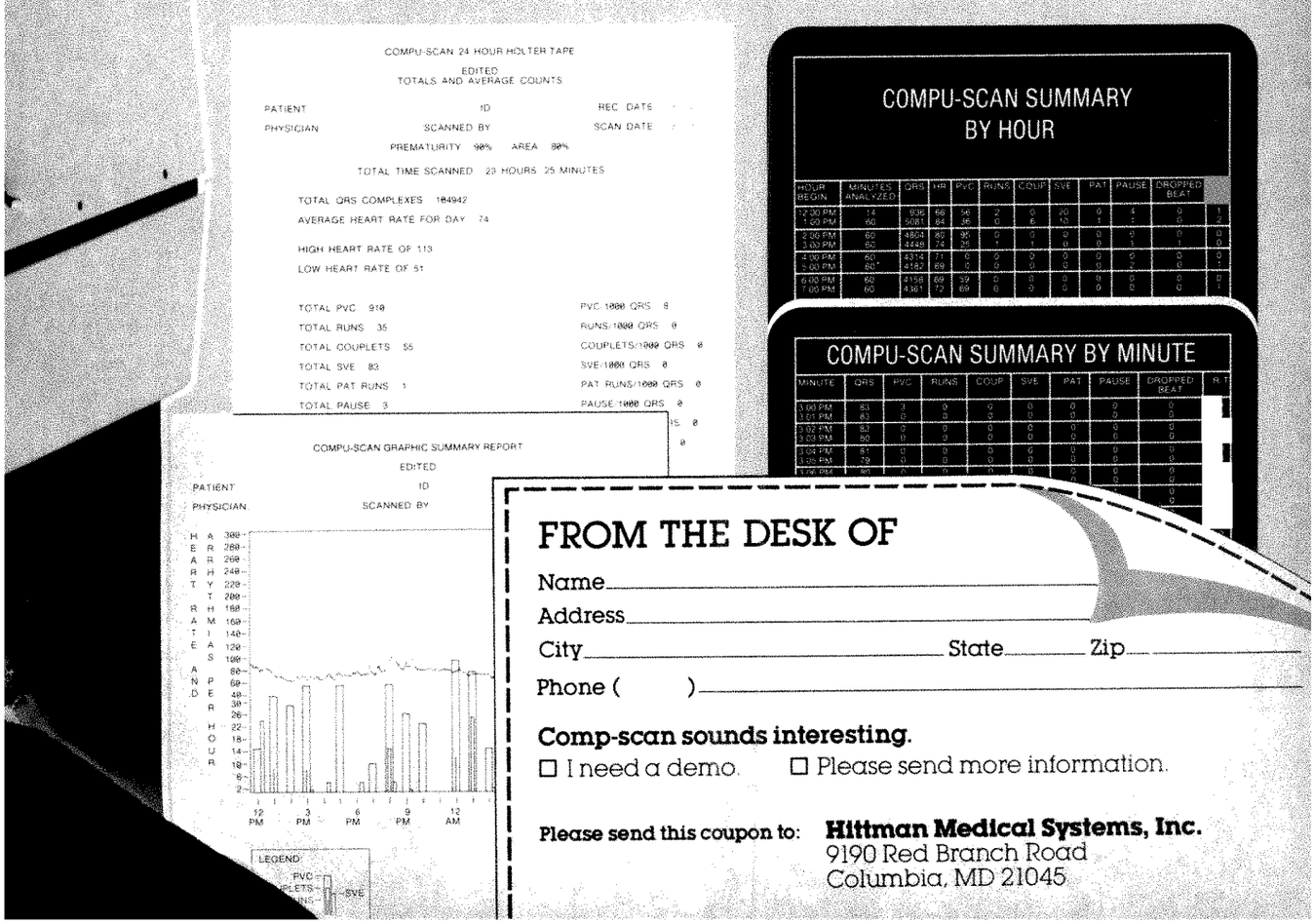
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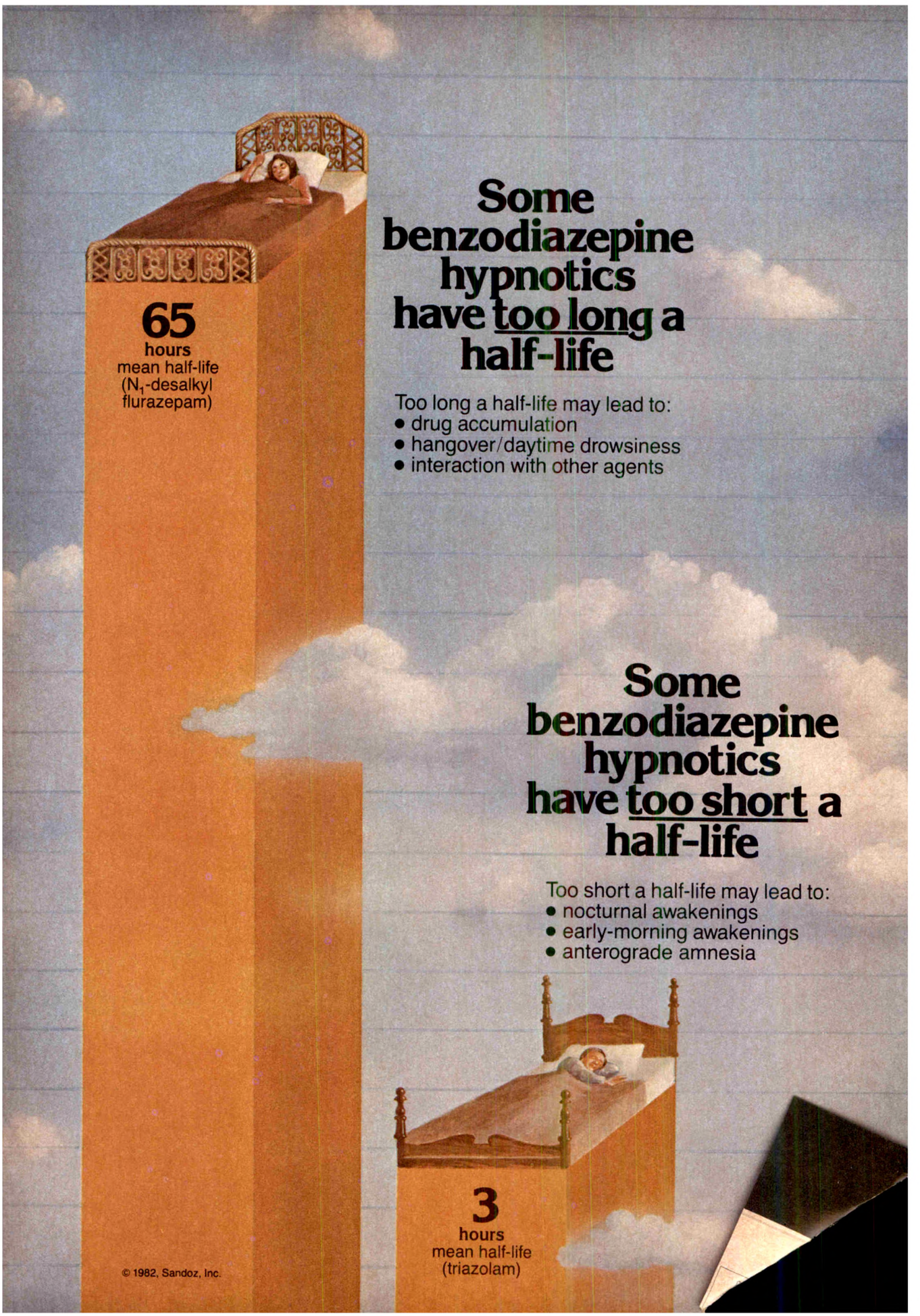
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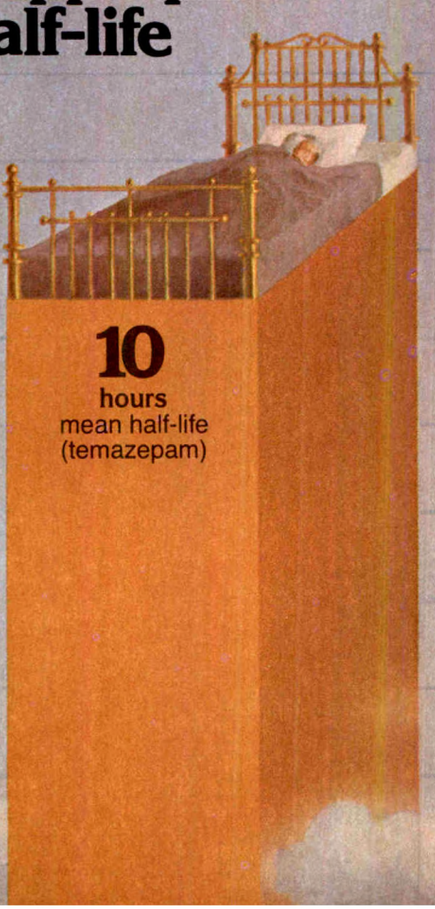

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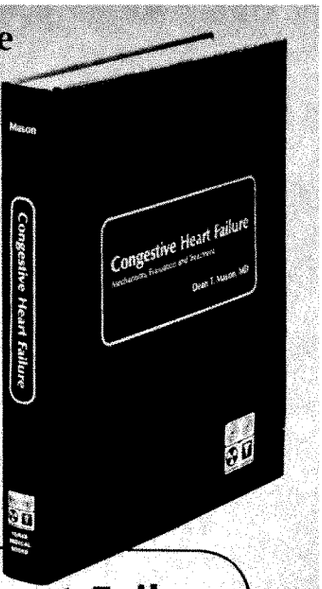
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### About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis.

President, American College of Cardiology; President, Western Society for Clinical Research.

Member of the American Board of Internal Medicine Cardiovascular Diseases.

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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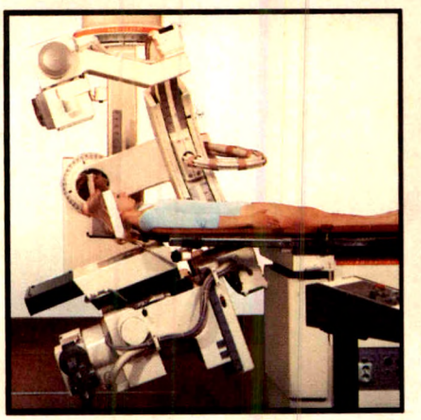
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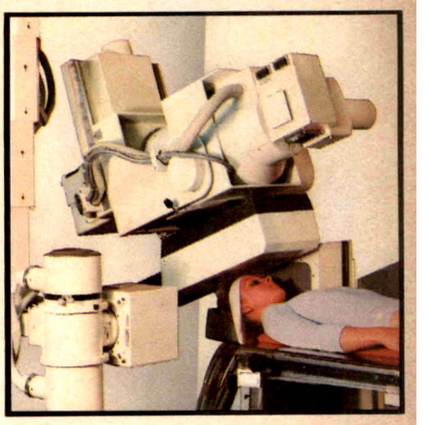
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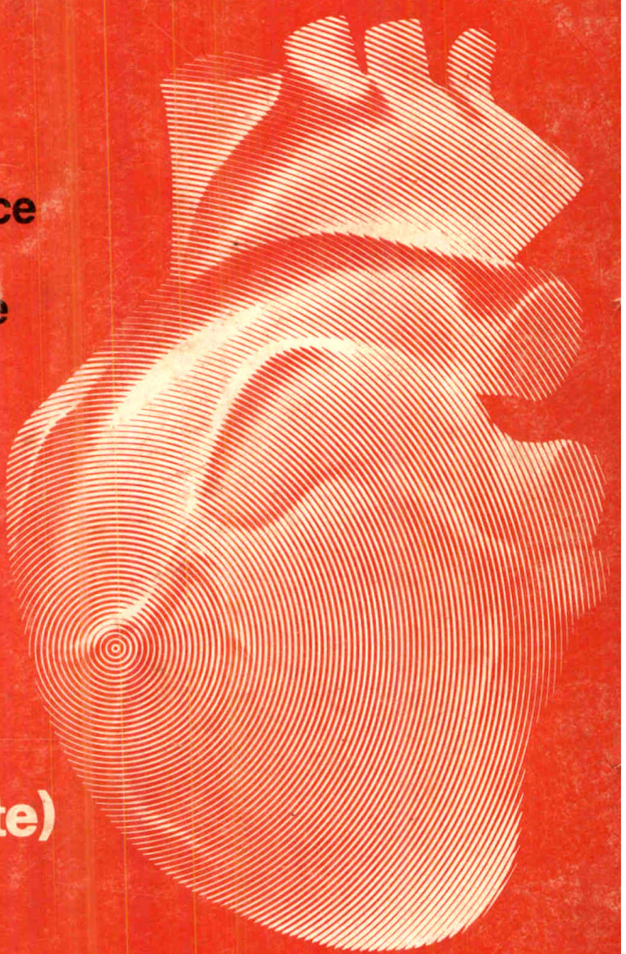
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| With tubocurare, succinylcholine and decamethonium | Potentiation of neuromuscular blockade. |
| With phenothiazines and reserpine | Additive cardiac depressive effects. |
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## Guest Editor: Norman M. Kaplan, MD


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## Proceedings of a Symposium:
## INITIAL THERAPY IN HYPERTENSION

**619 Introduction**
NORMAN M. KAPLAN

**621 New Approaches to the Therapy of Mild Hypertension**
NORMAN M. KAPLAN

Despite widespread acceptance of the diuretic-first, stepped-care approach to the treatment of hypertension, the extensive broadening of antihypertensive therapy to many millions more who are at relatively low risk from mild hypertension should bring about a reassessment of current practice. The use of other alternatives to a diuretic as initial therapy and the substitution of another single agent rather than the sequential addition of drugs should be given careful consideration in order to provide the most benefit at the least risk.

**628 Effect of Antihypertensive Agents on Lipid Metabolism**
RALPH CUTLER

Recent studies have shown that thiazides and chlorthalidone have an adverse effect on lipid metabolism by increasing plasma triglycerides, total cholesterol, and low density lipoprotein (LDL) cholesterol in mildly hypertensive patients. Loop diuretics also affected lipid metabolism adversely, but by lowering high density lipoprotein (HDL) cholesterol instead. Methyldopa has also been found to decrease HDL, while reserpine appears to be lipid neutral. Beta-adrenergic blocking agents generally increase triglycerides—with the exception of nadolol, which decreases them—or decrease HDL. Prazosin has no adverse effect on lipids.

**632 Negative Effects of Diuretic Drugs on Metabolic Risk Factors for Coronary Heart Disease: Possible Alternative Drug Therapies**
RICHARD P. AMES

Results of 8 major hypertension treatment trials, all using diuretic drugs as first-line drug therapy, indicate a uniform reduction in stroke and congestive heart failure (CHD) but no convincing benefit to CHD. The reason for this unexpected failure to control CHD is unclear, but metabolic studies indicate that other risk factors for CHD, including serum lipids and glucose intolerance, are negatively affected during therapy, to the point of offsetting the benefit from the lowering of blood pressure. A link between the disturbed glucose and lipid pathways is suggested by evidence that they are reversed proportionally after the discontinuance of diuretic-based therapy. Replacement of diuretic drugs as first-line therapy for mild and moderate hypertension may be appropriate.

**639 New Developments in Alpha-Adrenergic Receptor Pharmacology: Implications for the Initial Treatment of Hypertension**
WILSON S. COLUCCI

Recent advances in our understanding of alpha-adrenergic receptor subtypes has resulted in the development of alpha$_1$ selective antagonists which demonstrate important advantages over both non-subtype-selective alpha

blockers and non–receptor-blocking sympatholytic agents which globally disrupt sympathetic function. In contrast, alpha$_1$ selective blockade results in a nearly specific reduction in vascular tone, and hence blood pressure. Prazosin, the first of these agents to become clinically available, has proved of value in the treatment of patients with hypertension. In contrast to non–subtype-selective alpha-adrenergic antagonists and direct-acting vasodilators, prazosin's hypotensive action is accompanied by little or no increase in heart rate, plasma renin activity, or plasma norepinephrine level. Prazosin may be used alone or in combination with a diuretic to treat mild, moderate, or severe hypertension, and the antihypertensive effect is sustained during long-term therapy. The major side effect, postural hypotension after the first drug administration, is related to drug dose and intravascular volume depletion, and can be effectively prevented. Because of the adverse effects of diuretics and beta-adrenergic antagonists, as well as the growing evidence that these drugs adversely affect serum lipids, the role of alpha-adrenergic receptor blockade with prazosin as initial therapy of hypertension, particularly in young adults, should be seriously considered.

**644 Effectiveness of Prazosin as Initial Antihypertensive Therapy**

RONALD OKUN

In a substantial number of studies dating back to 1973 and earlier, prazosin has been shown to be an effective and well-tolerated agent when used as initial therapy in all degrees of hypertension. Prazosin lowers blood pressure by reducing total peripheral resistance, which is the underlying hemodynamic abnormality in most essential hypertension. It minimally affects heart rate, cardiac output, renal function, plasma renin activity, circulating catecholamines, and plasma electrolytes. It has no adverse effect on lipid, glucose, or uric acid metabolism. Its most potentially serious side effect, the so-called first-dose phenomenon, is rare; its occurrence can be further diminished and in many cases abolished by giving it as initial therapy before a diuretic, avoiding volume depletion, and giving a minimal initial dose at bedtime.

**651 Treating the Patient With Mild Hypertension and Renal Insufficiency**

J. CAULIE GUNNELLS, Jr.

Patients with impaired renal function are particularly susceptible to potential damage from hypertension even if mild. The aims of therapy in such patients are (1) protection of renal function and (2) prevention or delay of accelerated atherosclerosis. To this end, antihypertensive therapy is required that does not adversely affect the lipid profile and does not further impair renal function. Diuretic and beta-blocking drugs fail to meet these basic criteria fully. Central- and peripheral-acting drugs also fall short of achieving the therapeutic objective because of symptomatic side effects leading, in some patients, to poor compliance. The alpha$_1$-adrenergic blocking agent prazosin meets the 2 requirements and therefore may be particularly useful as initial therapy in these patients.

**657 Roundtable Discussion**

# Introduction

NORMAN M. KAPLAN, MD

Over the past 25 years since orally effective drugs have become available, we have witnessed a steady and significant increase both in the number of persons found to be hypertensive and in the proportion who are being treated. According to the most recent National Health Survey, more than half of all persons with hypertension in the United States had their condition diagnosed, treated, and controlled in the late 1970s, versus less than 1 of 8 in the early 1960s.

Despite this widespread attention over the last 25 years, the therapy of hypertension now seems to be in a state of uncertainty. The reasons for this uncertainty are multiple. First, as more and more patients with milder forms of hypertension are being identified, the evidence for the value of active drug therapy for these 30 million or more persons in the United States remains in question. Second, even less definitive information is known about the long-term adherence to and effectiveness from nondrug therapies. Although many believe that these therapies should be used, particularly in individuals with mild hypertension, their use in part must be based on faith—and the realization that they will do no harm. On the other hand, the potential for long-term harm from currently used drug therapies has surfaced, as they are given to more patients at relatively lower risk. This applies particularly to the widely used diuretic-first, stepped-care approach.

This Symposium was put together in order to examine these issues and to offer additional evidence in favor of alternative approaches to the treatment of hypertension in the future. The first report reviews the evidence that current approaches may not provide the maximal balance between benefits and risks.

Initiation of therapy with drugs other than diuretics is advocated in my review. Dr. Cutler reviews the now-extensive literature about disturbances in lipid metabolism which may be seen with a variety of antihypertensive agents, and then Dr. Ames takes particular aim at the negative effects of diuretics on risk factors for coronary heart disease.

As additional support for the rationale of alpha-receptor blockade for the initial therapy of hypertension, Dr. Colucci provides some new information about alpha-receptor pharmacology. Dr. Okun next examines the evidence concerning the appropriateness of prazosin as an alternative choice. Last, Dr. Gunnells considers the therapy of patients with varying degrees of renal insufficiency.

All in all, these reports should be a useful source of information about alternative approaches to the initial therapy of hypertension, an area of present uncertainty that may find new solutions in the near future.

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# New Approaches to the Therapy of Mild Hypertension

NORMAN M. KAPLAN, MD

**Concern about the initial use of diuretic agents under the stepped-care approach to the treatment of hypertension has been voiced before. Recently, however, the level of concern has risen as the results of various trials have questioned the safety of these agents in mild hypertension. Diuretic-induced hypokalemia has been reported in 10 to 30% of patients on long-term treatment. Recent studies show that hypokalemia may lead to previously unsuspected and potentially fatal arrhythmias, particularly after infarction. Increases in plasma cholesterol of 10 to 20 mg/dl may occur with diuretic therapy. Diuretics are also known to decrease glucose tolerance. Beta-adrenergic blocking drugs, although useful in many situations, are contraindicated in about 25% of the hypertensive population. These agents may also pose a long-term atherogenic risk because of their adverse effect on lipid and glucose metabolism.**

**If all these effects have the potential to increase the risk of coronary heart disease over the long term, then first-line administration of diuretic therapy and, to a lesser extent, beta-blocking therapy, to the 25 to 30 million Americans with diastolic pressure in the 90 to 100 mm Hg range must obviously be reassessed. Various alternative therapies, including withholding drugs for 6 months in patients with diastolic pressure of 90 to 100 mm Hg, using hygienic measures in patients not otherwise at high risk, and using other drugs such as the alpha$_1$-adrenergic inhibitor prazosin for initial therapy are discussed and evaluated.**

Recently, the stepwise addition of drugs, starting with a diuretic (Table I), has become the most widely used approach to the treatment of hypertension. The choice of a diuretic as the first drug has been advocated by expert clinicians, either as individuals or as members of committees, in the United States,[1] Canada,[2] England,[3] Sweden,[4] West Germany,[5] and Australia.[6] Every published large-scale clinical trial of the therapy of hypertension has used this approach.[7–11]

Objections have been raised to the uniform use of a diuretic as the first drug, mainly on the basis of the observed side effects and potential hazards of diuretics.[12] Laragh[13] was among the first to advocate the use initially of a beta-blocking drug in most patients, the choice to be based preferably on a renin profile. Some advocate a combination of a diuretic and a beta-blocking drug as ideal initial therapy,[14] whereas others suggest a beta-blocking agent for borderline and early hypertension and the combination of a thiazide-type diuretic and an adrenergic inhibitor, such as reserpine and guanethidine, for most with established essential hypertension.[15]

Currently, there are no large-scale, definitive data to document a substantial advantage in either efficacy or patient acceptance of any specific type of drug therapy. Two such trials are now underway, both comparing a diuretic with a beta-blocking drug, one involving 5,000 Swedish men,[16] the other 18,000 English patients.[17] It will likely be another 3 to 5 years before the results of these 2 trials are available.

In the meantime, the rationale for the use of a diuretic as the first and the combination of a diuretic and an adrenergic inhibitor as the second step in therapy needs reassessment. At least 2 other choices seem to be plausible: the first is the alternative of using a beta-blocking agent or another adrenergic inhibitor as the first drug; the second is the substitution of another single drug for the first one used if an inadequate response is obtained with the first, rather than the addition of the second drug to the first.

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**TABLE I Stepped-Care Regimens**

| Step | Drugs |
|---|---|
| 1 | Diuretic |
| 2 | Adrenergic inhibiting agents (in alphabetical order): |
| | Clonidine hydrochloride |
| | Methyldopa |
| | Metoprolol tartrate |
| | Nadolol |
| | Prazosin hydrochloride |
| | Propranolol hydrochloride |
| | Rauwolfia alkaloids |
| 3 | Vasodilator |
| | Hydralazine hydrochloride |
| 4 | Additional adrenergic inhibiting agent |
| | Guanethidine sulfate |

From the 1980 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1980;140:1280–1285. Copyright 1980 American Medical Association.

## Alternatives to a Diuretic First

The widespread use of diuretics as the first drug to treat hypertension arose empirically: they were effective, relatively well-accepted by patients, and capable of sustaining their antihypertensive action indefinitely. Other types of drugs (Table II) were tried as initial agents, but a tendency for fluid retention to blunt their effectiveness was recognized[18] and documented[19] (Table III). These increases in plasma volume were observed after only short-term use of the 4 drugs and presumably reflect a tendency by the kidneys of hypertensive patients to retain sodium and water whenever the blood pressure is decreased by nondiuretic agents (Fig. 1). This reactive fluid retention should not be looked upon as a side effect of these agents but rather as a "natural" counteraction to decreasing the blood pressure by kidneys that have their pressure-sodium excretion relation reset at a higher level. With vasodilators, an additional mechanism is involved, the activation of the renin-angiotensin system with secondary increases in aldosterone. Therefore, the use of a diuretic as initial therapy seemed logical: up to half the patients could be controlled on it alone, and if another drug were needed, the diuretic was usually required to obtain maximal effectiveness.

**TABLE II Antihypertensive Drugs Available in the United States**

| Volume Depleting Agents | Sympathetic Blocking Drugs | Vasodilators | Converting Enzyme Inhibitors |
|---|---|---|---|
| (Sodium restriction) | Peripheral | Hydralazine | Captopril |
| | Reserpine | Minoxidil | |
| Diuretics | Guanethidine | | |
| Thiazides and related drugs | | | |
| Chlorthalidone | Central | | |
| Metolazone | Methyldopa | Diazoxide | |
| | Clonidine | Nitroprusside | |
| Loop diuretics | Guanabenz | | |
| Furosemide | Beta-receptor | | |
| Potassium savers | Atenolol | | |
| Spironolactone | Metoprolol | | |
| Triamterene | Nadolol | | |
| Amiloride | Pindolol | | |
| | Propanolol | | |
| | Timolol | | |
| | Alpha-receptor | | |
| | Prazosin | | |

**TABLE III Hemodynamic Effects of Antihypertensive Drugs (Given for 7 Days While Patients Were Taking 110 mmol of Sodium per Day)**

| Drug (Approximate Dose) | Arterial Pressure (mm Hg) | | Plasma Volume (ml/kg) |
|---|---|---|---|
| Methyldopa | Before | 148 ± 7 | 38 ± 2 |
| (840 mg) | After | 118 ± 7 | 42 ± 2 |
| Guanethidine | Before | 143 ± 6 | 36 ± 4 |
| (30 mg) | After | 119 ± 5 | 44 ± 3 |
| Reserpine | Before | 149 ± 8 | 39 ± 2 |
| (1.4 mg) | After | 122 ± 5 | 43 ± 2 |
| Clonidine | Before | 156 ± 9 | 42 ± 3 |
| (0.5 mg) | After | 127 ± 9 | 48 ± 3 |

From Safar et al.[19]

At least 4 issues concerning the routine use of diuretics as the initial choice of therapy have arisen in the past few years. Two are related to doubts about the efficacy and safety of diuretics, one concerns the nature of the hypertensive patients being treated, and the fourth involves the availability of newer antihypertensive agents.

## Questions Concerning the Safety of Diuretic Agents

Numerous side effects are known to follow the continuous use of diuretics in the therapy of hypertension (Fig. 2). Some, such as postural hypotension, hyponatremia, and prerenal azotemia, are unusual or of little apparent consequence. Others, such as hyperuricemia and hypercalcemia, are common but seldom harmful. However, others may increase the risk of cardiovascular complications, reducing or blunting the protection provided by decreasing the blood pressure. These include hypokalemia, decreases in glucose tolerance, and increases in plasma cholesterol, a complication not shown in Figure 2 because its pathogenesis is not understood.

*Hypokalemia* appears in 10 to 30% of patients re-

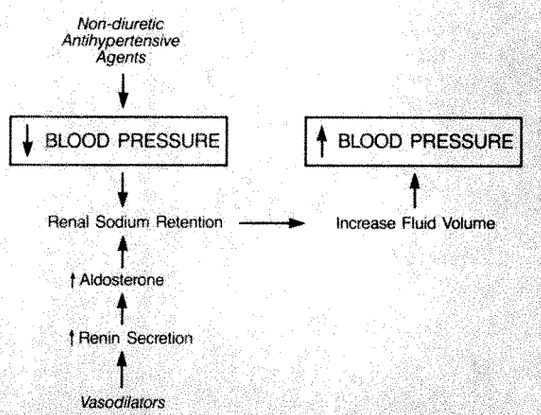



**FIGURE 1.** The manner by which nondiuretic antihypertensive agents may lose their effectiveness by renal sodium retention. (Reprinted, with permission, from Kaplan.[28])

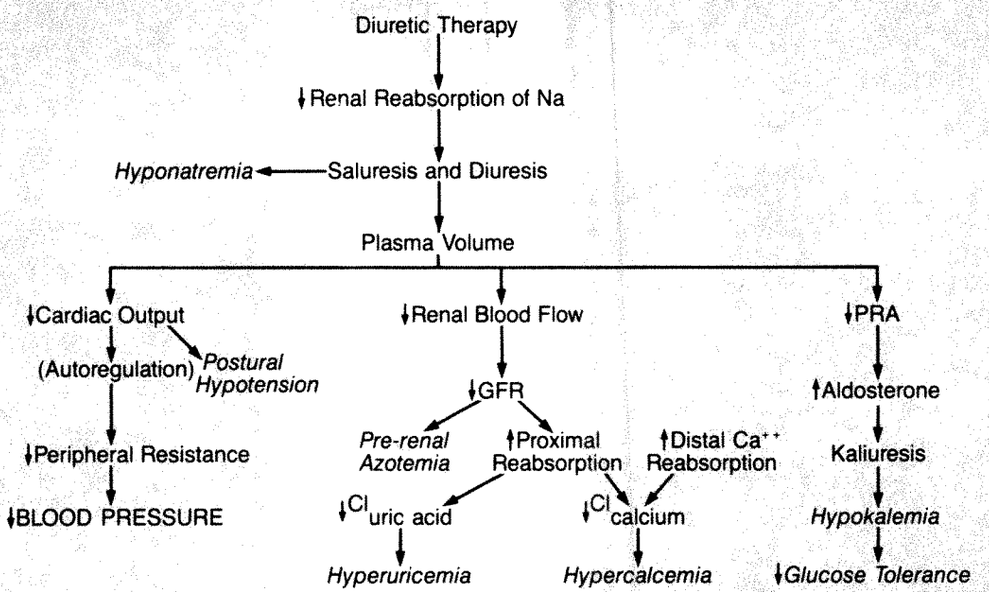



**FIGURE 2.** The mechanism by which chronic diuretic therapy may lead to various complications. (Reprinted, with permission, from Kaplan.[28])

ceiving long-term diuretic therapy[20] (Table IV). The 158 patients in this study were typical mildly hypertensive, middle-class, middle-aged English men and women who were on good diets and, therefore, likely representative of the majority of hypertensive subjects given diuretics.

The primary hazard of diuretic-induced hypokalemia is its tendency to increase myocardial irritability, inciting ventricular ectopic activity.[21] This change may become clinically apparent only when the myocardium experiences acute ischemia, as after acute myocardial infarction (Table V). The high frequency of ventricular fibrillation in hypokalemic patients is of concern because coronary artery disease is by far the most common cause of death among hypertensive individuals. The danger is known to be greater in those who are taking digitalis.

It may take acute stress such as acute myocardial infarction to expose this hazard from hypokalemia. With severe stress, plasma catecholamine levels increase to concentrations that have been shown to reduce plasma potassium levels by 0.5 to 0.6 mmol/liter[12] by accelerating the movement of potassium into cells. Moreover, catecholamines facilitate delayed postdepolarization[22] so that arrhythmias may arise during stress from both the direct effect of the catecholamines and the more intense hypokalemia in those already made susceptible by previous potassium losses.

**TABLE IV Effects on Plasma Potassium of Diuretic Agents in 158 Hypertensive English Patients**

| | Initial | 3 Months | 1 Year | 2 Years |
|---|---|---|---|---|
| Mean (mmol/liter) | 3.89 | 3.74 | 3.69 | 3.69 |
| % of patients 3.0–3.3 | 6 | 17 | 18 | 29 |
| % of patients 2.6–2.9 | 2 | 4 | 5 | 7 |

From Sandor et al.[20]

Thus, the usual diuretic-induced decrease in plasma potassium concentration of 0.6 mmol/liter[23] may be more hazardous than has been assumed. At least, these potential risks should serve to justify those steps that reduce diuretic wastage of potassium, namely, the use of the smallest effective dose of a diuretic, a reduced dietary sodium intake, and the concomitant use of potassium-sparing agents.

*Glucose intolerance* may accompany prolonged diuretic therapy. In the first 3 years of the Medical Research Council (MRC) trial, the incidence of impaired glucose tolerance was significantly higher in both men and women taking bendroflumethiazide than in those taking either a placebo or propranolol, but no differences in the mean random blood glucose levels were noted among the 3 groups.[17] The atherogenic potential of relatively small changes in glucose tolerance is unknown, but it poses another concern about the long-term safety of diuretic therapy.

In Figure 2, the decrease in glucose tolerance is shown to be caused by hypokalemia and there is some evidence

**TABLE V Ventricular Fibrillation (VF) After Acute Myocardial Infarction in Relation to Serum Potassium**

| Initial Serum Potassium | Patients (n) | Frequency of VF (%) per Population |
|---|---|---|
| ≤3.0 | 23 | 25 |
| 3.1–3.5 | 94 | 13 |
| 3.6–4.0 | 357 | 9 |
| 4.1–4.5 | 393 | 5 |
| 4.6–5.1 | 144 | 6 |
| ≥5.2 | 24 | 12 |

Data from Nordrehaug JD. Malignant arrhythmias in relation to serum potassium values in patients with an acute myocardial infarction. Acta Med Scand (Suppl) 1980;647:101–107.

for this causal connection.[24] Insulin resistance may also play a role because elevations in blood glucose have been closely correlated with higher plasma insulin levels.[25]

*Increases in plasma cholesterol* of 10 to 20 mg% frequently occur with diuretic therapy and are also correlated with higher plasma-insulin levels.[25] The atherogenic potential of a 20 mg/100 ml increase in plasma cholesterol can be shown by use of the Framingham data of the risks for coronary heart disease to completely reverse the reduction in risk provided by the 10 to 15 mm Hg decrease in systolic blood pressure that might be expected with chronic diuretic therapy.

## Questions Concerning the Efficacy of Diuretic Agents

All 3 of these biochemical aberrations may be responsible for increasing the cardiovascular risk. Separately or collectively they may be involved in the lesser protection from coronary artery disease that has been noted in most trials of therapy of hypertension, all of which used a diuretic as the first step in treatment. In all of these trials, antihypertensive therapy has been more effective in preventing strokes, congestive heart failure, aortic dissection, and progression of renal damage than in preventing coronary artery disease. In the Oslo study[10] *more* myocardial infarctions occurred in the treated patients. In both the Veterans Administration[7] and the Australian trials,[9] fewer fatal coronary events occurred in those given drug therapy, but the numbers were so small as not to reach statistical significance, whereas *more* nonfatal myocardial infarctions were noted in the treated patients, but did not reach statistical significance. Among those with mild hypertension in the Hypertension Detection and Follow-Up Program (HDFP) trial who were given more intensive therapy, that is, the stepped-care patients, there were 45% fewer deaths from myocardial infarction but 9% more deaths from "ischemic heart disease," giving an overall 20% decrease in deaths from coronary disease. Interpretation of the HDFP data is clouded by numerous problems, including the more intensive overall medical care provided stepped-care patients.[26]

The results of data on mortality from the massive Multiple Risk Factor Intervention Trial (MRFIT) cause further concern about the efficacy of treatment with the diuretic-first, stepped-care approach.[11] Almost 90% of the hypertensive men in the special intervention group were given antihypertensive drugs, 33% a diuretic drug alone, and 40% a diuretic plus an antiadrenergic drug (reserpine, methyldopa, or propranolol).[27] Among the less intensively treated patients, that is, the usual care half, fewer were given drug therapy and the mean decrease in diastolic blood pressure was 3.1 mm Hg less than that in the special intervention group. Among those who started with a diastolic pressure between 90 and 94 mm Hg, *more* coronary deaths occurred in the more intensively treated special intervention group, whereas those with a diastolic pressure >100 mm Hg were protected by more intensive therapy (Table VI). The same differential was noted in the Australian trial.[9]

**TABLE VI Multiple Risk Factor Intervention Trial: Mortality in Hypertensive Subjects Given Therapy**

| Initial Blood Pressure | Number | | CHD Deaths per 1,000 | | Total Deaths per 1,000 | |
|---|---|---|---|---|---|---|
| | SI | UC | SI | UC | SI | UC |
| 90–94 | 1,157 | 1,181 | 14.7 | 10.2 | 40.6 | 26.2 |
| 95–99 | 830 | 846 | 22.9 | 22.5 | 51.8 | 46.1 |
| ≥100 | 771 | 739 | 20.8 | 29.8 | 32.4 | 60.9 |
| Normal ECG | 2,785 | 2,808 | 15.8 | 20.7 | 35.9 | 43.4 |
| Abnormal ECG | 1,233 | 1,185 | 29.2 | 17.7 | 60.0 | 39.7 |

From Multiple Risk Factor Intervention Trial Research Group.[11]
CHD = coronary heart disease; ECG = electrocardiogram; SI = special intervention; UC = usual care.

Another disturbing set of figures from the MRFIT study is shown at the bottom of Table VI. Among all hypertensive subjects whose initial resting electrocardiogram was abnormal, those given more intensive therapy had significantly *more* coronary deaths. As of now, analyses relating coronary events to specific drugs and to specific laboratory data are not available, but the possibility that hypertensive subjects who start with an abnormal electrocardiogram would be even more susceptible to mischief from diuretic-induced hypokalemia must be considered.

Taken together, these data suggest that diuretics may provide less protection from the progression of coronary artery disease than their antihypertensive potency should offer. The antihypertensive potency of usual doses of a diuretic is comparable to that of moderate doses of a beta-blocking agent[4] or other adrenergic inhibitors.[28] Therefore, the biochemical aberrations that accompany the diuretic may detract from the protection they provide by reducing the blood pressure. Definitive evidence comparing the protection from coronary disease provided by diuretics versus beta-blocking agents will hopefully be forthcoming from the 2 ongoing European trials.[16,17]

## The Changing Hypertensive Population

The preceding litany of side effects and potential dangers from diuretics should not detract from their proven antihypertensive potency and the overall protection from cardiovascular diseases they provide in hypertensive subjects with diastolic pressure >100 mm Hg. However, we in the United States and likely practitioners everywhere are treating more and more patients with less elevated pressure, including many whose diastolic blood pressure is in the 90 to 100 mm Hg range. In the HDFP population, two thirds of all those with a diastolic pressure >90 mm Hg were in the 90 to 104 mm Hg range.[8] Such patients are at less risk from hypertension. Therefore, they can be provided less protection from a reduction in the blood pressure than can patients with higher pressures. As a result, any additional risk, no matter how small, from the therapy used to decrease the blood pressure must be weighed on a balance with correspondingly less counterweight. As an example, for

those with a level of blood pressure high enough to impose an additional 50% risk, the use of therapy that removes the excess risk while in itself adding a 10% risk can easily be defended as beneficial. However, for those with a lower level of blood pressure which in itself increases risk by only 10%, the use of such a therapy cannot be defended.

The treatment of mild asymptomatic hypertension is properly considered preventive medicine. The British epidemiologist Geoffrey Rose[29] emphasized the need for great caution in applying preventive measures to large groups of people: "If a preventive measure exposes many people to a small risk, then the harm it does may readily—as in the case of clofibrate—outweigh the benefits, since these are received by relatively few . . . . We may thus be unable to identify that small level of harm to individuals from long-term intervention that would be sufficient to make that line of prevention unprofitable or even harmful. Consequently we cannot accept long-term mass preventive medication."

If we accept the fact that there is some, albeit small, risk from the long-term use of diuretics, the administration of diuretic therapy to the 25 to 30 million Americans with diastolic pressure in the 90 to 100 mm Hg range must obviously be reconsidered. As I[30] and others[26,31] have suggested, the overall relative risk status of individual patients can be determined, using the Framingham data. Considering the potential risks and discomforts of drug therapy, a reasonable course might be to withhold drugs from those with diastolic pressure in the 90 to 100 mm Hg range who are otherwise at relatively low risk for at least 6 months while they are encouraged to follow nondrug therapy including weight reduction for the obese, moderate sodium restriction for all, and relaxation therapy for those who are willing. According to this view, only if the diastolic pressure remains >100 mm Hg is there a definite indication for drug therapy.

## Availability of Other Drugs

The fourth issue relates to the preceding 3: if diuretics pose various problems, are other drugs available that pose fewer problems and that therefore are alternative choices to the initial drug therapy of hypertension? One point alluded to before should be reiterated: there is little to distinguish the various available drugs listed in Table II as to antihypertensive efficacy in the majority of hypertensive subjects. Therefore, the choice of the initial drug should be based mainly on safety and side effects. Unfortunately, there are few controlled studies to document the differences among them. In the ongoing MRC trial, the percentage of patients who withdrew from treatment "owing to suspected adverse reactions" during the first 5 years totaled about 5% of those on placebo and about 15% of those on either bendroflumethiazide or propranolol.

Without firm data on which to base a decision, a review of the evidence on the major groups of currently available drugs is in order to come to some reasonable conclusions (Table VII).

*Beta-blocking drugs* are generally considered the most logical alternative, advocated most persistently by Laragh .[13] One major drawback of the use of nondiuretic antihypertensive drugs, their tendency to cause retention of sodium and water, which counteracts their effectiveness (Fig. 1), is less common with beta-blocking drugs. This decreased tendency to cause fluid retention is likely related to the greater inhibition of the renin-angiotensin-aldosterone system by beta-blocking drugs.[32] Patients whose renin system is "naturally" suppressed obtain a lesser antihypertensive effect from beta-blocking drugs.[13] A paradoxical increase in blood pressure was seen in 11% of 187 patients given propranolol alone, and these patients had the lowest levels of plasma renin activity.[32] However, in the majority of hypertensive subjects, less reactive fluid retention is likely to occur with administration of beta-blocking drugs than with other adrenergic inhibitors or vasodilators.

When the various side effects of beta-blocking drugs have been tallied, about 25% of hypertensive subjects should not receive them or will stop taking them. As monotherapy, they likely work less well in the elderly[33] and in blacks,[34] groups that generally start with lower renin levels, and groups in which the incidence of hypertension is relatively high.

Two disadvantages listed in Table VII deserve further comment. One, the increase in plasma triglycerides and the decrease in plasma HDL-cholesterol, although less marked with the more cardioselective agents,[35] may present as much of a long-range stimulus to atherogenesis as the increase in total cholesterol that accompanies diuretic therapy. The second disadvantage, the increase in peripheral resistance[36] related to blockade of vasodilatory peripheral vascular beta-receptors, is clinically a bother in colder climates where cold extremities are frequently observed, but also poses a more theoretic objection. Increased peripheral resistance is the underlying hemodynamic fault of hypertension. Drugs that lower peripheral resistance as they lower the blood pressure, such as diuretic agents, prazosin, and vasodilators, have an advantage over beta-blocking drugs because they relieve the underlying fault, whereas beta-blocking drugs increase the resistance further. Careful, controlled, long-term comparisons of these various agents are necessary to determine the clinical consequences of the mode of action of various agents.

One very important, but still unproved, advantage of beta-blocking drugs is their potential to prevent coronary events. Such prevention was amply shown in secondary trials involving patients who survived recent myocardial infarction.[37] However, primary prevention in patients with hypertension, who obviously are quite different from survivors of recent myocardial infarction, has not been shown. Hopefully, the 2 trials using beta-blocking drugs[16,17] will provide such evidence.

*Reserpine*, the first of the orally effective antihypertensive drugs to be widely used, has steadily lost ground in the face of unfounded accusations about its carcinogenicity and in the absence of any strong endorsement. It was the first of the second-step drugs in most clinical trials and apparently was somewhat mo

**TABLE VII Characteristics of Nondiuretic Antihypertensive Drugs**

| Drug | Advantages | Disadvantages |
|---|---|---|
| Beta-blocking agents | Lack of sedation, dry mouth<br>One a day<br>Relief from anxiety-related symptoms<br>Less volume retention<br>Possible protection from coronary heart disease | Serious side effects<br>Bronchospasm<br>Prolongation of insulin-induced hypoglycemia<br>Other side effects<br>Peripheral vasoconstriction<br>Reduced exercise tolerance<br>Fatigue, depression<br>Increased triglycerides<br>Decreased HDL-cholesterol<br>Increase in peripheral resistance<br>Less effect in elderly and blacks |
| Reserpine | Once a day | Serious side effects<br>Depression<br>Other side effects<br>Sedation<br>Nasal stuffiness |
| Methyldopa | . . . | Serious side effects<br>Hepatotoxicity<br>Other "autoimmune" reactions<br>Other side effects<br>Sedation, mental slowness<br>Impotence |
| Clonidine | . . . | Serious side effects<br>More frequent rebound if abruptly stopped<br>Other side effects<br>Sedation<br>Dry mouth |
| Prazosin | Lack of sedation, dry mouth<br>Decrease in peripheral resistance<br>No alterations in plasma lipids<br>No reduction in cardiac output<br>Low incidence of impotence<br>Kidney perfusion is maintained | First-dose hypotension (occurs rarely and is associated with patients who have been taking a diuretic drug)<br>Lassitude, headache, drowsiness |

effective than methyldopa or propranolol in the MRFIT study.[27] Regardless, it seems unable to compete with the newer drugs.

*Methyldopa* was by far the most widely used antihypertensive drug after diuretics, before the advent of beta-blocking drugs. Many practitioners continue to prefer it to all others, but much of that preference likely reflects the tenacity of prescribing habits. For those who are not bothered by sedation or mental dullness, the long-term safety of the drug remains reassuring despite the occasional development of serious "autoimmune" reactions.

*Clonidine* does everything that methyldopa does without the autoimmune reactions. Because of its shorter duration of action, its abrupt discontinuation may more frequently be followed by a rebound of the blood pressure or withdrawal symptoms, but those may occur when most antihypertensive drugs are abruptly stopped.[38]

*Prazosin* is an attractive alternative choice for initial therapy of hypertension. As a postsynaptic alpha$_1$-receptor blocking agent, prazosin acts as a vasodilator, relaxing the vascular smooth muscle. Because the alpha$_2$-receptors on the neuronal surface are not blocked, further release of norepinephrine is inhibited and neither tachycardia nor renin release occurs as with the use of direct-acting vasodilators. Furthermore, prazosin does not act on the heart, so cardiac output is not reduced and normal organ perfusion is well maintained. In specific studies, glomerular filtration rate and renal blood flow were maintained in patients on prazosin.[18,19]

Beyond the favorable hemodynamic effect, that is, a decrease in peripheral resistance, prazosin does not induce the other side effects related to beta-blockade, particularly alterations in plasma lipids.[39] However, administration of the first doses of prazosin may cause postural hypotension. Because this complication occurs mainly when the drug is given to patients who are volume-depleted from previous diuretic therapy,[40] it should be less common if the drug is used as initial treatment in hypertension.

*Guanabenz*, recently approved for use in the United States, was introduced as a centrally acting alpha-agonist similar to clonidine, with evidence that it causes no fluid retention,[41] so that it could be an appropriate drug to be used without a diuretic. However, the side effects of the drug may limit its use.

*Other drugs* not now available in the United States may serve as safe and effective alternatives when and if they are released. These include labetolol, which is a less likely candidate for initial therapy in most cases of mild hypertension because it causes rather frequent postural hypotension.[42]

## Substitution Therapy

Beyond the use of a drug other than a diuretic as initial therapy, the other major change that should be considered is the substitution of another agent as sole

therapy when the first is inadequate or intolerable. The "traditional" stepped-care concept is based on the sequential addition of drugs until the goal of therapy is achieved.

One rationale for substitution therapy is that some patients respond better to 1 class than to another. Despite the earlier generalization that all drugs have comparable antihypertensive potency, some patients respond differently to different drugs. As noted, the elderly and blacks seem to respond less well to beta-blocking agents. The reverse may also be true: young, white patients may respond better to beta-blocking drugs than to diuretics.[34] Without having ways to predetermine the likelihood of a good response, the clinician may logically try a different type of drug when the first is inadequate.

Part of this difference in response may be caused by differences in adherence to therapy with different drugs. If a patient develops such intolerable side effects as to require the discontinuance of the drug, the problem is usually obvious and a second agent can routinely be substituted. However, patients may not volunteer or admit problems with their drugs; rather, they may just not take them. For whatever reason, when a patient does not have the desired effect from the initial drug, a logical next step might be to stop the drug and try one from another category. Thereby, the patient may be more successfully treated with fewer medications.

**Conclusion:** Despite widespread acceptance of the diuretic-first, stepped-care approach, extensive broadening of antihypertensive therapy to many millions more who are at relatively low overall risk from mild hypertension should bring about a reassessment of current practice. The use of other alternatives to a diuretic as initial therapy and the substitution of another single agent rather than the sequential addition of drugs should be given careful consideration in order to provide the most benefit at the least risk.

## References


1. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The 1980 Report. Arch Intern Med 1980;140: 1280–1285.
2. **Sackett DL.** The hypertensive patient. 4. Stepped-care therapy. Can Med Assoc J 1979;121:145–148.
3. Editorial. Diuretic or beta-adrenergic blocker. Lancet 1981;1:763.
4. **Berglund G, Andersson O.** Beta-blockers or diuretics in hypertension? A six-year follow-up of blood pressure and metabolic side effects. Lancet 1981;1:744–747.
5. **Stumpe KO, Overlack A.** Diuretics, beta-blockers or both as treatment for essential hypertension. Br J Clin Pharmacol 1979;7:Suppl 2:189S–197S.
6. **Whitworth JA, Kincaid-Smith P.** Diuretics or beta-blockers first for hypertension? Drugs 1982;23:394–402.
7. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. JAMA 1967; 202:1028–1034.
8. Hypertension Detection and Follow-Up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program. JAMA 1979;242:2562–2571.
9. Management Committee. The Australian therapeutic trial in mild hypertension. Lancet 1980;1:1261–1269.
10. **Helgeland A.** Treatment of mild hypertension: a five-year controlled drug trial. Am J Med 1980;69:725–732.
11. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial. JAMA 1982;248:1465–1477.
12. **Dollery CT.** Does it matter how blood pressure is reduced? Clin Sci 1981;61:413s–420s.
13. **Laragh JH.** Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. Am J Med 1973; 55:261–274.
14. **Finnerty FA Jr.** Diuretics as initial treatment for essential hypertension. Br J Clin Pharmacol 1979;7:Suppl 2:185S–187S.
15. **Messerli FH.** Individualization of antihypertensive therapy: an approach based on hemodynamics and age. J Clin Pharmacol 1981;21:517–528.
16. **Wilhelmsen L, Berglund G, Elmfeldt D, Wedel H.** Beta-blockers versus saluretics in hypertension. Prev Med 1981;10:38–49.
17. Medical Research Council Working Party. Adverse reactions to bendroflumethiazide and propranolol for the treatment of mild hypertension. Lancet 1981;2:539–542.
18. **Finnerty FA Jr, Davidov M, Mroczek WJ, Gravrolovich L.** Influence of extracellular fluid volume on response to antihypertensive drugs. Circ Res 1970;26:Suppl 1:71–80.
19. **Safar ME, Weiss YA, Corvol PL, Menard JE, London GM, Milliez PL.** Antihypertensive adrenergic-blocking agents: effects on sodium balance, the renin-angiotensin system and haemodynamics. Clin Sci Mol Med 1975; 48:93s–95s.
20. **Sandor FF, Pickens PT, Crallan J.** Variations of plasma potassium concentrations during long-term treatment of hypertension with diuretics without potassium supplements. Br Med J 1982;284:711–715.
21. **Holland OB, Nixon JV, Kuhnert LV.** Diuretic-induced ventricular ectopic activity. Am J Med 1981;70:762–768.
22. **Cranefield PF.** Action potentials, afterpotentials, and arrhythmias. Circ Res 1977;41:415–423.
23. **Morgan DB, Davidson C.** Hypokalemia and diuretics: an analysis of publications. Br Med J 1980;280:905–908.
24. **Amery A, Bulpitt C, de Schaepdryver A, Fagard R, Hellemans J, Muteis A, Berthaux P, Deruyttere M, Dollery C, Forette F, Fund-Johansen P, Tuomileheto D.** Glucose intolerance during diuretic therapy: results of trial by the European Working Party on hypertension in the elderly. Lancet 1978;1:681–683.
25. **Ames RP, Hill P.** Improvement of glucose tolerance and lowering of glycohemoglobin and serum lipid concentrations after discontinuation of antihypertensive drug therapy. Circulation 1982;65:899–904.
26. **Freis ED.** Sounding board: Should mild hypertension be treated? N Engl J Med 1982;307:306–309.
27. **Cohen JD, Grimm RH Jr, Smith WM.** Multiple risk factor intervention trial. Prev Med 1981;10:501–518.
28. **Kaplan NM.** Clinical hypertension. 3rd ed. Baltimore: Williams & Wilkins, 1982:124.
29. **Rose G.** Strategy of prevention: lessons for cardiovascular disease. Br Med J 1981;282:1847–1851.
30. **Kaplan NM.** Whom to treat: the dilemma of mild hypertension. Am Heart J 1981;101:867–870.
31. **Alderman MH, Madhavan S.** Management of the hypertensive patient: a continuing dilemma. Hypertension 1981;3:192–197.
32. **Drayer JIM, Keim HJ, Weber MA, Case DB, Laragh JH.** Unexpected pressor responses to propranolol in essential hypertension. Am J Med 1976;60: 897–903.
33. **Bühler FR, Burkart F, Lutold BE, Kung M, Marbet G, Pfisterer M.** Antihypertensive beta blocking action as related to renin and age; a pharmacologic tool to identify pathogenic mechanisms in essential hypertension. Am J Cardiol 1975;36:653–669.
34. VA Cooperative Study Group. Comparison of propranolol and hydrochlorothiazide for the initial therapy of hypertension. I. Results of short-term titration with emphasis on racial differences in response. JAMA 1982; 248:1996–2003.
35. **Day JL, Metcalfe J, Simpson CN.** Adrenergic mechanisms in control of plasma lipid concentrations. Br Med J 1982;284:1145–1148.
36. **Lund-Johansen P.** Hemodynamic consequences of long-term beta-blocker therapy: a 5-year follow-up study of atenolol. J Cardiovasc Pharmacol 1979;1:487–495.
37. **Hampton JR.** Should every survivor of a heart attack be given a beta-blocker? Br Med J 1982;285:33–36.
38. **Houston MC.** Abrupt cessation of treatment in hypertension: consideration of clinical features, mechanisms, prevention and management of the discontinuation syndrome. Am Heart J 1981;102:415–430.
39. **Leren P, Helgeland A, Holme I, Foss PO, Hjermann I, Lund-Larsen PG.** Effect of propranolol and prazosin on blood lipids. The Oslo Study. Lancet 1980;2:4–6.
40. **Stokes GS, Graham RM, Gain JM, Davis PR.** Influence of dosage and dietary sodium on the first-dose effects of prazosin. Br Med J 1977;1:1507–1508.
41. **Walker BR, Hare LE, Deitch MW, Gold JA.** Comparative effects of guanabenz alone and in combination with hydrochlorothiazide as initial antihypertensive therapy. Curr Ther Res 1982;31:764–775.
42. **Brogden RN, Heel RC, Speight TM, Avery GS.** Labetolol: a review of its pharmacology and therapeutic use in hypertension. Drugs 1978;15: 251–270.

# Effect of Antihypertensive Agents on Lipid Metabolism

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**Diuretics and adrenergic blocking agents have been used extensively in the treatment of hypertension. Recent studies have indicated that the thiazides and chlorthalidone have an adverse effect on lipid metabolism, by increasing plasma triglycerides, total cholesterol, and low density lipoprotein cholesterol in mildly hypertensive patients. These same agents produced little change in high density lipoprotein cholesterol. On the other hand, the loop diuretic furosemide adversely affected the cholesterol ratio by lowering high density lipoproteins (HDL) instead of increasing very low density lipoproteins (VLDL) or low density lipoproteins (LDL). The centrally acting drug methyldopa has also been reported to lower HDL, while another centrally acting drug, reserpine, appears to be lipid-neutral. Practically all the beta blocking agents increase triglycerides or decrease HDL, thus yielding an adverse cholesterol ratio. The alpha$_1$-adrenergic blocking agent prazosin has been shown in several studies to have no adverse effect on the lipid profile.**

Among major risk factors for coronary heart disease (CHD), hypertension is perhaps the most readily treatable, either by hygienic measures or, when these are not enough, by drug therapy. Although not the soundest therapeutic practice, the use of diuretic agents has eliminated the need for sodium restriction in many mild, asymptomatic patients who were not willing to limit their dietary salt intake. On the other hand, cessation of smoking and lowering of high blood lipids, the other 2 major CHD risk factors, usually demand greater sacrifices in life-style. Nevertheless, Americans as a whole have achieved considerable changes in this regard, as shown by their lowered consumption of cigarettes, eggs, butter, cream, and other items potentially detrimental to their health.

In the past decade or two, antihypertensive agents have been increasingly used as first-line drugs in controlling moderate to severe hypertension. Lately, the use of these agents has been recommended also for the treatment of the mildest forms of hypertension, with a view to avoiding the complications that may develop later on in the course of the disease. Yet a number of large intervention trials have failed to show any substantial benefit of blood pressure-lowering on CHD mortality. In fact, according to the recent Multiple Risk Factor Intervention Trial (MRFIT), CHD mortality did not decrease after stepped-care treatment of hypertension, counseling for cigarette smoking and dietary advice for lowering blood cholesterol levels as compared with a similar population who received only their usual sources of health care in the community. This is in marked contrast to the significant improvements in stroke, heart failure, and renal failure that have been reported as a result of controlling high blood pressure.

The lack of impact of blood pressure-lowering on CHD mortality has raised the question of whether the antihypertensive agents commonly used may be offsetting the potential benefits of such a reduction. The effects of these agents on hemodynamics and metabolism have been cited as probable causes. Some antihypertensive agents may impair perfusion and function of certain organs by reducing cardiac output; others by creating hyperdynamic states which may be detrimental to the patient; and still others by increasing peripheral resistance instead of lowering it. Furthermore, some agents are known to cause potentially hazardous potassium depletion, increase serum levels of lipids, glucose, and uric acid, or increase plasma renin activity. Taken singly, some of these effects may not pose a significant risk, but together they add up to what could be a serious threat to the hypertensive patient.

## A Brief Look at Lipid Metabolism

Dietary lipids are absorbed through the small intestine and reach the blood mainly in the form of chylomicrons. Other lipid fractions are synthesized within the liver and gut from primitive metabolites such as acetate. High density lipoproteins (HDL) and very low density

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**TABLE I Correlation of HDL, LDL, and Blood Pressure With Risk of CHD in 4 Years**

| | Years | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Mortality risk ratio | 0.5 | 1.0 | 2.0 | 3.0 |
| LDL/HDL ratio* | 1.0 | 3.6 | 6.3 | 8.0 |
| Total cholesterol/HDL cholesterol* | 3.4 | 5.0 | 9.6 | 23.4 |

From Gordon et al.[3]
* Both the LDL/HDL ratio and the total cholesterol/HDL ratio are expressed here so that an increase in either is detrimental while a decrease would be favorable. Other investigators have used the reverse ratios (HDL/LDL and HDL/total cholesterol) so that an increased ratio would be favorable and a decreased ratio detrimental.

lipoproteins (VLDL) are both synthesized in the liver. LDL and triglycerides result from the splitting of VLDL by an enzyme. LDL is the lipoprotein which carries most of the serum cholesterol. Borne by the bloodstream, the cholesterol-rich LDL fraction from the liver apparently enters the coronary artery wall and deposits its cholesterol load in the intima, where it may initiate or perpetuate the process of atherosclerotic plaque formation. The HDL fraction, also carried by the blood stream, reaches the arterial wall, where it seems to play a protective role against the formation or progression of atherosclerosis by removing the cholesterol deposited by LDL and returning it to the liver for further metabolism and excretion through the hepatobiliary system.

Levy,[1] after many years of gathering data about lipid profiles from major clinical centers throughout the United States, reported a definite correlation between increased serum LDL cholesterol concentrations and the prevalence of CHD, whether manifested as angina pectoris, myocardial infarction, or simply as angiographic evidence of coronary vessel disease. Miller et al[2] were among the first to note an inverse correlation between HDL cholesterol and CHD prevalence. Data generated from the Framingham study[3] showed that the cholesterol ratio (total cholesterol to HDL cholesterol) was higher among men and women with clinical evidence of CHD than among those at standard risk. Total cholesterol is made up of VLDL, LDL, and HDL. Increases in both the ratio of total cholesterol to HDL and the ratio of LDL to HDL were found to be associated with an increased risk of mortality (Table I).

## Effect of Antihypertensive Drugs on Lipids

Several studies have examined the effects of diuretics and adrenergic inhibitors commonly used in the treatment of hypertension on the cholesterol ratio and on the various lipoproteins.

**Diuretic agents:** Grimm et al[4] recently showed that hydrochlorothiazide and chlorthalidone increase plasma triglycerides, and total cholesterol in mildly hypertensive patients, and that this effect can be countered or modulated by a diet low in saturated fats and high in polyunsaturated fats (Table II). Chlorthalidone increased LDL cholesterol also. These particular agents produced very little change in HDL cholesterol levels. However, various types of diuretics appear to differ significantly in this respect. In a study comparing the lipid effects of chlorthalidone, hydrochlorothiazide, and furosemide, Ames and Hill[5] showed that furosemide had no significant effect on the lipid profile by lowering HDL rather than by increasing LDL or VLDL (Table III). The ratio of total cholesterol to HDL cholesterol was significantly elevated in the furosemide group, and this effect occurred at comparatively lower antihypertensive doses of this drug than of the other 2 agents.

**Adrenergic inhibitors:** The second major group of drugs used in the treatment of hypertension are the adrenergic inhibiting or blocking agents. This class of drugs is made up of agents that act centrally—methyldopa and clonidine—and agents that act peripherally—guanethidine, reserpine, alpha blockers, and beta blockers. Beta-blocking agents, it should be noted, also may have some central action that has not been clearly defined.

*Reserpine and methyldopa:* In the study cited earlier, Ames and Hill[5] also compared the lipid effects of reserpine and methyldopa and showed variable changes (Table IV). The ratio of total cholesterol to HDL cholesterol was increased by both agents,* but the increase reached statistical significance only in the group treated with methyldopa. While HDL cholesterol levels were decreased by both drugs, only methyldopa produced a

* It should be noted that under the definition of the cholesterol ratio used here, an increase in the ratio would be detrimental and a decrease beneficial. Other investigators use a different definition of the cholesterol ratio (HDL/LDL + VLDL), and in such a case an increased ratio would be beneficial and a decreased ratio detrimental.

**TABLE II Effects of Hydrochlorothiazide, Chlorthalidone, and Chlorthalidone Plus Diet on the Lipid Profile of 60 Men With WHO Class 1 Hypertension Treated for 6 Weeks (Changes in Serum Lipids Are in mg/dl)**

| | Placebo | Hydrochlorothiazide | Chlorthalidone | Chlorthalidone + Diet |
|---|---|---|---|---|
| Plasma triglycerides | −7 | +28* | +23* | +18* |
| Plasma cholesterol | +2 | +15* | +19* | + 3 |
| VLDL cholesterol | −4 | + 4* | + 2* | + 3* |
| LDL cholesterol | +2 | + 9 | +14* | − 2 |
| HDL cholesterol | +3 | + 3 | + 2 | + 2 |

From Grimm et al.[4]
* $p < 0.05$.

**TABLE III Effects of Three Classes of Diuretics on Lipid Metabolism After 12 Months of Treatment (Changes in Serum Lipids Are in mg/dl)**

| | Chlor-thalidone | Hydrochloro-thiazide | Furo-semide |
|---|---|---|---|
| Triglycerides | +36* | +39 | +22 |
| Cholesterol | +15* | +12* | +1 |
| HDL cholesterol | +1 | −1 | −10 |
| Total cholesterol/HDL cholesterol | +0.1 | +0.2 | +0.6* |
| Diastolic blood pressure (mm Hg) | −13* | −7* | −1 |

From Ames and Hill.[5]
* $p < 0.05$.

**TABLE IV Effect of Sympatholytics on Lipid Metabolism After 12 Months of Treatment (Changes in Serum Lipids Are in mg/dl)**

| | Reserpine | Methyldopa |
|---|---|---|
| Triglycerides | −9 | +1 |
| Cholesterol | +1 | −5 |
| HDL cholesterol | −4 | −7* |
| Total cholesterol/HDL cholesterol | +0.8 | +0.9* |
| Diastolic blood pressure (mm Hg) | −12* | −9* |

From Ames and Hill.[5]
* $p < 0.05$.

statistically significant change. However, the lipid effects of these 2 agents await further confirmation because this was a very small study.

*Alpha and beta blocking agents:* There are many differences among the beta-blocking agents. Not only are they variously selective with respect to their beta-receptor activity—some affect the heart more specifically, while others have a general effect on receptors over the whole body—but they may also possess intrinsic sympathomimetic activity (alprenolol, oxprenolol, and pindolol), or lack this property (propranolol, nadolol, metoprolol, and timolol). Such differences may account for the divergent findings reported by various investigators concerning the lipid effects of these agents.

The one consistent finding is that all beta-blocking agents appear to produce remarkable increases in triglyceride levels—with the exception of nadolol, which causes a dramatic decrease—and a decrease in HDL cholesterol with the exception of pindolol (Table V). However, triglycerides are believed to have a much less significant correlation with atherogenesis than the other lipids and lipoproteins. Few data are available about the effects of beta-blocking agents on HDL, LDL, and VLDL cholesterol values. Studies that have examined these lipid fractions report quite variable results, and these may be explainable on the basis of differences in the population studies, lipid assays used, and the type, dosage, and duration of drugs given. All beta blockers appear to lower HDL cholesterol, except possibly pindolol.

Using a three-way crossover design, the Oslo Study[6] compared the commonly used beta-blocking agent, propranolol, with the only available selective $alpha_1$-blocking agent, prazosin, in the same group of patients to determine the effects of these drugs on serum lipids and on blood pressure when administered singly or in combination. The effects on blood pressure were comparable when the drugs were used as monotherapy, but lower pressures were achieved under combined therapy, and this may be attributable to the additive effects of the different blocking mechanisms of these 2 agents. Prazosin had no adverse effect on blood lipids. On the other hand, propranolol alone resulted in a reduction in HDL, an increase in triglycerides, and a reduction in the ratio of HDL to LDL + VLDL.

The results of this study appear to indicate that prazosin does not adversely affect the lipid profile.

## Clinical Implications

For many years diuretic agents have constituted the standard initial drug therapy for hypertension. Numerous short- and long-acting diuretic agents became available to the physician, and very few were associated with obvious clinical problems, except for hypokalemia, hyperglycemia, and hyperuricemia, all of which were considered either inconsequential or readily correctable. Because of the effectiveness of diuretics and the ease of treatment with these agents, many clinicians today still use them as first-step therapy for hypertensive patients. However, in view of recent findings with regard to metabolic effects, including newer hazards caused by hypokalemia, and the adverse effects of these drugs on the cholesterol ratio, we must ask ourselves whether the same results could not be obtained from other drugs without incurring the risks posed by the diuretics.[7]

As for the adrenergic inhibitors, the lipid effects of propranolol and some of the other beta-blocking agents also seem to be pointing in the same adverse direction. Beta-blocking agents, in addition, are contraindicated for various reasons in a sizable percentage (20 to 25%) of the hypertensive population. Furthermore, they may adversely affect renal function (especially propranolol), and all beta blockers reduce cardiac output and may increase peripheral resistance. Beta-blocking agents have a number of less serious but bothersome effects, such as fatigue, depression, and hallucinations, which may impinge on the quality of life.

As for some of the other adrenergic blockers, the centrally acting agents (methyldopa, clonidine) not only affect lipid metabolism, but also have other side effects such as dry mouth, depression, and impotence, which make them less than ideal from the standpoint of patient compliance.

Side effects of prazosin are mild and transient. The major one is postural hypotension (dizziness, weakness, and so on), which is most pronounced after initial administration and then declines markedly during long-term therapy. Rarely is discontinuation of the drug necessary.

Hydralazine and minoxidil also have serious side effects, mainly the production of a hyperdynamic circulation and tachycardia in patients with a normal baroreceptor reflex, and the triggering of angina or myocardial infarction in predisposed patients. These drugs usually require the concomitant use of a beta-blocking

**TABLE V Effects of Beta-Blocking Agents (Other Than Propranolol) Over Various Periods of Treatment**

| Drug (Dose, mg/day) | Duration (mo) | TC (mg/dl) | TG (mg/dl) | LDL-C (mg/dl) | VLDL-C (mg/dl) | HDL-C (mg/dl) |
|---|---|---|---|---|---|---|
| Atenolol (100–200) | 6 | +1.5 | +24.5 | – | – | – |
| Atenolol (100) | 3 | 0 | 0 | – | – | −10 |
| Nadolol (50–200) | 2.5 | +1.5 | −14.5 | −2 | +29 | −3 |
| Metoprolol (50–400) | 3 | – | +9 | – | – | −13 |
| Metoprolol (100–200) | 4 | −6.5 | +11 | −7 | −6 | −6 |
| Pindolol (10–20) | 6 | −4.0 | +1 | – | – | +4 |

TC = total cholesterol; TG = triglycerides; LDL-C = low density lipoprotein cholesterol; VLDL-C = very low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol.

agent, which to some extent redresses their adverse effects. But while the addition of a beta-blocking agent reduces the elevated heart rate, it does not entirely correct the hyperdynamic condition, since neither the beta blocker nor hydralazine nor minoxidil affects the venous side of the circulation. Therefore, vasoconstriction prevails in the capacitance vessels, venous return remains high, and the high cardiac output is only partly reduced, if at all.

## Discussion

Given the many new antihypertensive agents introduced in recent years, the 1980s seem to be the decade in which it is not only possible but appropriate to move away from a standardized approach toward a more individualized therapy to meet specific treatment objectives. Certainly, in young patients with hypertension who may be facing a lifelong prospect of drug therapy, consideration of the lipid profile and other side effects of conventional agents becomes quite important. If the physician continues to be inclined to give diuretics, today's evidence strongly suggests that he should monitor lipid levels. If the lipid profile does not change after a few weeks of therapy, it is probably safe to continue treatment, at least from the standpoint of lipids.

On the other hand, if the patient's cholesterol ratio is abnormal to begin with, another type of antihypertensive agent that does not adversely affect lipids should certainly be tried. Other considerations regarding the use of diuretics, including hypokalemia, hyperglycemia, and hyperuricemia, should be kept in mind in specific patients, and this may require frequent monitoring of serum potassium, glucose, and uric acid levels.

**Conclusion:** In looking for other possible initial therapies, prazosin appears to offer a very attractive alternative. Prazosin effectively lowers blood pressure by reducing total peripheral resistance; it does not significantly affect heart rate or cardiac output; it has no adverse effect on lipids, glucose, uric acid, or renin; it does not adversely affect renal function; and it rarely produces sexual disturbances. Its main adverse reaction—postural hypotension, which may on rare occasions lead to syncope—can frequently be avoided by careful administration of the first dose, as has been pointed out by other participants. Other side effects are generally mild and transient, and the drug is usually well accepted by the patients.

## References


1. **Levy RI.** Cholesterol, lipoproteins, apoprotein and heart disease: present status and future prospects. Clin Chem 1981;27:653–662.
2. **Miller NE, Forde OH, Thelle DS, Mjøs OD.** The Tromso Heart Study. High density lipoprotein and coronary heart disease: a prospective case-controlled study. Lancet 1977;1:965–968.
3. **Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR.** High density lipoprotein as a protective factor against coronary heart disease: The Framingham Study. Am J Med 1977;62:707–714.
4. **Grimm RH Jr, Leon AS, Hunninghake DB, Lenz K, Hannan P, Blackburn H.** Effects of thiazide diuretics on plasma lipids and lipoproteins in mildly hypertensive patients: a double-blind controlled trial. Ann Intern Med 1981;94:7–11.
5. **Ames RP, Hill P.** Antihypertensive therapy and the risk of coronary heart disease. J Cardiovasc Pharmacol 1982;4:Suppl 2:S206–S212.
6. **Leren P, Helgeland A, Holme I, Foss PO, Hjermann I, Lund-Larsen PG.** Effect of propranolol and prazosin on blood lipids. The Oslo Study. Lancet 1980; 2:4–6.
7. **Lowenstein J, Neusy A-J.** The biochemical effects of antihypertensive agents and the impact on atherosclerosis. J Cardiovasc Pharmacol 1982;4:Suppl 2:S262–S264.

# Negative Effects of Diuretic Drugs on Metabolic Risk Factors for Coronary Heart Disease: Possible Alternative Drug Therapies

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**The results of 8 major hypertension treatment trials, all using diuretics as first-line therapy, show a clear-cut reduction in stroke and congestive heart failure, but coronary heart disease (CHD) is not consistently benefited. It is unclear why CHD is not controlled, but diuretics can subtly upset metabolic risk factors for CHD, among which are lipid and glucose concentrations. Although these metabolic disturbances appear clinically unimpressive, risk table analysis reveals that they can offset or even reverse the benefits of reducing blood pressure. A link between glucose intolerance and increased serum lipid concentrations during diuretic-based therapy is suggested by multiple correlations between them. Replacement of diuretics as first-line therapy for mild and moderate hypertension should therefore be considered. Spironolactone seems to counter the adverse metabolic effects, but its effect on lipoproteins needs more study. A drug that does not disturb glucose and lipid metabolism would seem preferable. Thus prazosin is a promising candidate.**

The many hypertension treatment trials performed worldwide have conclusively demonstrated that control of hypertension reduces the incidence of stroke and congestive heart failure.[1–5] One might also expect a reduction in coronary heart disease (CHD) because hypertension is one of the major risk factors for CHD, according to epidemiologic studies.[6,7] However, this expectation of improvement has not been borne out.[5,8] Because CHD is responsible for the largest number of deaths among patients with cardiovascular disease, its lack of response in hypertension to conventional therapy based mainly on diuretic drugs constitutes a major problem in cardiovascular care. To date, efforts to solve this problem have been largely unsuccessful. However, potentially useful alternative approaches should be considered, particularly as a result of the data recently published from the Multiple Risk Factor Intervention Trial (MRFIT).[8]

MRFIT presents perhaps the strongest case against the proposition that drug treatment of hypertension—at least in its mildest forms—protects against CHD. Moreover, some of the results of this trial lead to the hypothesis to be put forth here: The breakdown in the link between treatment of hypertension and improvement in CHD may be due to metabolic disturbances induced by conventional diuretic therapy. Diuretic drugs, although highly effective in reducing blood pressure, have a detrimental effect on other risk factors for CHD, thereby offsetting the positive influence of hypertension control.

Commissioned by the National Heart, Lung, and Blood Institute (NHLBI) specifically to ascertain whether reduction in severity of risk factors would result in a lowering of coronary death rates, this massive MRFIT study was performed over a 7-year period by 250 investigators in 22 institutions and involved nearly 13,000 high-risk men aged 35 to 57 years who had no clinical evidence of CHD at entry.[8] The highly surprising results that were obtained may have been due in part to the fact that the study design did not include a placebo control group. Instead, subjects were classified into special intervention (SI) and usual care (UC) groups for test and control, respectively.

The SI group received intensive sessions in smoking cessation, cholesterol-lowering by dietary changes and weight control, and treatment of hypertension. Hypertension was treated when diastolic blood pressure was >89 mm Hg on 3 consecutive clinic visits. Treatment started with an attempt at weight reduction if indicated, followed by thiazide-type diuretic drugs given according to the well-known stepped care sequence. The

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**TABLE I Hypertension Trials and CHD Mortality**

| Trial | Cases (n) | Duration (yr) | CHD Mortality |
|---|---|---|---|
| Freis—VA (1967) | 143 | 1.5 | P-1, T-0 |
| Freis—VA (1970) | 380 | 3 | P-11, T-6 |
| Smith—PHS (1977) | 389 | 7 | P-2, T-2 |
| Morgan (1978) | 192 | 1–5 | U-1, T-9 |
| HDFP (1979) | 10,940 | 5 | RC-69, SC-51 |
| Oslo (1980) | 785 | 5 | U-2, T-6 |
| Australia (1980) | 3,427 | 4 | P-8, T-2 |
| MRFIT (1982) | 8,011* | 6 | UC-79, SI-80 |

* The MRFIT study included a total of 12,866 and the average follow-up lasted 7 years. The results shown here represent the 8,011 participants who had hypertension. The 4,855 men who did not have hypertension are not considered in this report because the focus of this discussion is on hypertension.

HDFP = Hypertension Detection and Follow-Up Program; MRFIT = Multiple Risk Factor Intervention Trial; P = placebo group; PHS = Public Health Service; RC = referred care group; SC = stepped care group; SI = special intervention; T = treatment group; U = untreated group; UC = usual care group; VA = Veterans Administration.

goal of treatment was to lower diastolic pressure by 10 mm Hg or below 85 mm Hg, whichever was lower. Diuretic dosage was increased to 100 mg/day, if tolerated, before a second drug was added. Reserpine and methyldopa were the preferred second step drugs. Later in the trial, propranolol became available, but it was used in fewer than half of the hypertensive patients.

UC men were referred with the MRFIT risk factor report to their personal physicians for advice. The UC men were examined annually by the MRFIT staff, and a report of the findings was always sent to the personal physicians.

A relatively high mortality was predicted in the UC group because of the high CHD risk status and a belief a decade ago that community physicians were slighting risk factors. This situation would allow the UC group to serve as a control group without denying them standard care. However, this expectation proved wrong. Instead, there was a startling equivalence in the number of deaths from CHD for both groups: 124 in the UC group and 115 in the SI group. Among the 8,000 patients with hypertension (4,000 in each group), which is the focus of our interest in this discussion, there was also an equivalence of CHD deaths: 79 in the UC group and 80 in the SI group. The overall mortality was substantially lower than anticipated in the UC group, thus diminishing the statistical power of the comparison.

Notwithstanding flaws in the design, 2 valuable pieces of information can be gleaned from this study. First, considerable treatment for hypertension was administered to both groups, although the SI group did receive somewhat more. Smoking and cholesterol levels were reduced for both groups, again a little more in the SI group. Thus, risk factors were improved in *both* groups, and overall death rates from CHD were reduced in both groups compared with predictions based on Framingham results. This finding supports the concept that risk factors are important in the causation of CHD and that control of these factors does indeed reduce the incidence of CHD.

The second important point to be brought out in this trial is that the 2 groups showed equivalent mortality rates, even though vigorous drug treatment dropped blood pressure lower in the (stepped care) SC group. This result suggests that intensifying treatment of hypertension with the traditional mode of diuretic therapy produces no extra protection against CHD.

In view of the foregoing observations and the known metabolic side effects of diuretic drugs, the question arose whether it is the diuretic therapy itself that might be causing detrimental changes in other risk factors for CHD aside from hypertension.

## Comparison of Results From Various Trials

Table I compares the results of MRFIT with those from other studies utilizing diuretic drugs as first-line treatment.

There is only 1 study that reports findings in direct opposition to those obtained in MRFIT. This study, the Hypertension Detection and Follow-Up Program (HDFP), was also sponsored by the NHLBI.[10,11] In 14 communities scattered throughout the United States, 10,940 subjects with high blood pressure were randomly assigned to either SC or referred care (RC [control]) groups. At the end of the 5-year period, control of blood pressure was consistently better for the SC than for the RC group. Furthermore, mortality from all causes was 17% lower in the SC group relative to the RC group (6.4 versus 7.7%, $p < 0.01$). Overall, there were 69 deaths from myocardial infarction in the RC group and 51 in the SC group. On the face of it, these findings suggest that management of hypertension is important for reducing mortality in the population with high blood pressure. However, there was no placebo control group in this trial, and placebo control is generally the most reliable paradigm for a study of this nature. The double blind placebo control study design is important because it obligates the investigators to treat all patients similarly, thereby equalizing all aspects of medical care other than the drug regimen. Referring control patients to other physicians causes unequal medical surveillance between control and experimental groups. Because the experimental group received free, enthusiastic, and close supervision, illness may have been detected early and converted from a fatal to a nonfatal outcome (formally published results to date report only mortality data). Thus, it is not clear, because of the several differences in management between control and experimental groups, that the small difference in blood pressure control between groups accounts for the lower coronary mortality. This point must be emphasized because none of the placebo controlled clinical trials using diuretics as first-line therapy reported improvement in CHD with treatment.[1,2,4,12]

A second cautionary note about HDFP results is that mortality from a category termed "other ischemic heart disease" was equal in the step-care and referred care groups, that is, 80 and 79 cases, respectively. Therefore, the total number of deaths from myocardial infarction plus other ischemic heart disease would be 131 and 148 for the step care and referred care groups, respectively. This represents a difference in CHD mortality between groups of 11.6%. Thus, even in HDFP the improvement in CHD mortality may not be as great as publicized.

**TABLE II Effects of Chlorthalidone on Serum Lipids (n = 17)**

| | Control | Treatment | p |
|---|---|---|---|
| Total cholesterol (mg/dl) | 217 | 237 | 0.01 |
| Triglycerides (mg/dl) | 96 | 114 | 0.01 |
| HDL cholesterol (mg/dl) | 53 | 50 | NS |
| Total cholesterol/ HDL cholesterol ratio | 4.3 | 4.7 | 0.05 |
| Drug dose (mg/day) | ... | 80 | ... |
| Duration (mo) | ... | 4 | ... |

NS = not significant.

**TABLE III Changes in Serum Lipid Concentrations (± Standard Error of the Mean) After Cessation of Diuretic-Based Antihypertensive Therapy**

| Serum Lipids | During Therapy | After Cessation of Therapy |
|---|---|---|
| Total cholesterol (mg/dl) | 235 ± 8 | 217 ± 6* |
| Triglycerides (mg/dl) | 127 ± 11 | 100 ± 8* |
| HDL cholesterol (mg/dl) | 48 ± 2 | 49 ± 2 |
| Total cholesterol/HDL cholesterol ratio | 5.1 ± 0.3 | 4.5 ± 0.2* |

* $p < 0.01$.

There is 1 other study with results that might be construed as somewhat supportive of the HDFP findings: the Australian national trial, reported on in 1980.[4] This was a controlled therapeutic treatment trial involving 3,427 men and women with mild hypertension who were followed up for an average of 4 years. The number of deaths from CHD was small in this study but amounted to 8 in the control group and 2 in the treatment group. This difference fell just short of the usual $p < 0.05$ level of significance.

The mortality data in the Australian study are in harmony with the HDFP findings, but the total number of CHD events, i.e., both fatal and nonfatal coronary disease, was not significantly different between groups. There were 109 coronary events in the placebo group and 98 in the treatment group. As suggested previously,[13] a possible explanation for this discrepancy is that coronary disease was not actually prevented by treatment, but rather that potentially fatal events were rendered nonfatal by the pharmacologic lowering of cardiac afterload. Thus, the more favorable hemodynamic status of the treatment group may explain the reduced number of deaths, while CHD was not reduced overall.

In opposition to the findings of the HDFP and the Australian national trial are the results obtained in the 1978 Morgan study, which was also derived from the Australian population.[14] This was a small study involving 192 elderly men with mild hypertension observed over a variable period of 1 to 5 years. In the untreated and the sodium-restricted groups combined, 1 death occurred from myocardial infarction whereas in the group given a thiazide diuretic as initial therapy 9 deaths were observed. CHD deaths were significantly higher in the thiazide group.

Thus, a large disparity exists between the results reported in the HDFP and Australian national studies, and those obtained in the Morgan study. Four other major trials that utilized diuretic drugs as first-line therapy reported outcomes somewhere between these extremes.

The most interesting of these trials was the Oslo Study.[5] In this study, designed to evaluate the effect of therapy on cardiovascular complications, 785 patients treatment (406) and nontreatment (379) groups and were followed up for 5 years. Treatment consisted of hydrochlorothiazide as initial drug and methyldopa or propranolol as second step therapy. Although no difference between groups was seen in total mortality or cardiovascular mortality, the number of CHD deaths was higher in the treatment group (Table I). In analyzing total cardiovascular events, i.e., fatal and nonfatal endpoints, the expected reduction in cerebrovascular episodes was offset by an increase in CHD events (13 in control, 20 in treated patients). While not statistically significant, this difference certainly constitutes an unfavorable trend, and one that was not anticipated at the outset of the study.[5]

As did MRFIT and the Australian national trial, the 3 remaining major hypertension studies that should be mentioned showed essentially no difference in the incidence of CHD between their treatment and control groups. The first of these was the Veterans Administration trial, directed by Freis, which was published in 1967.[1] In comparison with later studies, this was a small trial involving only 143 patients with severe hypertension. Over a period of 18 months, 1 sudden death and 2 nonfatal heart attacks were reported in the placebo-treated group and none in the treatment group, a statistically insignificant result.

This study was followed by a second Veterans Administration trial in 1970, in which 380 patients with mild or moderate hypertension were observed for an average of 3 years.[2] On analysis, 3 fatal myocardial infarctions and 8 sudden deaths occurred in the placebo group; in the drug-treated group 2 fatal myocardial infarctions and 4 sudden deaths were observed. The difference between groups again was insignificant.

The third study, performed in 1977 by Smith from the Public Health Service (PHS) Group,[12] included approximately 400 patients with mild hypertension, who were followed up for a relatively long period of time. The average follow-up was 7 years, with some patients being observed for 9 years. Despite this long follow-up, only 2 CHD deaths were reported in the placebo group and 2 in the drug-treated group. Examination of the total number of myocardial infarctions, both fatal and nonfatal, revealed 6 occurrences in the control group and 7 in the treatment group—essentially no difference at all.

Summing up the results of these 8 major trials, all of which employed diuretic drugs as first-line therapy, only 1 study (HDFP) supported the premise that the incidence of CHD could be lowered by treatment of hypertension.[9,10] The Morgan Study and the Oslo Study actually showed a worsening of CHD with antihyper-

**TABLE VI Probability of CHD in 6 Years During Diuretic-Based Therapy and After Therapy Was Stopped***

| | During Therapy | After Cessation of Therapy |
|---|---|---|
| Cholesterol (mg/dl) | 235 | 217 |
| Systolic blood pressure (mm Hg) | 133 | 151 |
| Glucose intolerance | Yes | No |
| Probability | 8.8% | 7.6% |

* Probability table for a 55-year-old man was used.[15] This table was closest to the average age of our patients.

know to what extent the changes could offset the beneficial effect of decreasing blood pressure on CHD risk in patients with hypertension. We used the coronary probability table developed from the Framingham study[15] and employed data from the patients studied during and after cessation of therapy.[9] Table VI shows that the probability of CHD was actually somewhat increased during therapy with diuretic drugs.

Although this analysis seems to overstate the case, it does provide a clue as to why it has proved so difficult to reduce the incidence of CHD with conventional diuretic therapy: Risk factors other than hypertension are negatively influenced and may therefore neutralize or even eliminate the benefits of reducing blood pressure.

## Possible Alternatives

Beta-blocking drugs have been suggested as first-line therapy for hypertension because of their antirenin and cardioprotective effects.[24,25] Indeed, an uncontrolled study in which beta blockers served as initial therapy for hypertension reported a reduction in CHD.[26] However, the cardioprotective effect has been demonstrated in relatively short-term studies.[25,27,28] A long-term study of oxyprenolol showed an increased incidence of CHD in some groups of patients.[29] Several beta blockers have an adverse influence on serum lipids and lipoproteins, an effect most evident in long-term study.[30–32] Thus, it is possible that an early benefit resulting from improved electrical stability might become reversed as the adverse lipid alteration exerts its slowly developing effect.

To determine whether potassium-sparing diuretic drugs might have a role in this context, we studied 23 hypertensive patients exhibiting raised total cholesterol during treatment with chlorthalidone. As shown in Table VII, when spironolactone was substituted for chlorthalidone in randomized fashion, total cholesterol decreased. When these patients resumed taking chlorthalidone, total cholesterol increased again. In contrast, a control group that continued taking chlorthalidone throughout the same interval of time showed no noteworthy change in total cholesterol. Whereas this information is promising, data are needed on lipoprotein fractions. Further study of potassium-sparing diuretic drugs used alone and in combination with thiazide agents seems warranted.

Several short-term studies indicate that prazosin, an alpha$_1$-adrenergic blocking agent, has no adverse effects on serum lipids and lipoproteins.[32–38] If long-term trials clearly prove its sustained antihypertensive efficacy and lack of adverse lipid effects, prazosin could well become the drug of choice in the initial treatment of mild and moderate hypertension. However, considering the widespread acceptance and applicability of diuretic therapy,[31] a clinical trial may be needed to test a diuretic-based regimen (of proved efficacy against stroke and congestive heart failure) against an alternative regimen (of presumed efficacy against CHD based on lipid effects but unproved in the prevention of stroke and congestive heart failure). Before even considering such a trial, the best alternative regimen would need to be identified. Drug selection would rest on the net effect on CHD probability (estimated from risk tables[15] or coefficients[16]) based on long-term changes in blood pressure, glucose tolerance, lipids and lipoproteins.

**TABLE VII Serum Cholesterol and Triglyceride Levels During Randomized Substitution of Spironolactone for Chlorthalidone: Comparison With Patients Continuing on Chlorthalidone**

| Group | Total Cholesterol (mg/dl) | Triglycerides (mg/dl) |
|---|---|---|
| Spironolactone group (n = 11) | | |
| Initial chlorthalidone period | 261 | 210 |
| Spironolactone period | 237* | 152 |
| Final chlorthalidone period | 254 | 150 |
| Chlorthalidone group (n = 12) | | |
| Initial chlorthalidone period | 265 | 167 |
| Middle chlorthalidone period | 263 | 155 |
| Final chlorthalidone period | 252 | 150 |

* $p < 0.05$ versus the initial and final chlorthalidone periods for this group. Also $p < 0.05$ versus the middle period in the chlorthalidone group. Cholesterol did not differ between groups in the initial and final chlorthalidone periods.

**Conclusions:** Diuretic-based antihypertensive therapy has been shown to cause an increase in total cholesterol and triglycerides. It can also lead to glucose intolerance and insulin resistance, in addition to other adverse effects reported earlier on potassium, chlorides, uric acid, and renin levels. The fact that lipid alterations correlate with glucose intolerance suggests there is a link between these pathways or that a common mechanism may be involved. This may prove to be the reason that diuretic therapy did not reduce mortality greatly in the MRFIT study and other major CHD studies.

Quantitatively, the changes in coronary risk factors, including glucose, lipids, and systolic blood pressure, during diuretic-based antihypertensive therapy may even increase the probability of developing CHD.

Prazosin, an agent that does not have an adverse effect on lipids, glucose, potassium, uric acid or renin, may be a preferable choice for initial therapy in hypertension. It is effective alone or it can be added for enhanced effectiveness. It needs to be tested against diuretic drugs in a long-term study to document its superiority, using the results of all risk factor changes during therapy as the index of relative merit.

## References


1. Veterans Administration Cooperative Study Group on Antihypertensive Agents: effects of treatment on morbidity in hypertension: I. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA 1967;202:1028–1034.
2. Veterans Administration Cooperative Study Group on Antihypertensive Agents: effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressures averaging 90 through 114 mm Hg. JAMA 1970;213:1143–1152.
3. **Beevers Dg, Fairman MJ, Hamilton M, et al.** Antihypertensive treatment and the course of established cerebral vascular disease. Lancet 1973;1: 1407–1409.
4. Report by the management committee. The Australian therapeutic trial in mild hypertension. Lancet 1980;1:1261–1267.
5. **Helgeland A.** Treatment of mild hypertension. A five-year controlled drug trial. The Oslo Study. Am J Med 1980;69:725–732.
6. **Gordon T, Kannel WB.** Premature mortality from coronary heart disease. The Framingham Study. JAMA 1971;215:1617–1625.
7. **Rosenman RH, Brand RJ, Sholtz RI, Friedman M.** Multivariate prediction of coronary heart disease during 8.5 year follow-up in the Western Collaborative Group Study. Am J Cardiol 1976;37:903–910.
8. Multiple Risk Factor Intervention Trial Research Group: Multiple Risk Factor Intervention Trial. JAMA 1982;248:1465–1477.
9. **Ames RP, Hill P.** Improvement of glucose tolerance and lowering of glycohemoglobin and serum lipid concentrations after discontinuation of antihypertensive drug therapy. Circulation 1982;65:899–904.
10. Hypertension Detection and Follow-Up Program Cooperative Group: Five-Year Findings of the Hypertension Detection and Follow-Up Program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 1979;242:2562–2571.
11. Hypertension Detection and Follow-Up Program Cooperative Group: Five-Year Findings of the Hypertension Detection and Follow-Up Program. II. Mortality by race, sex and age. JAMA 1979;242:2572–2577.
12. **Smith WM.** Treatment of mild hypertension. Results of a ten-year intervention trial. Circ Res 1977;(Suppl 1) 40:98–105.
13. **Freis ED.** Should mild hypertension be treated? N Engl J Med 1982;307: 306–309.
14. **Morgan TO, Adams WR, Hodgson M, Gibbend RW.** Failure of therapy to improve prognosis in elderly males with hypertension. Med J Aust 1980; 2:27–31.
15. **Insull W Jr.** Coronary Risk Handbook: Estimating Risk of Coronary Heart Disease in Daily Practice. New York: Am Heart Association, 1973.
16. **Kannel WB, Castelli WP, Gordon T.** Cholesterol in the prediction of atherosclerotic disease. Ann Intern Med 1979;90:85–91.
17. **Wolff FW, Parmley WW.** Further observations concerning the hyperglycemic activity of benzothiadiazines. Diabetes 1964;13:115–121.
18. **Carliner NH, Schelling JL, Russell RP, Okun R, Davis M.** Thiazide and phthalimidine-induced hyperglycemia in hypertensive patients. JAMA 1965;191:535–540.
19. **Andersen OO, Persson I.** Carbohydrate metabolism during treatment with chlorthalidone and ethacrynic acid. Br Med J 1968;2:798–801.
20. **Fajans SS, Floyd JC Jr, Knopf RF, Rull J, Guntsche EM, Conn JW.** Benzothiadiazine suppression of insulin release from normal and abnormal islet tissue in man. J Clin Invest 1966;45:481–492.
21. **Gabbay KH, Hasty K, Breslow JL, Ellison RC, Bunn HF, Gallop PM.** Glycosylated hemoglobins and long-term blood glucose control in diabetes mellitus. J Clin Endocrinol Metab 1977;44:859–864.
22. **McFarland KF, Catalano EW, Day JF, Thorpe SR, Baynes JW.** Nonenzymatic glucosylation of serum proteins in diabetes mellitus. Diabetes 1979;28:1011–1014.
23. **Schnider SL, Kohn RR.** Glucosylation of human collagen in aging and diabetes mellitus. J Clin Invest 1980;66:1179–1181.
24. **Bühler FR, Laragh JH, Baer L, Vaughan ED Jr, Brunner HR.** Propranolol inhibition of renin secretion. A specific approach to diagnosis and treatment of renin-dependent hypertensive diseases. N Engl J Med 1972;287: 1209–1214.
25. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801–807.
26. **Bergiund G, Sannerstedt R, Andersson O, Wedel H, Wilhelmsen L, Hansson L, Sivertsson R, Wikstrand J.** Coronary heart disease after treatment of hypertension. Lancet 1978;1:1–5.
27. **Hjalmarson Å, Elmfeldt D, Herlitz J, Holmberg S, Málek I, Nyberg G, Rydén L, Swedberg K, Vedin A, Waagstein F, Waldenström A, Waldenström J, Wedel H, Wilhelmsen L, Wilhelmsson C.** Effect on mortality of metoprolol in acute myocardial infarction: a double-blind randomised trial. Lancet 1981;2:823–827.
28. β-blockers Heart Attack Study Group. The β-blocker heart attack trial. JAMA 1981;246:2073–2074.
29. **Taylor SH, Silke B, Ebbutt A, Sutton GC, Prout BJ, Burley DM.** A long-term prevention study with oxyprenolol in coronary heart disease. N Engl J Med 1982;307:1293–1301.
30. **Lehtonen A, Viikari J.** Long-term effect of sotalol on plasma lipids. Clin Sci Mol Med 1979;57:405s–407s.
31. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Comparison of propranolol and hypochlorothiazide for the initial treatment of hypertension. II. Results of long-term therapy. JAMA 1982; 248:2004–2011.
32. **Day JL, Simpson N, Metcalfe J, Page RL.** Metabolic consequences of atenolol and propranolol in treatment of essential hypertension. Br Med J 1979;1:77–86.
33. **Leren P, Foss PO, Helgeland A, Hjermann I, Holme I, Lund-Larsen PG.** Effect of propranolol and prazosin on blood lipids. The Oslo study. Lancet 1980;2:4–6.
34. **Kokubu T, Itoh I, Kurita H, Ochi T, Murata K, Yuba I.** Effect of prazosin on serum lipids. J Cardiovasc Pharmacol 1982;4(Suppl 2):S228–S232.
35. **Gemma G, Montanari G, Suppa G, Paralovo A, Franceschini G, Mantero O, Sirtori CR.** Plasma lipid and lipoprotein changes in hypertensive patients treated with propranolol and prazosin. J Cardiovasc Pharmacol 1982;4(Suppl 2):S233–S237.
36. **Havard CWH, Khokhar AM, Flax JS.** Open assessment of the effect of prazosin on plasma lipids. J Cardiovasc Pharmacol 1982;4(Suppl 2): S238–S241.
37. **Lithell H, Waern U, Vessby B.** Effect of prazosin on lipoprotein metabolism in premenopausal hypertensive women. J Cardiovasc Pharmacol 1982; 4(Suppl 2):S242–S244.
38. **Lowenstein J, Neusy A-J.** The biochemical effects of antihypertensive agents and the impact on atherosclerosis. J Cardiovasc Pharmacol 1982;4(Suppl 2):S262–S264.

# New Developments in Alpha-Adrenergic Receptor Pharmacology: Implications for the Initial Treatment of Hypertension

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**The vascular postsynaptic alpha$_1$ receptor is the major locus through which adrenergically determined vascular tone is mediated. Therefore, blockade of this receptor is a particularly specific approach to the major pathophysiologic defect in hypertension—an elevation of peripheral vascular resistance. Although the mechanism responsible for this increase in peripheral vascular resistance in hypertension is not known, it is apparent that the sympathetic nervous system plays a key role. In addition, considerable evidence suggests that a common abnormality in hypertension is an increase in the sensitivity of vessels to alpha-adrenergic stimulation, a defect potentially located at the alpha-receptor level. Basic radioligand binding studies of vascular alpha$_1$ receptors, in fact, demonstrate that the affinity, or avidity, of binding of these sites is under the regulation of both neural and humoral factors.**

**Although diuretics, and more recently, beta-adrenergic blocking agents, have been utilized for the initial treatment of hypertension, recent information about the adverse effects of these agents has led to a reappraisal of the role of alpha-receptor blockade as a rational approach to the initial treatment of hypertension.**

The central role of the adrenergic nervous system in the development and maintenance of hypertension has long been appreciated. Not surprisingly, adrenergic blocking agents of many different types have been widely utilized in the therapy of hypertension. Agents such as reserpine, alpha-methyldopa, clonidine, and guanethidine result in a *nonspecific* suppression of sympathetic nervous system activity. Therefore, although these agents are effective in lowering blood pressure, they also cause a number of side effects which often make them unacceptable as "first-line" antihypertensive therapeutic agents. More recently, beta-blocking agents have proven effective in the lowering of blood pressure, and have been suggested as initial therapy of hypertension. Paradoxically, most beta-adrenergic blockers may result in an *increase* in peripheral vascular resistance due to blockade of vascular beta$_2$ receptors, stimulation of which results in vasodilation. Nevertheless, beta-blockers work because other indirect effects act to overcome the direct vasoconstriction resulting from beta blockade.

During the last 10 years, information in the field of alpha-adrenergic receptor pharmacology has greatly expanded. Understanding of how the two alpha-receptor subtypes mediate distinct physiologic functions has provided us with a sound basis for the development of alpha$_1$ selective antagonists that inhibit only that portion of adrenergic function involved in the maintenance of vascular tone, thereby bypassing many of the adverse effects of nonspecific sympatholytic agents. In particular, the alpha$_1$ selective antagonist, prazosin, has proved to be an effective antihypertensive agent. In view of these advances, it is appropriate to reevaluate the traditional "stepped" care of the hypertensive patient.

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## New Concepts in Alpha-Adrenergic Receptor Pharmacology

For many years, it has been known that the actions of the sympathetic nervous system on the tissues under its control are mediated by either of 2 receptor types, designated alpha and beta.[1] These receptor types are defined by their response patterns to stimulation by a series of catecholamines. *Alpha*-receptor sites respond maximally to epinephrine and norepinephrine, and much less so to isoproterenol. Conversely, *beta*-receptor sites respond maximally to isoproterenol and less so to norepinephrine and epinephrine. Beta-receptors are subdivided into $beta_1$ and $beta_2$ receptors. $Beta_1$ receptors primarily mediate cardiac responses, while $beta_2$ receptors mediate vascular and bronchial smooth muscle relaxation.

More recently it has also been appreciated that there are 2 subtypes of alpha-receptors, designated $alpha_1$ and $alpha_2$ (Fig. 1).[2–4] In general, alpha-receptors located *postsynaptically* on the vascular smooth muscle cell are the $alpha_1$ subtype, whereas receptors which are located *presynaptically* on the sympathetic nerve ending are of the $alpha_2$ subtype. Blockade of the postsynaptic $alpha_1$ receptor results in relaxation of vascular smooth muscle, and a fall in blood pressure. It is only recently that the physiologic function of the presynaptic $alpha_2$ receptor has been appreciated. Based on many types of information, it now appears that stimulation of the presynaptic $alpha_2$ receptor by norepinephrine, which has been released from the nerve ending, results in a reduction of further release of norepinephrine from that nerve ending.[4] In addition, norepinephrine or epinephrine which enters the synaptic cleft from the circulation may also result in a reduction in norepinephrine release. Thus, the presynaptic $alpha_2$ receptor forms part of a feedback loop which maintains the local level of sympathetic activity, and hence, vascular tone.

$Alpha_1$ and $alpha_2$ receptors are distinguishable by their pharmacologic specificities for various antagonist drugs.[3] Thus, $alpha_1$ receptors have a particularly high affinity (avidity of binding) for drugs such as prazosin, and a very low affinity for drugs such as clonidine or yohimbine, a drug that has been of particular value in the pharmacologic study of $alpha_2$ receptors. Conversely, $alpha_2$ receptors show very high affinity for clonidine or yohimbine, and extremely low affinity for prazosin. These types of pharmacologic specificity can be demonstrated by several techniques including physiologic experiments and, as will be discussed later, radioligand binding assay methods.

A more recent development is the understanding that postsynaptic alpha-receptors may be of either the $alpha_1$ subtype, the $alpha_2$ subtype, or a mixture of both subtypes. Although it previously was assumed that all postsynaptic alpha-receptors in blood vessels were of the $alpha_1$ subtype, it now is apparent that at least in certain blood vessels, some of the postsynaptic receptors may be of the $alpha_2$ subtype.[5,6] Interestingly, it appears that these $alpha_2$ receptors are located away from the sympathetic nerve endings, whereas $alpha_1$ receptors

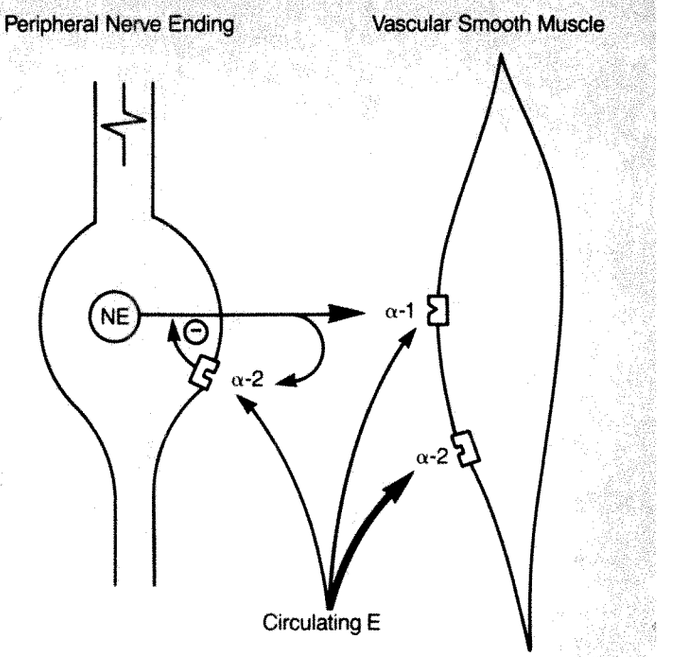



**FIGURE 1.** Schematic representation of the alpha-adrenergic receptor subtypes on peripheral nerve endings (presynaptic) and vascular smooth muscle (postsynaptic). Contraction of vascular smooth muscle is mediated primarily by $alpha_1$ receptors, whereas $alpha_2$ receptors located on peripheral nerve endings inhibit norepinephrine (NE) release, thereby providing local feedback control of sympathetic vasoconstriction. Recent data indicate that some vascular postsynaptic receptors are of the $alpha_2$ subtype. (Reprinted with permission, from Colucci WS, Braunwald E. Adrenergic receptors: new concepts and implications for cardiovascular therapeutics. In: Conti CR, Brest A, eds. Cardiovas Clin, in press, 1983.)

appear to be located within close proximity to the nerve ending.[5] A consequence of this fact is that the concentration of released norepinephrine is very high at $alpha_1$ receptors, and extremely low by the time it has diffused to the extrasynaptic $alpha_2$ receptors. Based on these observations, it is possible that $alpha_2$ receptors in blood vessels represent primarily a back-up system which gains importance in times of stress when circulating catecholamines are elevated to levels adequate to stimulate extrasynaptic $alpha_2$ receptors.

## Physiologic Significance of Alpha-Receptor Subtypes

Administration of phentolamine or phenoxybenzamine results in a *nonselective* blockade of alpha-adrenergic receptors. Thus, both the postsynaptic receptor on the vascular smooth muscle cell and the *presynaptic* receptor on the peripheral nerve ending are blocked. As discussed earlier, blockade of the presynaptic $alpha_2$ receptor results in an increased release of neuronal norepinephrine which then may result in attenuation of the desired postsynaptic blockade, and, in addition, may circulate systemically to result in such undesirable side effects as tachycardia and tremulousness. Blockade with an $alpha_1$ selective agent such as prazosin, on the other hand, does not affect the presynaptic $alpha_2$ re-

ceptor, thus leaving the negative feedback loop for norepinephrine *intact*, and circumventing the undesirable cardiac and systemic effects of increased norepinephrine release. Consequently, the use of an alpha$_1$ selective blocker makes physiologic and pharmacologic sense in the therapy of hypertension.

The differential physiologic effects of alpha$_1$ selective versus nonselective alpha blockade are illustrated in Figure 2. In this study, prazosin and phentolamine were administered to dogs in doses which lowered mean arterial pressure to the same degree.[7] When pressure was lowered with prazosin, there was a negligible effect on circulating plasma norepinephrine levels, whereas an equal lowering of blood pressure with phentolamine produced a marked increase in plasma norepinephrine. A similar elevation of circulating norepinephrine in humans might be seen during states of stress or strenuous exercise.

## A Potential Role of Vascular Alpha-Receptors in Hypertension

Although the fundamental cause of essential hypertension still is not known, it is clear that increased vascular tone is a primary hemodynamic derangement. Some of the possible causes of this increase in vascular tone include increased sympathetic nervous system activity, an increase in vascular *sensitivity* to catecholamines or to other vasoactive substances, increased activity of the renin-angiotensin-aldosterone system, or decreased local or circulating vasodilator substances.

Evidence of an increased sympathetic nervous system outflow in patients with essential hypertension has been inconclusive. Circulating levels of norepinephrine, which are thought to represent neuronal activity are, in general, not elevated in hypertensive patients.[8] Recently, however, there has been evidence that hypertensives may have elevated levels of epinephrine which is derived primarily from the adrenal medulla.[9]

Another potential cause of hypertension is an *increased sensitivity* to vasoconstrictor stimuli. In fact, a large literature suggests that increased vascular sensitivity in hypertension, and in many cases this hypersensitivity is demonstrable for norepinephrine.[10,11] However, it has previously been impossible to specifically implicate the alpha-receptor as the *site* of this abnormality. Recently, it has been possible to use direct radioligand binding studies of vascular alpha$_1$ receptors in order to begin approaching this question. These studies utilize a radioactive probe such as tritium-labeled prazosin to quantify both the *number* and *affinity* (avidity of binding) of alpha$_1$ receptors in vascular smooth muscle.

Under normal assay conditions, the alpha$_1$ receptors are occupied by the radioactive probe (Fig. 3). As varying concentrations of alpha-agonists or antagonists are competed with the radioligand, displacement curves can be obtained which indicate the affinity of the receptor for each of the compounds tested. A shift of the binding curve to the left indicates an increase in receptor affinity, whereas a shift of the curve to the right indicates a decrease in affinity.

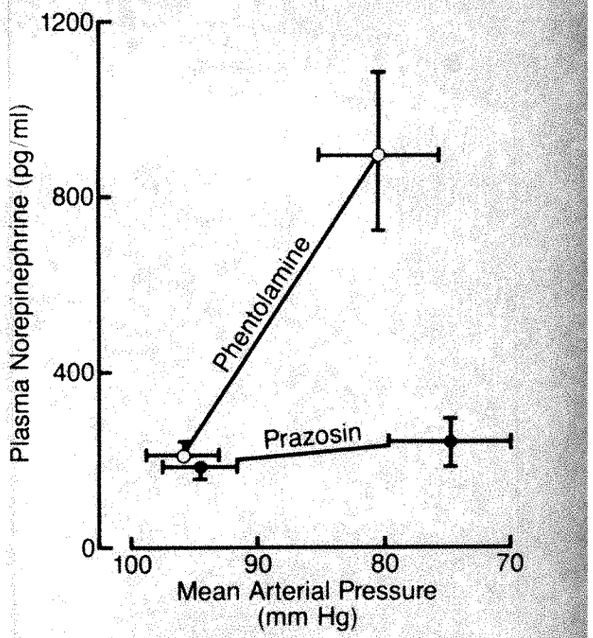



**FIGURE 2.** Relative effects of equihypotensive doses of phentolamine and prazosin on the plasma norepinephrine concentration in conscious dogs. The postphentolamine concentration of norepinephrine is significantly elevated ($p < 0.05$), whereas there is no significant change in norepinephrine concentration after prazosin. (Modified from Saeed M, et al.[7])

Using this approach, we recently have been able to demonstrate that the affinity of the vascular alpha$_1$ receptor is regulated by (among other things) the estrogen sex hormones.[13] As shown in Figure 4, the effect of estrogens is to increase vascular alpha$_1$ receptor affinity, as signified by a leftward shift in the binding curve in females as compared to males. After ovarectomy, this difference is abolished further implicating the role of estrogens. Likewise, the administration of estrogens to male rats results in a leftward shift in the binding curve, or an increase in affinity.

These observations may be relevant to the mechanism of birth-control-pill–induced hypertension. Perhaps more important, though, these data demonstrate that the affinity of the vascular alpha$_1$ receptor is in a dynamic state; the absolute affinity being regulated by various neural and humoral influences. Potentially, an abnormally high affinity of vascular alpha$_1$ receptors could be a basic underlying defect in essential hypertension. Although we do not yet know the answer to this question, it is an area of active investigation.

## Treatment of Hypertension With Prazosin

Prazosin is a versatile antihypertensive agent which is effective alone or with other types of antihypertensives in the therapy of mild, moderate, or severe hypertension.[14] Prazosin's antihypertensive action is due to a decrease in peripheral vascular resistance as a result of blockade of vascular alpha$_1$ receptors. However, unlike other vasodilators such as hydralazine and minoxidil which require concomitant beta-adrenergic

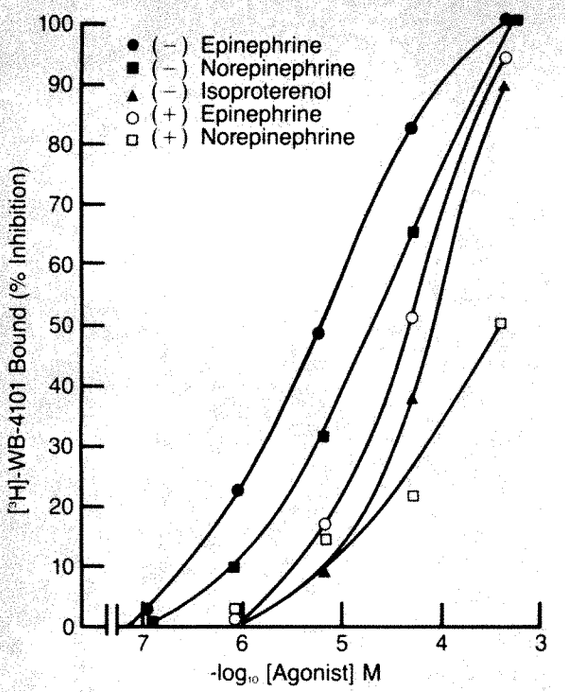



**FIGURE 3.** Inhibition of the binding of an alpha$_1$ selective radioligand ($^3$H-WB-4101) to vascular alpha$_1$ receptors by various catecholamines. The location of each curve represents the *affinity* of the alpha$_1$ receptor for that compound. (Reprinted from Colucci WS et al,[12] with permission of the American Heart Association.)

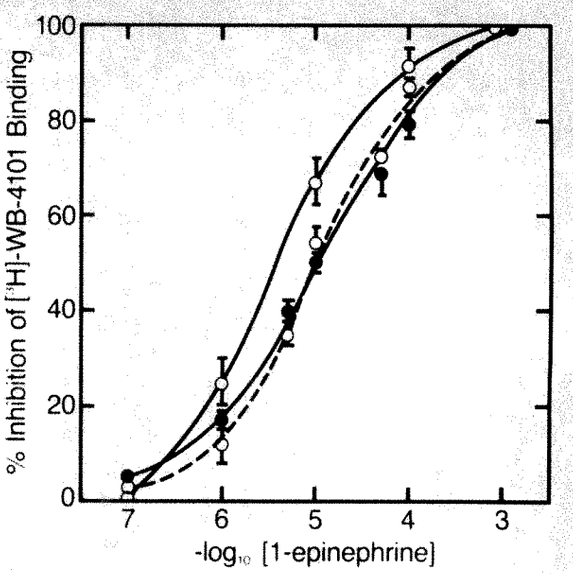



**FIGURE 4.** As in Figure 3, the location of the l-epinephrine curve indicates the affinity of the alpha$_1$ receptor. The affinity of binding is higher in female rats (**open circles**) than in male rats (**closed circles**), whereas the difference is no longer evident after ovarectomy (**open circles separated by broken line**). (Reprinted from Colucci et al,[13] with permission of the American Heart Association.)

blockade in order to be effective (and therefore are generally reserved for Step 3 use), prazosin may be used as a Step 1, Step 2, or Step 3 agent without beta-adrenergic blockade. This is because prazosin's antihypertensive effect is accompanied by little or no increase in heart rate, plasma renin activity, or circulating catecholamine levels.

Prazosin may be used alone to treat mild-to-moderate hypertension, and may be particularly useful when therapy with other Step 1 agents such as diuretics or beta blockers is undesirable. The well-known adverse effects of diuretic and beta-blocking drugs, and recent growing evidence that both classes of drugs adversely affect serum lipids makes their long-term use less than ideal, and suggests that their role as Step 1 therapy needs to be reevaluated, particularly in young adults with mild or moderate hypertension.[15] Since alpha$_1$ selective blockade with prazosin is effective, associated with few adverse effects, and does not adversely affect serum lipids, it deserves serious consideration as Step 1 therapy.

Prazosin is also effective when used with a diuretic or in combination with other antihypertensive agents. The low incidence of limiting side effects during chronic therapy has made prazosin a popular alternative to nonspecific adrenergic inhibitors such as reserpine, alpha-methyldopa, clonidine, and guanethidine. Prazosin is effective in patients with moderate-to-severe hypertension, and may be used in place of hydralazine. Prazosin's effects are additive to those of diuretics, beta-adrenergic blockers, and essentially all other antihypertensive agents. Prazosin may be a highly effective agent alone or with a beta-blocker for the presurgical management of patients with severe hypertension due to pheochromocytoma.[16] Despite extensive clinical trials for periods of therapy ranging from weeks to years, there is virtually no evidence of attenuation of prazosin's antihypertensive effect during chronic therapy.[17,18]

In hypertensive patients with normal renal function, prazosin has no significant effect on glomerular filtration rate or effective renal plasma flow. In hypertensive patients with renal insufficiency, glomerular filtration rate is either unchanged or increased. Although prazosin is primarily metabolized by the liver, some data suggest that drug levels may be higher, elimination half-life prolonged, and the degree of protein-bound drug reduced in patients with chronic renal insufficiency. These alterations in drug pharmacokinetics may account for clinical reports of increased drug potency in renal insufficiency. Used alone or in combination, prazosin is an effective antihypertensive agent in dialysis patients with volume-responsive or volume-independent hypertension.

The major side effect of prazosin therapy in patients with hypertension is postural hypotension, which is usually most pronounced after the initial drug administration, and therefore has been referred to as the "first-dose phenomenon." This complication is dose-related. In a group of 74 hypertensive patients initially treated with a 2-mg dose of prazosin, 2 patients had syncope and 10 others had significant symptoms of postural hypotension such as dizziness, weakness, or palpitations.[19] However, when the same 12 patients were rechallenged with a 0.5-mg dose 3 weeks after

control subjects. During prazosin therapy, blood viscosity was reduced in proportion to the decrease in perfusion pressure, so that total blood flow was largely unchanged. Prazosin preferentially reduced blood viscosity in the precapillary resistance vessels, while hardly affecting the viscous resistance to flow in the capacitance (venous) vessels. This action might explain the greater effect of prazosin on the peripheral arterial bed, although the drug is also known to affect peripheral resistance in the venous side of the circulation. In this same study, plasma renin activity, creatinine clearance, as well as daily excretion of sodium, potassium, and aldosterone were similar before and during treatment with prazosin, whereas microcirculatory blood flow and organ perfusion were well maintained.

Prazosin is rapidly and almost completely absorbed after oral administration.[2] Peak plasma concentrations are achieved within 2 to 3 hours after a dose. Prazosin is extensively metabolized by the liver, with more than 90% of an oral dose being eliminated through the feces and the remainder through the urine.[2] This antihypertensive drug does not significantly affect renal function.[4] However, its hepatic metabolism calls for caution when the drug is administered in patients with impaired liver function.

Prazosin has had no adverse effect on lipid metabolism[5-13] and has not altered glucose[14] or uric acid metabolism.[5]

## Use of Prazosin in the General Hypertensive Population

Numerous studies report that prazosin, given as single-agent therapy in the initial treatment of hypertension, is effective in reducing blood pressure in the general population with mild, moderate, and severe hypertension. Most common reactions to prazosin are generally mild and transient and include dizziness, headache, drowsiness, lack of energy, weakness, palpitations, and nausea. Rarely, a so-called "first-dose phenomenon" involving postural hypotension, syncope, or both may occur, but can usually be avoided by careful initiation of prazosin treatment (see section on Initiation and Titration of Therapy). In at least 1 study by Fauchald,[15] the first-dose effect did not occur in patients in whom diuretics were withheld and prazosin was instituted at a small dose. Apparently, volume-depleted patients are more likely to experience the postural effects of the first dose of therapy, thus arguing for initiation of drug therapy with prazosin and the later addition of a low-dose diuretic when necessary. Prazosin does not cause the marked increases in heart rate, vascular headaches, and flushing episodes often seen with direct-acting vasodilators, nor does it decrease cardiac output and heart rate as do beta-blocking drugs or cause potassium depletion as do diuretics. Therefore, prazosin seems an especially logical choice in the asymptomatic patient starting on long-term antihypertensive therapy. The lack of adverse effects on lipid, glucose, and uric acid metabolism further enhances its appropriateness.

Because most direct-acting vasodilators such as hydralazine and minoxidil have severe side effects and usually require concomitant use of a beta-blocking agent to blunt their hyperdynamic effects, they generally are used as step 3 drugs in the stepped-care approach to therapy recommended by the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. In contrast to these vasodilators, prazosin is recommended as a Step 2 drug by this Committee and can be used alone as Step 1, Step 2, or Step 3 therapy, without a beta-blocking drug because it usually does not affect heart rate, plasma renin activity, or plasma catecholamine levels.[1] Nevertheless, because some patients taking prazosin may accumulate fluid (although not as much as do those on hydralazine),[1] the addition of a diuretic agent may be necessary at some point in their therapy. Salt restriction is advisable if maximal effectiveness is to be achieved.

**Clinical experience:** After nearly 10 years in clinical use, prazosin, when used alone, has been an effective agent over the entire range of hypertension. Table I summarized the results of many studies in which the drug was used as single-agent therapy.[16]

Studies dating back to 1973 and earlier suggest that the optimal effect of prazosin is reached within 4 to 6 weeks in mild hypertension and within 8 weeks in moderate to severe hypertension. Harter and Delmez[16] conducted a study in 22 patients on chronic hemodialysis. Eleven patients were treated with prazosin alone (Fig. 1). Eight of these were volume-responsive, 2 volume-independent, and 1 had high-renin hypertension. The baseline predialysis blood pressure was 184 ± 5/102 ± 2 mm Hg, and after 3 months on prazosin it decreased to 154 ± 3/77 ± 3 mm Hg. Adequate control was maintained throughout the 6-month period of observation.

Kincaid-Smith,[17] who by 1977 had treated about 500 hypertensive patients with prazosin over 5 years, reported that this agent was effective when used alone in the majority of patients, including those with severe hypertension. In 16 patients treated with prazosin alone over 4 weeks, increasing the dose from 0.5* mg 3 times a day to 5 mg 3 times a day reduced the supine systolic blood pressure from 194 to 142 mm Hg and the supine diastolic pressure from 118 to 84 mm Hg. Prazosin was well tolerated by the patients.

O'Connor et al[18] compared the efficacy of prazosin with that of propranolol in a crossover study of 12 patients with essential hypertension, each treated for 1 month with placebo, prazosin alone, and propranolol alone. Both active drugs were titrated upward until the blood pressure was normalized and then kept constant for 1 month. The mean prazosin dose was 5.8 mg/day and the mean propranolol dose was 170 mg/day. Both drugs normalized systemic blood pressure, including

* In this clinical trial, tablets rather than capsules were used. Prazosin capsules are the only dosage form presently available in the United States. Prazosin, 0.5 mg, is unavailable in the United States. Because of lower bioavailability of the capsule formulation, when a dose of 0.5 mg of prazosin is referred to in the present study, it should be considered equal in antihypertensive activity to a 1 mg capsule of prazosin.

**TABLE I Summary of Results From Studies Demonstrating the Efficacy of Prazosin as Single-agent Therapy for Hypertension (Total, 324 Patients)**

| Study | Supine BP (mm Hg) | | Net BP Reduction (mm Hg) Over Baseline* | n | Prazosin Mean Dose/Day (mg) |
|---|---|---|---|---|---|
| | Baseline | Prazosin | | | |
| Harter and Delmez[17] | 184/102 | 154/77 | 30/25 | 11† | 16 |
| Kincaid-Smith[18] | 194/118 | 142/84 | 52/34 | 16 | 15 |
| O'Connor et al[19] | 156/108 | 135/85 | 21/23 | 12 | 5.8 |
| Letcher et al[4] | 178/104 | 158/94 | 20/13 | 11 | 10 |
| Mulvihill-Wilson et al[20] | 157/99 | 142/91 | 15/8 | 11 | . . . |
| Turner et al[21] | 166/107 | 141/89 | 25/18 | 50 | 6.8 |
| NDA data[22] | 168/102 | 153/89 | 15/13 | 101 | . . . |
| Smith et al[23] (mean arterial pressure) | 134 | 121 | 13 | 38 | . . . |
| Fernandes et al[24] (average diastolic pressure) | 116 | 104 | 12 | 48 | 13 |
| Adriaensen and Vryens[25] | (Normalized supine | | | 20 | 3 |
| Bolli and Simpson[26] | BP in 65%) | | 16/12 | 6 | 9.9 |

* All reductions from baseline are statistically significant.
† Dialysis patients.
BP = blood pressure.

systolic, diastolic, and mean arterial pressure, although the final diastolic and mean arterial pressure was somewhat lower with propranolol (Table II). Glomerular filtration rate, renal plasma flow, and renal blood flow all decreased significantly during propranolol treatment, whereas they were preserved during prazosin treatment (Table II).

Letcher et al[3] evaluated therapy with prazosin alone in 11 patients who received a mean dose of 10 mg/day. Seated blood pressure decreased from a baseline of 178/107 to 158/94 mm Hg after 4 weeks of therapy at the maintenance dose level. Heart rate and body weight were similar before and during prazosin therapy.

In a double-blind, placebo-controlled, randomized, crossover study by Mulvihill-Wilson et al,[19] the efficacy of prazosin as single-agent therapy was compared with that of phenoxybenzamine in 11 patients with essential hypertension. Both drugs produced similar significant reductions in standing blood pressure, but only prazosin caused a significant decrease in supine blood pressure from 157/99 to 142/91 mm Hg (Table III). Prazosin was well tolerated by most patients in this study.

Turner et al[20] treated 50 mild to severely hypertensive patients with an initial dose of 1 mg titrated upward until satisfactory control was achieved or a maximal dose of 20 mg/day was reached. Twenty-four achieved satisfactory control with prazosin alone (standing blood pressure of 168/103 mm Hg was reduced to 134/82 mm Hg) and of these 20 became normotensive. The remaining 26 required the addition of a beta-blocking agent, together with a thiazide diuretic in 14 patients. Although prazosin alone produced a mean blood pressure reduction of 21/13 mm Hg in this group of 26, the combined therapy achieved a further reduction of 21/15 mm Hg.

When 101 patients, half of whom had moderate to severe hypertension, were treated with up to 20 mg/day of prazosin for 8 weeks (Table IV),[21] almost 50% became normotensive (diastolic <90 mm Hg), and the supine diastolic pressure was reduced to <100 mm Hg in 75% of the patients. Average blood pressure was reduced from 168/102 to 153/89 mm Hg. A decrease in severity of illness was reported in 83% of the patients.

Smith et al[22] reported on 38 patients treated with

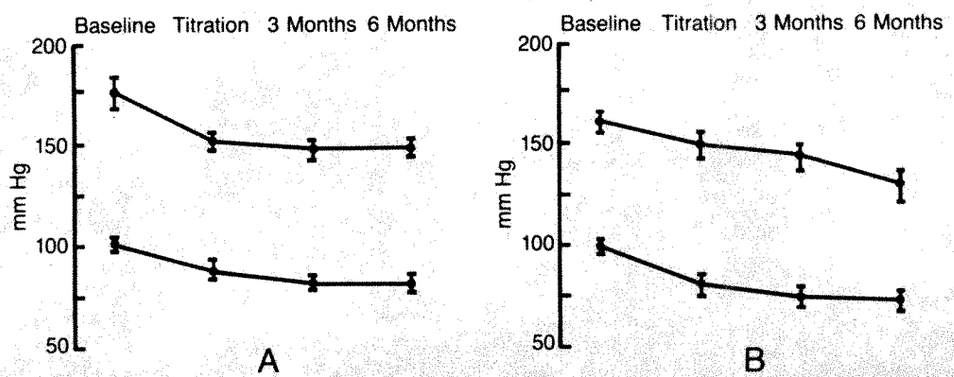



**FIGURE 1.** Blood pressure response to prazosin in 11 chronic dialysis patients with volume-responsive hypertension (mean ± standard error of the mean). **A,** Blood pressure reading taken just before dialysis. **B,** blood pressure reading taken just after dialysis. (Adapted from Harter and Delmez,[16] with permission.)

**TABLE II Systemic and Renal Hemodynamic Variables in 12 Patients With Essential Hypertension Treated for 1 Month Each With Placebo, Propranolol, and Prazosin***

| Drug | Blood Pressure (mm Hg) | | | Glomerular Filtration Rate (ml/min) | Renal Plasma Flow (ml/min) | Filtration Fraction | Renal Blood Flow (ml/min) |
|---|---|---|---|---|---|---|---|
| | Systolic | Diastolic | Mean Arterial Pressure | | | | |
| Placebo | 156.3 ±5.0 | 107.7 ±2.7 | 122.7 ±3.0 | 106.8 ±6.4 | 597.8 ±46.5 | 0.19 ±0.02 | 1,086.0 ±93.7 |
| Propranolol | 124.8 ±4.8† | 76.4 ±2.6† | 91.9 ±3.0† | 90.7 ±5.3† | 523.0 ±22.4‡ | 0.18 ±0.01 | 929.9 ±45.3‡ |
| Prazosin | 134.6 ±3.5† | 85.4 ±2.2†§ | 101.6 ±2.3†§ | 104.8 ±4.0 | 612.8 ±29.2 | 0.18 ±0.01 | 1,082.4 ±64.0 |

* Reprinted, with permission, from O'Connor et al.[18]
† $p < 0.01$ versus placebo.
‡ $p < 0.05$ versus placebo.
§ $p < 0.05$, prazosin versus propranolol.

**TABLE III Mean (± Standard Error of the Mean) Levels of Body Weight, Pulse, Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP) at the End of 4 Weeks of Placebo, Prazosin, and Phenoxybenzamine***

| Variable | Placebo | | Prazosin | | Placebo | | Phenoxybenzamine | |
|---|---|---|---|---|---|---|---|---|
| | Supine | Standing | Supine | Standing | Supine | Standing | Supine | Standing |
| Body weight (kg) | 77.3 ± 5.2 | | 77.3 ± 5.8 | | 76.0 ±5.4 | | 77.3 ± 6.7 | |
| Pulse (beats/min) | 71.8 ±2.9 | 83.5 ±5.0 | 76.4 ±3.9 | 89.2 ±3.9 | 75.4 ±4.4 | 82.5 ±4.1 | 74.5 ±3.7 | 95.8 ±6.6† |
| SBP (mm Hg) | 157 ±6.3 | 157 ±3.2 | 142.3 ±5.9† | 133.6 ±4.8† | 153.6 ±6.5 | 150.9 ±3.7 | 156.3 ±7.5 | 139 ±8.0‡ |
| DBP (mm Hg) | 98.9 ±2.0 | 108 ±3.0 | 90.5 ±2.7† | 91.5 ±3.8† | 97.8 ±3.7 | 107 ±2.4 | 94.5 ±2.8 | 94.5 ±6.5‡ |

* Reprinted, with permission, from Mulvihill-Wilson et al.[19]
† $p < 0.005$ versus placebo.
‡ $p < 0.05$ versus placebo.

**TABLE IV Response to 8 Weeks of Therapy With Prazosin (up to 20 mg/day) in 101 Patients With All Grades of Hypertension[21]**

| | Mean Reduction of Blood Pressure (mm Hg) | Other Criteria of Response | Percentage of Patients |
|---|---|---|---|
| Supine (n = 101) | 15/13 | Diastolic <90 | 48.5 |
| | | Diastolic <100 | 75.3 |
| | | Improvement in severity | 83.5 |
| Standing (n = 101) | 20/16 | Diastolic <90 | 39.8 |
| | | Diastolic <100 | 80.6 |
| | | Improvement in severity | 83.7 |

prazosin alone. Mean arterial pressure in the supine position decreased from a control level of 134 to 121 mm Hg after 6 months of therapy with prazosin.

Fernandes et al[23] used prazosin alone (6 to 10 mg/day) in 48 ambulatory patients with essential hypertension for 4 to 6 months after a preliminary 4-to-10-week period of placebo administration. Treatment with prazosin produced a significant reduction in blood pressure in both the supine and the standing position. There was a 10% decrease (from 116 to 104 mm Hg) in the average supine diastolic blood pressure and an 11% decrease (from 117 to 101 mm Hg) in the average standing diastolic pressure. Prazosin was well tolerated.

Adriaensen and Vryens[24] determined that in blood pressure reduction 3 mg/day of prazosin was approximately equal to 750 mg/day of methyldopa in a group of 20 patients with mild to moderate fixed essential hypertension. Prazosin normalized the blood pressure (supine diastolic <90 mm Hg) in 65% (13 of 20) of the patients; methyldopa produced a similar response in only 45% (9 of 20). Although the blood-pressure–lowering effect of prazosin was already noticeable in the first week of therapy, optimal effects were reached between the fourth and sixth weeks. The investigators thought that such a progressive blood-pressure–decreasing effect was an advantage, especially in subjects demonstrating the effects of arterial aging. Prazosin alone had no effect on serum levels of electrolytes, glucose, or uric acid.

Bolli and Simpson[25] successfully treated 24 hypertensive patients with prazosin, 6 of them with prazosin alone. In the 6 patients who received prazosin as the sole antihypertensive agent,* the mean decrease in supine and standing blood pressure was 16/12 and 18/16 mm

* These investigators used initial doses greater than those currently recommended.

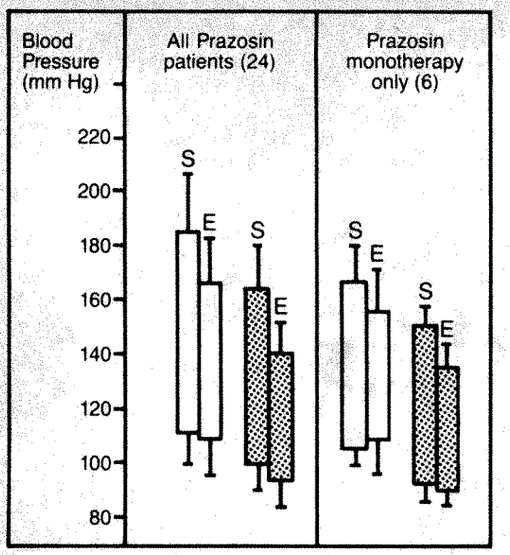



**FIGURE 2.** Mean blood pressure before (**paired white columns**) and during (**paired dark columns**) prazosin therapy. Standard deviations are indicated in **vertical lines.** E = erect; S = seated. (Adapted from Bolli and Simpson,[25] with permission.)

Hg, respectively (Fig. 2). The mean daily dose in this group was 9.9 mg.

Prazosin, therefore, has been shown over the years to be an effective antihypertensive agent when used alone as initial therapy in a large percentage of patients. In addition, it also elicits good blood pressure decrease when used concomitantly with other antihypertensive agents.

**Initiation and titration of therapy:** Current recommendations in the United States call for an initial dose of 1 mg 2 or 3 times a day. This dosage may be slowly titrated upward to a maximal total daily administration of 40 mg in divided doses. The therapeutic dosage most commonly used in this country has ranged from 6 to 15 mg daily in divided doses. Prazosin seems to have a dose-related plateau, probably reflecting full blockade of alpha-adrenergic receptors. Hence, >20 mg/day usually does not increase efficacy. However, a few patients may benefit from further increases to 40 mg daily in divided doses. Most patients can be maintained adequately on a twice-daily regimen.

In clinical experience with 22,000 patients receiving an initial dose of 1 mg of prazosin,[21] syncope was reported in 1 of 667 patients (0.15%). Although the incidence of syncope is low, patients should be cautioned to avoid situations in which injury could result if syncope should occur during initiation of therapy.

Preexisting sodium depletion from either dietary sodium restriction or diuretic therapy may contribute to the occurrence of the first-dose phenomenon with prazosin.[2] Fauchald et al[15] reported that when diuretics were withheld for 1 day before initiation of prazosin therapy, the first dose of prazosin was administered at bedtime, and the initial dose was limited to 0.5 or 1.0 mg,* no case of first-dose syncope occurred in a series of 1,151 hypertensive patients; also, symptomatic postural hypotension declined as therapy proceeded.

Too rapid dosage increases of prazosin or the introduction of another antihypertensive agent into the regimen of a patient taking large doses of prazosin also have been associated occasionally with syncopal episodes.[26] Such episodes can be minimized by slow, gradual increases in prazosin and by careful introduction of any additional antihypertensive agents, when needed.

## Prazosin as Initial Therapy in Hypertensive Subpopulations

Prazosin is particularly useful and appropriate across the broad spectrum of hypertensive individuals. In addition, the many hemodynamic and metabolic advantages of prazosin make it particularly appropriate in certain populations with complicated hypertension.

**Patients with impaired renal function:** Thiazide diuretics lose much of their antihypertensive effectiveness in the presence of renal insufficiency and therefore are usually replaced by powerful loop diuretics such as furosemide in patients with renal impairment.[27] As with beta-blocking drugs, propranolol causes a decrease in glomerular filtration rate, renal blood flow, and renal plasma flow.[18] These functions were preserved during prazosin therapy.

So far as medical treatment is concerned, except for the severity of hypertension and the need to consider the effect of different drugs on renal function, no major differences in treatment exist between patients with renovascular hypertension and those with essential hypertension.[17] Patients with an underlying renal cause and those with impaired renal function responded well to prazosin.[28-30]

**Hemodialysis:** The plasma concentrations of prazosin are not affected by hemodialysis.[31] Harter and Delmez[16] preferred to use prazosin in patients on chronic hemodialysis because methyldopa could cause somnolence and impotence (compounding conditions already present in patients on dialysis); hydralazine is associated with cephalgia and tachycardia. Prazosin was also preferred because it can easily be titrated to large doses, has minimal side effects, and is well accepted.

Adequate control of pre- and postdialysis blood pressure was maintained throughout a 12-month study[16] in all patients treated with prazosin alone (Fig. 1). Prazosin alone was most effective in 16 patients with volume-responsive hypertension whose persistent high blood pressure was due to interdialysis weight gain. Prazosin was well tolerated by most patients.

Goldberg et al[11] pointed out that uremic patients treated with hemodialysis developed accelerated atherosclerosis. Among the factors thought to be responsible are hypertension and abnormal lipid and carbohydrate metabolism. Hypertension and hyperlipidemia are very common and may be major coronary risk fac-

* See footnote in section on Clinical Experience.

tors in this subpopulation. Therefore, in treating hypertensive patients on dialysis, agents used must have no adverse effect on serum lipids. Hyperlipidemia in this group is characterized by hypertriglyceridemia and reduced high density lipoprotein (HDL) cholesterol. In this pilot survey, dialysis patients on propranolol had increased plasma triglyceride levels and reduced HDL concentrations, whereas those on prazosin had no adverse effect.

**Heart block:** Prazosin does not significantly affect the electrical conduction of the heart and can be used safely in hypertensive patients who also have conduction problems.

**Bronchospasm:** Prazosin can safely be used in patients with hypertension who also have obstructive bronchospastic disease.

**Diabetes mellitus:** Thiazide diuretics can trigger diabetes or aggravate preexisting hyperglycemia[32] because they increase blood glucose levels and can even lead to nonketotic hyperosmolar coma. The hyperglycemic properties of diuretics are also related to the hypokalemic effect of these drugs. Prazosin can be used safely in hypertensive patients with diabetes or hyperglycemia because it has minimal or no effects on glucose metabolism.[14]

**Effects on lipid metabolism:** Diuretics such as chlorthalidone and hydrochlorothiazide significantly increase plasma total cholesterol, VLDL cholesterol, and plasma triglycerides; chlorthalidone increased LDL cholesterol as well.[33] Recently, Ames and Hill[34] indicated that methyldopa significantly lowers the serum levels of protective HDL cholesterol. Propranolol and atenolol[35] and, to a lesser extent, the cardioselective beta-adrenergic blocking agents such as metoprolol decrease the HDL cholesterol and increase triglyceride concentrations.

The actual clinical benefit of decreasing elevated blood lipid levels in hypertensive patients has not been clearly established, although some studies have found a definite correlation between the mortality from coronary heart disease and decreasing the lipid levels (through reduced intake of saturated fats, no smoking, and increased exercise) in normotensive subjects.[36] Hopefully, decreasing the blood pressure by drug therapy will further reduce mortality from coronary heart disease. However, several large trials, including the recent Multiple Risk Factor Intervention Trial (MRFIT),[37] suggest that decreasing the blood pressure with a number of drugs including thiazides, chlorthalidone, methyldopa, reserpine, guanethidine, and propranolol may fail to produce any clear cut benefit in terms of mortality from coronary heart disease. We might hypothesize that the adverse metabolic effects of these drugs (including increases in very low density lipoprotein (VLDL) + LDL and decreases in HDL) negated the beneficial effect expected from decreasing the blood pressure. No similar trials have yet been conducted with prazosin, but other studies have shown it to have no adverse effect on lipid metabolism.

**Hyperuricemia:** Prazosin has no effect on uric acid metabolism[5] and therefore can be used in hypertensive patients with gout or hyperuricemia without the need to add an antigout agent, thus simplifying therapy and encouraging compliance with the regimen.

## Side Effects

The side effects of prazosin therapy, which include dizziness, lightheadedness, headache, drowsiness, weakness, and palpitation, are generally mild and transient and seldom require discontinuation of the drug. Sexual dysfunction, which may occur with some other antihypertensive agents such as methyldopa, diuretics, and reserpine, is uncommon with prazosin.[38]

As previously indicated, the most significant side effect of prazosin is the "first-dose phenomenon." Syncopal episodes may occur in rare instances, usually after the initial dose. However, withholding diuretics for 1 day before initiating prazosin therapy, limiting the initial dose to 1 mg, and taking it at bedtime are all helpful in eliminating many of the initial adverse effects. Fluid retention necessitating the addition of a diuretic sometimes develops on long-term therapy with prazosin.

**Drug interactions:** In patients who initially receive prazosin but who need more antihypertensive effect, the required dose of diuretic or beta-blocking drug or both is reduced, thus avoiding some of the adverse effects of these additional drugs.

In clinical practice prazosin has been administered without any adverse drug interactions with cardiac glycosides (digitalis and digoxin), hypoglycemics (insulin, chlorpropamide, phenformin, tolazamide, and tolbutamide), tranquilizers and sedatives (chlordiazepoxide, diazepam, and phenobarbital), antigout agents (allopurinol, colchicine, and probenecid), antiarrhythmics (procainamide and quinidine), as well as analgesics, antipyretics, and anti-inflammatory agents (propoxyphene, aspirin, indomethacin, and phenylbutazone). Hypertension may develop in patients given prazosin who are also receiving a beta-blocker such as propranolol.

**Conclusions:** In a substantial number of studies dating back to 1973 and before, prazosin given as initial single therapy was an effective and well tolerated antihypertensive agent in all degrees of hypertension (mild, moderate, and severe).

Prazosin decreases blood pressure by reducing total peripheral resistance, which is the underlying hemodynamic problem in most patients with essential hypertension. It does not affect, or minimally increases, cardiac output, heart rate, plasma renin activity, plasma catecholamines, or plasma electrolytes. It has no adverse effect on glucose, uric acid, or lipid metabolism. It does not affect renal function in otherwise normal hypertensive patients and may enhance renal function in patients with concomitant heart failure.

The mild side effect profile of prazosin and its lack of adverse metabolic actions make this drug an attractive choice as initial therapy because it may provide more benefits over the long term than do the first-line agents currently used to treat hypertension. If combined therapy with a diuretic or a beta-blocking agent is re-

iired, the choice of prazosin as initial therapy may ake it possible to reduce the dose of the concomitant ug.

The "first-dose phenomenon" is rare when initial ses of 1 mg of prazosin, preferably taken at bedtime, e used.

## References


**Colucci WS.** Alpha-adrenergic receptor blockade with prazosin: consideration of hypertension, heart failure, and potential new applications. Ann Intern Med 1982;97:67–77.

**Graham RM, Pettinger WA.** Prazosin. N Engl J Med 1979;300:232.

**Letcher RL, Chien S, Laragh JH.** Changes in blood viscosity accompanying the response to prazosin in patients with essential hypertension. J Cardiovasc Pharmacol 1979;1(Suppl b)S8–S20.

**Curtis JR, Bateman FJA.** Use of prazosin in management of hypertension in patients with chronic renal failure and in renal transplant recipients. Br Med J 1975;4:432–434.

**Leren P, Eide I, Foss OP, Helgeland A, Hjerman I, Holme I, Kjeldsen SE, Lund-Larsen PG.** Antihypertensive drugs and blood lipids. J Cardiovasc Pharmacol 1982;4(Suppl 2):S222–S224.

**Velasco M, Silva H, Morillo J, Pellicer R, Urbina-Quintana A, Hernandez-Pieretti O.** Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. J Cardiovasc Pharmacol 1982;4(Suppl 2):S225–S227.

**Kokubu T, Itoh I, Kurita H, Ochi T, Murata K, Yuba I.** Effect of prazosin on serum lipids. J Cardiovasc Pharmacol 1982;4(Suppl 2):S228–S232.

**Gemma G, Montanari G, Suppa G, Paraiovo A, Francischini G, Mantero O, Sirtori CR.** Plasma lipid and lipoprotein changes in hypertensive patients treated with propranolol and prazosin. J Cardiovasc Pharmacol 1982;4(Suppl 2):S233–S237.

**Havard CWH, Khokhar AM, Flax JS.** Open assessment of the effect of prazosin on plasma lipids. J Cardiovasc Pharmacol 1982;4(Suppl 2): S238–S241.

**Lithell H, Waern U, Vessby B.** Effect of prazosin on lipoprotein metabolism in premenopausal hypertensive women. J Cardiovasc Pharmacol 1982; 4(Suppl 2):S242–S244.

**Goldberg AP, Tindira C, Harter HR.** Coronary risk in patients with endstage renal disease: interaction of hypertension with hyperlipidemia. J Cardiovasc Pharmacol 1982;4(Suppl 2):S257–S261.

**Lowenstein J, Neusy A-J.** The biochemical effects of antihypertensive agents and the impact on atherosclerosis. J Cardiovasc Pharmacol 1982;4(Suppl 2):S262–S264.

**Leren P, Helgeland A, Holme I, Foss PO, Hjermann I, Lund-Larsen PG.** Effect of propranolol and prazosin on blood lipids. The Oslo Study. Lancet 1980;2:4–6.

**Leichter SB, Baumgardner B.** Effects of chronic prazosin therapy on intermediary metabolism in diabetic patients. J Cardiovasc Med 1981;(Special Suppl) 38.

**Fauchald P, Helgeland A, Storm-Mathisen H.** Treatment of hypertension with prazosin: an open study in general practice. In: Rawlins MD, Geyer G, Bleifeld W, eds. Proceedings of the European Prazosin Symposium, Vienna, 24th–25th November, 1978. Amsterdam: Excerpta Medica, 1979;85–93.

**Harter HR, Delmez JA.** Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. J Cardiovasc Pharmacol 1979;1(Suppl 6):543–555.

**Kincaid-Smith P.** Prazosin in the treatment of hypertension. Med J Aust 1977;(Special Suppl)2:27–28.

**O'Connor DT, Preston RA, Sasso EH.** Renal perfusion changes during treatment of essential hypertension: prazosin versus propranolol. J Cardiovasc Pharmacol 1979;1(Suppl 6):S38–S42.

**Mulvihill-Wilson J, Graham RM, Pettinger W, Muckleroy C, Anderson S, Gaffney FA, Blomqvist CG.** Comparative effects of prazosin and phenoxybenzamine on arterial blood pressure, heart rate, and plasma catecholamines in essential hypertension. J Cardiovasc Pharmacol 1979;1(Suppl 6):S1–S7.

**Turner AS, Watson OF, Brocklehurst JE.** Prazosin in hypertension: clinical studies with special reference to initiation of therapy. Med J Aust 1977; (Special Suppl)2:33–37.

Data on file, Pfizer Laboratories Division, New York, NY.

**Smith IS, Fernandes M, Kim KE, et al.** A three-phase clinical evaluation of prazosin. Prazosin Clinical Symposium. Postgrad Med 1975.

**Fernandes M, Smith IS, Weder A, Kim KE, Gould AB, Busby P, Swartz C, Onesti G.** Prazosin in the treatment of hypertension. Clin Sci Mol Med 1975;48:181s.

**Adriaensen H, Vryens R.** Clinical trials: prazosin in the treatment of hypertension. The Practitioner 1975;214:268–273.

**Bolli P, Simpson FO.** Experience with prazosin in the treatment of hypertension. Prazosin Clinical Symposium. Postgrad Med Spec. No., Nov 1975, 69–76.

**Stokes GS, Graham RM, Gain JM, Davis PR.** Influence of dosage and dietary sodium on the first-dose effects of prazosin. Br Med J 1977;1:1507–1509.

**Ulvila JM, Kennedy JA, Lamberg JD, Scribner BH.** Blood pressure in chronic renal failure. JAMA 1972;220:233.

**Hua ASP, MacDonald IM, Myers JB, Kincaid-Smith P.** Studies with prazosin—a new effective hypotensive agent. I. Clinical study of prazosin in combination with other antihypertensive agents. II. Two double-blind crossover studies comparing the effects of prazosin and hydralazine. Med J Aust 1976;1:559–561.

**Kincaid-Smith P, Fang P, Laver MC.** A new look at the treatment of severe hypertension. Clin Sci Mol Med 1973;45:75s–85s.

**Kincaid-Smith P.** The treatment of resistant hypertension. Drugs 1976; 11(Suppl 1):78–86.

**Leslie BR, Laragh JH.** Hypertension in chronic renal disease. Cardiovasc Rev Rep 1982;3:149.

**Lewis PJ, Petrie A, Kohner EM, Dollery CT.** Deterioration of glucose tolerance in hypertensive patients on prolonged diuretic treatment. Lancet 1976;1:564–566.

**Grimm RH Jr, Leon AS, Hunninghake DB, Lenz K, Hannan P, Blackburn H.** Effects of thiazide diuretics on plasma lipids and lipoproteins in mildly hypertensive patients. Ann Intern Med 1981;94:7–11.

**Ames RP, Hill P.** Antihypertensive therapy and the risk of coronary heart disease. J Cardiovasc Pharmacol 1982;4(Suppl 2):S206–S212.

**England JDF, Simmons LA, Gibson JC.** The effect of metoprolol and atenolol on plasma high density lipoprotein levels in man. Clin Exper Pharmacol Physiol 1980;7:329–333.

**Hjermann I, Velve Byre K, Holme I, Leren P.** Effect of diet and smoking intervention on the incidence of coronary heart disease: report from the Oslo study group of a randomized trial in healthy men. Lancet 1981;2: 1303–1310.

Multiple Risk Factor Intervention Trial Research Group. Multiple risk factor intervention trial. Risk factors changes and mortality result. JAMA 1982; 248:1465–1477.

**Lipson LG, Moore D, Pope AM, Todd FJ, Avilla SM.** Sexual dysfunction in hypertensive diabetic men. J Cardiovasc Med 1981;(Special Suppl).

# Treating the Patient With Mild Hypertension And Renal Insufficiency

J. CAULIE GUNNELLS, Jr., MD

**The Hypertension Detection and Follow-up Program (HDFP) first demonstrated that treatment of patients with mild hypertension (90 to 104 mm Hg diastolic) could reduce morbidity and mortality in coronary heart disease (CHD). Previous studies had already shown the beneficial effect of blood pressure reduction on renal disease, heart failure, and cerebrovascular disease. When uncontrolled, mild hypertension in the patient with renal disease will lead to further deterioration of renal function. To prevent this and other complications (such as atherosclerosis) of hypertension, whether primary or secondary, one should place these patients on antihypertensive therapy. However, standard stepped-care therapy with diuretic drugs and beta-blocking agents is now under reevaluation in view of the potential adverse effect of these agents on serum lipid and renal function. Beta-blocking drugs, further more, tend to increase peripheral resistance, a he modynamic effect opposite to that desired in thes patients. Other drugs, acting centrally or peripherall on the nervous system, also have some undesirabl features in addition to troublesome side effects Prazosin, a vasodilator and effective antihyperten sive agent with a different mechanism of action, ha no adverse action on lipids and renal functior lowers peripheral resistance, and does not caus many of the side effects that limit use of the othe drugs. It therefore appears to be a good choice fo initial therapy in mild to moderate hypertension wit associated renal insufficiency.**

The proposition that lowering high blood pressure could reduce cardiovascular morbidity and mortality was clearly demonstrated for the first time by the Veterans Administration Study.[1] Conducted over 10 years ago, this study definitely showed that antihypertensive drug therapy could prevent complications of hypertension such as hemorrhagic stroke, renal failure, left ventricular failure, and aortic dissection. However, it failed to demonstrate any significant benefit in preventing the so-called atherosclerotic complications of hypertension, including coronary heart disease (CHD).

On the basis of that study, general guidelines regarding indications for therapy in hypertensive patients (Table I) were established. Patients with severe hypertension (diastolic blood pressure ≥120 mm Hg) required immediate evaluation and treatment. Treatment was also indicated for patients whose diastolic blood pressure fell within the range of 105 to 119 mm Hg.

From these beginnings, the concept of "stepped care" for the treatment of high blood pressure also evolved (Fig. 1). This approach, which usually calls for sodium restriction and a diuretic agent as the first step, followed by stronger measures if necessary, has been effective in bringing the blood pressure of moderate to severe hypertensive patients under control.

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However, the Veterans Administration Study faile to address clearly the problem of the patient with mil hypertension (diastolic pressure in the range of 90 to 10 mm Hg). An important question has been whether o not the physician should institute antihypertensiv treatment in such patients and, if so, what drug an under what regimen.[2] A secondary issue may be th implication of what such a treatment, or lack of it, woul hold for the patient with renal insufficiency.

In late 1979 and early 1980, the Hypertension De tection and Follow-up Program (HDFP)[3] addresse some of these questions by studying approximatel 11,000 patients with diastolic blood pressure levels o 90 to 104 mm Hg. For the first time the study demon strated the effectiveness of treating mild hypertensior Reducing blood pressure by only 10 mm Hg was foun to be beneficial in decreasing the CHD mortality rat in this group.

The vast majority (70%) of all hypertensive patient in the United States have mild hypertension, well withi the range of 90 to 105 mm Hg (Fig. 2). Thus, if we accep the recommendation to treat mild hypertension, w automatically create an enormous number of patient who must undergo drug therapy.

We must ask whether the benefit relative to the ris involved in treating these patients is really worth it, a issue previously addressed by Freis[2] and brought int sharper focus along with other questions in certain se lect patients as reported in the Multiple Risk Facto Intervention Trial (MRFIT).[4] The overall benefit o previous antihypertensive drug regimens (that i

**TABLE I Recommended Action for Sustained Elevations of Diastolic Blood Pressure**

| | |
|---|---|
| 120 mm Hg or higher | Immediate evaluation and treatment indicated |
| 105–119 mm Hg or higher | Treatment indicated |
| 90–104 mm Hg | Individualize treatment according to risk factors |

From the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, 1977.

stepped-care) is clearly established. Very long experience with diuretic drugs has established these agents as the cornerstone of blood pressure therapy. However, with increasing awareness of the long-term biochemical changes produced by them important questions have been raised regarding the possible effects of diuretic therapy on the atherosclerotic potential of hypertension, namely that seen in CHD. Diuretic drugs are known to have potentially serious side effects,[5–8] including a few—such as volume contraction, hypokalemia, alterations in carbohydrate tolerance, elevation of serum lipid and uric acid levels which may be troublesome to patients with renal insufficiency. Beta-blocking drugs also have been reported to adversely affect lipid, glucose, and uric acid concentrations. Furthermore, because patients with renal impairment are susceptible to accelerated atherosclerosis and premature cardiovascular complications, the relation between antihypertensive drugs and their effect on other risk factors for CHD (such as the lipid profile) needs study. Taking into consideration the long-standing success of diuretic and beta-blocking drugs in the hypertensive population, should we reexamine the way in which we initiate therapy, particularly in patients with mild to moderate hypertension with and without renal involvement? It will not do merely to stop treating mild hypertension with drugs. Unfortunately, the disease and its consequences continue to progress in many patients, unless appropriate drug therapy is used.

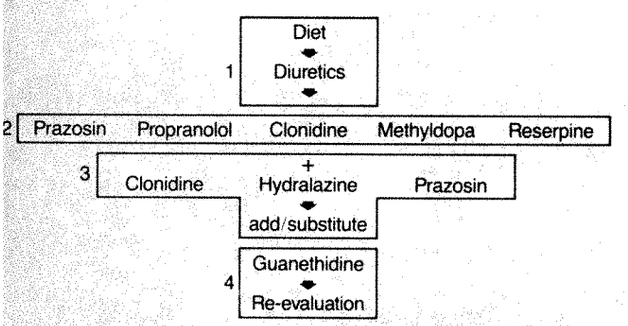



**FIGURE 1.** Stepped-care approach to therapeutic goal. (Modified from the 1980 Report of the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure.)

## Renal Involvement: Primary and Secondary

Renal disease can be both the cause and the result of hypertension.[9] In either case, the aims of treatment for the patient with mild hypertension and renal disease are twofold: (1) protect kidney function, and (2) prevent the complications of high blood pressure, especially atherosclerosis, to which renally impaired patients are prone. This latter aim applies even in patients undergoing dialysis.[10]

The natural progression of untreated primary (essential) hypertension is grim (Fig. 3). One of the major hemodynamic effects in essential hypertension is an early and sustained increase in peripheral vascular resistance, which eventually leads to accelerated atherosclerosis. Sooner or later, this results in target organ damage. Left uncontrolled, hypertension causes irreparable damage to the kidney, leading to end-stage renal disease. The Veterans Administration Study[1] clearly demonstrated that effective treatment of hypertension reduces the incidence, prevalence, and subsequent development of renal insufficiency.

Renal impairment is a definite possibility in patients with mild hypertension. Up to 3% of patients with mild to moderate hypertension (90 to 125 mm Hg diastolic), as reflected by minimal changes in the optic fundi (grades I and II), will show progression to renal insufficiency over a 5- to 7-year period (Table II). With persisting hypertension, about 3 to 5% will show evidence of renal damage. The important point to be made here is that if these patients with mild to moderate hypertension are treated, the progression toward renal insufficiency can be reduced to almost zero.

For patients with grade III fundi (with hemorrhages and exudates) and diastolic pressure ≥125 mm Hg, the situation is worse: 7 to 12% will progress to renal failure in 5 years (Table III). Furthermore, only 10 to 15% will be alive in 10 years. But even in this group, treatment can reduce the progression to renal failure—particularly in those who present with initially normal renal function—to <5% in 5 years.[11] It is now realized that by treating hypertension we protect kidney function and reduce the incidence of renal insufficiency. If we weigh the cost of dialysis against daily intake of medication, the choice becomes even clearer.

We see a slightly different picture with secondary hypertension caused by parenchymal disease (such as glomerulopathies, the tubulointerstitial and infiltrative diseases, and so on ). Table IV lists some causes and mechanisms of parenchymal renal disease with coexistent hypertension. The management of hypertension in these patients, regardless of the cause of the disease, is similar with both primary and secondary hypertension.[9] Ideally, one should be able to treat the underlying primary glomerulopathies and similar diseases, but unfortunately these may progress independently of blood pressure therapy. However, by instituting antihypertensive therapy, we can offer some degree of protection from vascular (especially cerebrovascular) deterioration.[12] This is particularly beneficial in diabetic patients and in patients with renovascular disease. And,

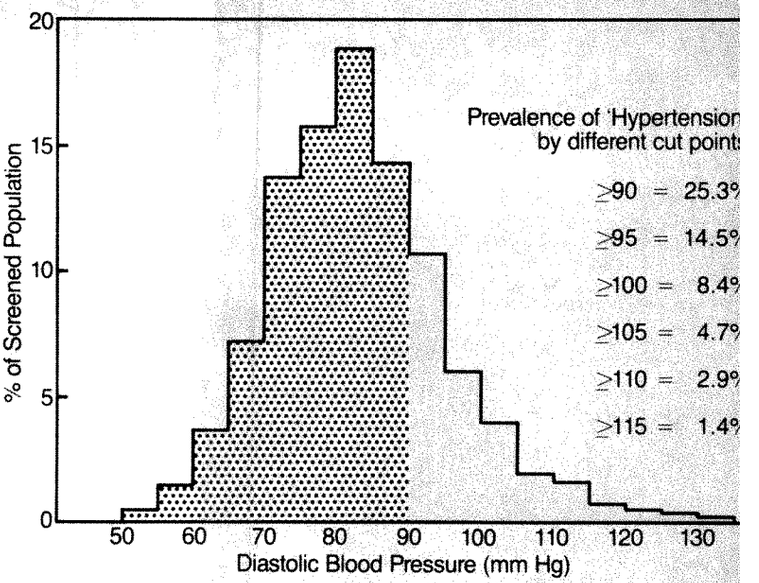



**FIGURE 2.** Frequency of distribution of diastolic blood pressure at home screening of 158,906 persons, 30 to 69 years of age. (Hypertension Detection and Follow-up Program, 1973–1974.) Note that a great majority of those with hypertension (diastolic blood pressure ≥90 mm Hg) have a diastolic blood pressure in the range of 90 to 104 mm Hg (mild hypertension). (From Hunt JC, Cooper T, Frohlich ED, Gifford RW, Kaplan NM, Laragh JH, Maxwell MH, Strong CG (eds). Hypertension Update Mechanism, Epidemiology, Evaluation, Management. From the program Dialogues in Hypertension, Hunt JC (ed). Copyright 1980 Health Learning Systems, Bloomfield, NJ.)

indeed, control of blood pressure will offer some degree of protection of renal function and involvement from primary hypertension.

Management of the patient with renal disease and associated hypertension is similar to treatment of the patient with primary hypertension and secondary renal involvement, with 1 exception. In the former group, we seek to treat the underlying disease (if a treatment is available) in order to stop the particular abnormality from progressing (Table V). Good control of blood pressure, however, is a must. In patients whose kidneys are deficient in their ability to excrete salt and water, we would first reduce salt intake and institute appro priate diuretic therapy. The great majority of thes patients with significant renal impairment will usuall require a potent loop diuretic drug such as furosemid which affects renal function only minimally.

In patients with renal disease, cholesterol ratios ar often unfavorably balanced in the direction of athero genic fractions. The plasma concentration of hig density lipoprotein (HDL) cholesterol, which correlate inversely with coronary risk (the lower the concentra tion, the greater the risk), is low in these patients.[13,1 Thus the ratio of antiatherogenic HDL cholesterol t

**TABLE II Natural History and Results of Treatment in Mild to Moderate Primary Hypertension**

| |
|---|
| Grades I and II fundi, mild to moderate hypertension (90 to 125 mm Hg diastolic): |
| Only 1.5 to 3% of these patients will show progression to renal insufficiency in 5 to 7 years. |
| About 3.0 to 5.0% will progress to renal failure in 15 to 20 years but up to 10% will show evidence of renal damage. |
| Treatment reduces this to almost zero. |

**TABLE III Natural History and Results of Treatment in Severe Primary Hypertension**

| |
|---|
| Grade III fundi, severe hypertension (≥125 mm Hg diastolic): |
| About 7 to 12% of these patients will progress to renal failure in 5 years. |
| Only 10 to 15% will be alive in 10 years. |
| Treatment reduces the progression to renal failure (in those with initially normal renal function) to <5% in 5 years. |

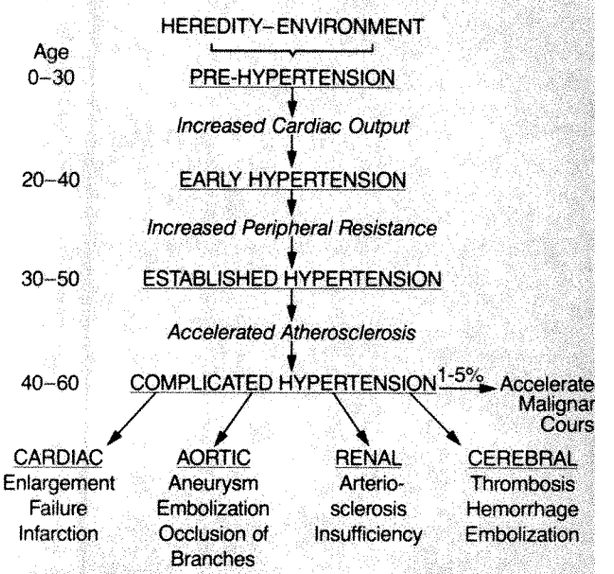



**FIGURE 3.** The natural history of untreated essential hypertension (From Kaplan N, Clinical Hypertension, 2nd ed. Baltimore: William & Wilkins, 1978:87.)

**With Hypertension**

Causes
- Glomerulopathies with or without nephrosclerosis
- Interstitial renal disease
  - Pyelonephritis
  - Obstructive disease
  - Polycystic disease
- Infiltrative renal disease (metabolic)
  - Diabetic—mainly nephrosclerotic
  - Amyloidosis
- Renovascular disease
- Most diseases producing a "pure" nephrotic syndrome and normal renal function do not have hypertension as a prominent feature

Mechanisms
- Salt/volume dependent
- Renin dependent
- Combination

he atherogenic low density lipoprotein (LDL) cholesterol is frequently low, suggesting that clearance of holesterol from the peripheral tissues may be impaired. These patients may also have a defect in the clearance f triglycerides and thus an elevated plasma triglyceride evel, which has also been associated with increased risk or coronary heart disease, although to a lesser degree han LDL.[15] Therefore, because patients with renal isease are susceptible to accelerated atherosclerosis nd to premature cardiovascular complications, therapy hould be aimed at favorably altering the cholesterol atio (or at least not making it worse) and reducing erum triglycerides in addition to reducing blood ressure.

## Criteria for an Ideal Antihypertensive Drug in Patients With Renal Impairment

In the management of hypertension with the aim of verall kidney protection, there are several requirements for an ideal drug.

First, we need an agent that is effective in reducing lood pressure without adversely affecting renal function.

Second, because peripheral vascular resistance is sually increased in patients with renal insufficiency, hile cardiac output remains normal or slightly elevated, we would like to have an agent that reduces peipheral resistance, and has little effect on cardiac utput.

Third, the agent should be effective at all levels of lomerular filtration rate (GFR). In this interest, the oute or mode of excretion should be known and, if ecessary, appropriate dosage adjustments can be ade.

Fourth, the ideal agent should not have adverse rug-drug interactions. So many of today's patients are n multiple drug regimens that it would be wise not to ave the antihypertensive drug interfere with the beneficial effect of another agent, and vice versa. For example, the inadvertent addition of some nonsteroidal nti-inflammatory drugs may bring about a redistribution of renal function in patients with marginal or reduced intravascular volume.[16]

Fifth, a main eventual aim in all these patients is volume expansion control, which leads to a further reduction in blood pressure without adverse effects on renal and cardiac function. The agent should be free from the effects of inappropriate volume expansion which has previously been well demonstrated in classic vasodilators.

Finally, the drug should not adversely affect other risk factors for CHD. Increases in other risk factors are now believed to be a major reason for the lack of impact of blood pressure lowering on CHD mortality and morbidity.

How do the presently available antihypertensive drugs measure up to these criteria?

## Available Antihypertensive Agents

**Diuretic drugs (thiazides):** These agents have proved very effective in lowering high blood pressure, when used either alone or in combination with other therapy. They tend to change peripheral vascular resistance in the right direction, but may decrease cardiac output (through volume contraction) in some patients.

More than any other class of antihypertensive agents, diuretic drugs accomplish the goal of volume expansion control. However, in patients with renal impairment, diuretic drugs may also pose a potentially serious hazard. The physician should be careful not to use these drugs in excess, because undesirable volume contraction and dehydration may result. This, in turn, could lead to further impairment of renal blood flow and glomerular filtration, thus exacerbating the underlying renal insufficiency. In these patients, loop diuretic drugs such as furosemide, which have minimal effect on renal function, are usually preferred.

The main problems with diuretic agents lie in their biochemical side effects, particularly in their adverse actions on serum potassium, lipids, glucose, uric acid, renin, and magnesium. Diuretic use poses a significant risk of spontaneous arrhythmias in patients whose potassium tends to be below or slightly above 3.0 mEq/liter.[17] Without careful laboratory monitoring in the patient with renal disease, routine potassium replacement therapy poses local and systemic hazards as well. McMahon et al[18] has shown that many of the potassium

**TABLE V Management of Chronic Parenchymal Renal Disease Associated With Hypertension**

- Treat the underlying disease
- Good control of blood pressure is a must
- Reduce salt intake
- Use diuretics
  - Thiazides (Metolazone)
  - Furosemide
- Do not volume contract the patient
- Add standard antihypertensives (avoid guanethidine)

chloride substitutes are associated with erosion and symptomatic bleeding lesions in the gastrointestinal tract. Because the patient with renal disease is at equal or greater risk for the development of hyperkalemia, the use of potassium-sparing diuretic drugs (such as spironolactone, triamterene, and amiloride), alone or in combination with other diuretic drugs, should be avoided. Potassium levels should be kept as stable and normal as possible, especially in patients with known coexistent heart disease. Because so many patients are unaware of their silently progressing heart disease, they may be at risk if their potassium balance is disturbed.[19] The prudent physician, in treating the hypertensive patient with renal disease, will take a serum potassium reading before giving diuretic drugs and monitor this important electrolyte often along with continuing observance of any change in GFR.

Diuretic drugs have been shown to have a detrimental effect on blood lipids. Concentrations of the atherogenic low density and very low density lipoproteins (VLDL), as well as total cholesterol and triglycerides, may be altered and add to the risk of coronary heart disease. If therapy will be lifelong, as is often the case, the aggravation of risk factors could cancel any benefit derived from reducing the blood pressure. A 1978 report by Gluck et al[20] reported that chlorthalidone, furosemide, and mefruside increased LDL levels, with mean increases ranging from 8 to 15%. Other studies have shown that some antihypertensive drugs adversely affect blood lipids.[21–24] When choosing diuretics as an antihypertensive agent, these potential adverse effects should be taken into consideration.

**Beta-blocking drugs:** These agents have gained wide acceptance for their ability to control hypertension. However, by blocking the beta receptor in the vasculature, beta-blocking drugs tend to increase peripheral resistance, which is the opposite of the effect one wishes to achieve in the hypertensive patient.[9] Symptomatically, this becomes quite obvious in patients with Raynaud's disease, peripheral vascular occlusive disease, or even in other patients in cold climates. Patients may report cold, painful, or tender feet or hands because of impaired peripheral circulation.

The mechanism by which beta-blocking drugs reduce blood pressure seems to be related to their ability to reduce the release of renin from the kidneys and to significantly lower cardiac output. The reduced cardiac output may present a number of problems (except in patients with a hyperdynamic circulation, in whom such a reduction might be beneficial). For the patient with impaired renal function, decreased cardiac output means reduced kidney perfusion. Thus, renal blood flow, renal plasma flow, and glomerular filtration are reported as adverse effects of some beta-blocking drugs.[25,26]

Beta-blocking drugs share with diuretic agents some of the adverse lipid, glucose, and uric acid effects. Most selective and nonselective beta-blocking agents increase triglycerides or lower HDL cholesterol, or both.[27,28] The Oslo Study,[27] designed to evaluate the long-term drug treatment of uncomplicated mild hypertension in middle-aged men, found that propranolol reduced th antiatherogenic lipid fraction HDL by 13%, raise serum triglycerides by 24%, and worsened the choles terol ratio by 15.2%. A study in Montreal[28] noted tha both metoprolol and propranolol increased the choles terol ratio. These effects may partly explain the con tinuing unchanged incidence and mortality from CHD especially when beta-adrenergic blockade is combine with diuretic drugs.

In addition, beta-adrenergic blockade is contraindi cated in 25 to 30% of patients with hypertension be cause of adverse effects on bronchial asthma, franl heart failure, advanced degrees of heart block, periph eral vascular disease, sinus bradycardia, and insulin dependent diabetes mellitus.[9]

It should be pointed out that beta-blocking drugs ar useful in patients with classic angina pectoris, in thos with a hyperdynamic circulation, in certain types o supraventricular arrhythmias, and as protection afte infarction. Like all nondiuretic agents, beta-blockin drugs cause fluid retention, though not as extensivel as certain vasodilators and central-acting drugs.

**Prazosin:** Contrary to the action of beta-blockin drugs, prazosin, a selective postsynaptic alpha-adren ergic blocking agent, does not increase peripheral vas cular resistance and does not impair peripheral circu lation. In fact, it reduces total peripheral resistance Moreover, prazosin does not adversely affect rena function, and indeed may actually improve it in som patients.[29] These 2 factors make it attractive for use i patients with renal disease.

Prazosin does not have many of the unwanted he modynamic and metabolic side effects of other anti hypertensive drugs. It effectively reduces blood pressur without significantly affecting cardiac output or hear rate. As we have just pointed out, prazosin decrease peripheral vascular resistance. It does not have an ad verse effect on potassium and does not lead to hazardou hypokalemia, nor does it cause elevations in blood glu cose or uric acid, making it suitable for diabetic subject and patients with gout.

Prazosin does not adversely affect the lipid profile which is a critical attribute for patients with renal dis ease. The Oslo Study[27] also compared prazosin witl propranolol and found that prazosin had no adverse effect on blood lipids.

Prazosin may cause fluid retention in some patients but not to the extent of the classic vasodilators (hy dralazine and minoxidil) or the central-acting agent (methyldopa and clonidine). Prazosin makes it possibl to attain control of blood pressure in a significant per centage of the population, even when administered a low doses. There is a less than 1% incidence of syncop when prazosin is administered in a low initial dose ( mg, 2 or 3 times daily).[29] Whether or not a patient wil experience syncope depends both on initial dosage an on volume contraction. Syncope can be avoided in mos cases by using the drug as initial therapy, before diureti drugs are administered.

**Other antihypertensive agents:** Because of trou blesome symptomatic side effects, central- and pe

pheral-acting adrenergic drugs such as methyldopa ıd reserpine are not used as often as they were before ıe advent of beta-blocking drugs. (However, clonidine an exception.) Beta-blocking drugs seemed preferable ecause they did not cause as many or as serious central ervous system effects (dry mouth, depression, sexual ysfunction, and so on). These drugs, especially cloni- ıne, are effective blood pressure lowering agents with otency equal to that of the other agents discussed.[9] hey may be used in patients with normal as well as ıpaired renal function.

The classic vasodilators (hydralazine and minoxidil) roduce a hyperdynamic circulation, with the possibility angina and myocardial infarction in susceptible ersons. Therefore, they require the use of a beta-ad- nergic blocking agent to counter some of these effects. ittle is known about the lipid effects of these vasodi- tors. They also produce significant fluid retention hen used alone. Prazosin, however, although it is also vasodilator, avoids some of these problems simply ecause of its different mechanism of action.

Another type of vasodilator, captopril, acts through ill another mechanism. This agent inhibits the con- erting enzyme that controls the production of angio- nsin II, a potent vasoconstricting agent, thus lowering ıe amount that reaches the peripheral vascular smooth uscle cell. Although captopril does cause peripheral ıscular resistance to decrease, it has led to such renal normalities as proteinturia, decreased renal function, ıe nephrotic syndrome, and membranous glomerulo- ephritis. Therefore, in patients with renal impairment, would seem more appropriate, when possible, to use ı agent such as prazosin that does not adversely affect omerular filtration or renal blood flow.

**Conclusions:** Patients with impaired renal function e particularly susceptible to the ravages of hyper- nsion, even when it is only mild. The 2 primary aims therapy in such patients are to protect their renal ınction and prevent or delay the atherosclerotic pro- ss, which in these patients may already be accelerated. his, in turn, sets 2 main requirements for an ideal an- hypertensive agent in patients with renal insufficiency: should not unfavorably affect the lipid profile, nor rther impair an already inadequate renal function. ldditional criteria to keep in mind are the same as for her hypertensive subgroups.

Of the available drugs, diuretic and beta-blocking ugs fail to meet the basic criteria entirely. Central- ıd peripheral-acting adrenergic drugs also fall short ecause of symptomatic side effects. Due to its lack of lverse effects on lipids and on renal function, only azosin, among the antihypertensive drugs clinically ailable today, seems to fulfill these 2 main require- ents. In addition, prazosin lacks most of the metabolic ıd hemodynamic adverse effects of other antihyper- tensive agents and, therefore, should be considered a logical choice for first-line therapy in patients with mild to moderate hypertension, with or without renal im- pairment.

## References


1. Veterans Administration Cooperative Study Group on Antihypertensive Agents. JAMA 1967;202:1028–1034; JAMA 1970;213:1143–1152; Circulation 1972;45:991–1004.
2. **Freis ED.** Sounding Board: Should mild hypertension be treated? N Engl J Med 1982;307:306–309.
3. Hypertension Detection and Follow-Up Program Cooperative Group. Five-Year Findings of the Hypertension Detection and Follow-Up Program. I. Reduction of mortality in persons with high blood pressure. JAMA 1979; 242:2562–2571.
4. Multiple Risk Factor Intervention Trial. Risk Factor Changes and Mortality Results. JAMA 1982;248:1465–1477.
5. **Sandor FF, Pickens PT, Crallan J.** Variations of plasma potassium concentration during long-term treatment of hypertension with diuretics without potassium supplements. Br Med J 1982;284:711–715.
6. **Murphy MB, Lewis PJ, Kohner E, Schumer B, Dollery CT.** Glucose intolerance in hypertensive patients treated with diuretics: a fourteen-year follow-up. Lancet 1982;2:1293–1295.
7. **Grimm RH Jr, Leon AS, Hunninghake DB, Lenz K, Hannan P, Blackburn H.** Effects of thiazide diuretics on plasma lipids and lipoproteins in mildly hypertensive patients. Ann Intern Med 1981;94:7–11.
8. **Bulpitt CJ.** Serum uric acid in hypertensive patients. Br Heart J 1975;12: 1210–1215.
9. **Gunnells JC, Jr.** The treatment of systemic hypertension. In: The Heart. 5th ed. New York: McGraw-Hill, 1982;1196–1220.
10. **Goldberg DP, Tindira C, Harter HR.** Coronary risk in patients with endstage renal disease: interaction of hypertension with hyperlipidemia. J Cardiovasc Pharmacol 1982;4:Suppl 2:257–261.
11. **Dranov J, Skyler JF, Gunnells JC Jr.** Malignant hypertension. Arch Intern Med 1974;133:791.
12. Five-Year Findings of the Hypertension Detection and Follow-Up Program. III. Reduction in stroke incidence among persons with high blood pressure. JAMA 1982;247:633–638.
13. **Brunzell JD, Albers JJ, Haas LB, Goldberg AP, Agadoa L, Sherrard DJ.** Prevalence of serum lipid abnormalities in chronic hemodialysis. Metabolism 1977;26:903–910.
14. **Bagdade JD, Albers JJ.** Plasma high density lipoprotein concentrations in chronic-dialysis and renal-transplant patients. N Engl J Med 1977;296: 1436–1439.
15. **Goldberg AP, Applebaum-Bowden DM, Bierman EL, Hazzard WR, Haas CB, Sherrard DJ, Bronzell JD, Huttunen JK, Ehnholm C, Nikkila EA.** Increase in lipoprotein lipase during clofibrate treatment of hypertriglyceridemia in patients on hemodialysis. N Engl J Med 1979;301:1073–1076.
16. **Levenson DJ, Simmons CE, Brennan, BM.** Arachidonic acid metabolism, prostaglandin and the kidney. Am J Med 1982;72:354–373.
17. **Holland OB, Nixon JV, Kuhnert LV.** Diuretic-induced ventricular ectopic activity. Am J Med 1981;70:762–768.
18. **McMahon FG.** Management of essential hypertension. Mount Kisco, NY: Futura Publishing, 1978:101–104.
19. **Nordrehaug JD.** Malignant arrhythmias in relation to serum potassium values in patients with an acute myocardial infarction. Acta Med Scand (Suppl 1) 1980;647:101–107.
20. **Glück Z, Baumgarten G, Weidman P, Peheim E, Bachmann C, Mordasini R, Flammer J, Keusch G.** Increased ratio between serum $\beta$ and $\alpha$-lipoproteins during diuretic therapy: an adverse effect? Clin Sci Mol Med 1978;55:325S–328S.
21. **Ames RP, Hill P.** Increase in serum lipids during treatment of hypertension with chlorthalidone. Lancet 1976;1:721–723.
22. **Goldman AI, Steele BW, Schnaper HW, Fitz AE, Frohlich E, Perry HM.** Serum lipoprotein levels during chlorthalidone therapy. JAMA 1980;244: 1691–1695.
23. **Lowenstein J, Neusy AJ.** The biochemical effects of antihypertensive agents and the impact on atherosclerosis. J Cardiovasc Pharmacol 1982;4:Suppl 2:5262–5264.
24. **Ames RP, Hill P.** Antihypertensive therapy and the risk of coronary heart disease. J Cardiovasc Pharmacol 1982;4:Suppl 2:5206–5212.
25. **Bauer JH, Brooks CS.** The long-term effect of propranolol on renal function. Am J Med 1979;66:405–410.
26. **Ibsen H, Sedenberg-Olsen P.** Changes in glomular filtration rate during long-term treatment with propranolol in patients with arterial hypertension. Clin Sci 1973;44:128–134.
27. **Leren P, Helgeland A, Holme I, Foss PO, Hjepman I, Lund-Larsen PG.** Effect of propranolol and prazosin on blood lipids. The Oslo Study. Lancet 1980;2:4–6.
28. **Bielman P, Leduc G.** Effects of metoprolol and propranolol on lipid metabolism. Int J Clin Pharmacol Biopharm 1979;17:378–382.
29. **Colucci WS.** Alpha-adrenergic receptor blockade with prazosin. Ann Intern Med 1982;97:67–77.

# Roundtable Discussion

## Moderator: J. Caulie Gunnells, Jr.

**DR. GUNNELLS:** As moderator, let me address the first question to Dr. Kaplan: One of the aims of this Symposium was to look at initial antihypertensive therapy and examine some of the controversies surrounding the widespread use of diuretics. We also wanted to consider other methods of treatment, and in particular to look at prazosin as a possible alternative as an initial therapeutic agent. Would you care to comment about physicians' patterns in choosing antihypertensive drugs, the rationale behind their choices, and where you think we stand at present in the selection of the initial agent to treat primary hypertension?

**DR. KAPLAN:** We all grew up with the idea that diuretics were effective, that they were the easiest to use, and the least expensive agents. Effectiveness is one point that needs to be reemphasized since it has not been adequately stated. There is little difference, as far as therapeutic effectiveness is concerned, when one looks at careful comparisons between a diuretic in a reasonable daily dosage and any of the other drugs, including reserpine, methyldopa, clonidine, prazosin, and various beta-blocking agents. They all seem to have about the same effect on blood pressure.

In general, therefore, the attitude has been that a single morning dose of a moderate to long-acting diuretic agent would be appropriate for beginning therapy. However, with the hazards and potential problems of diuretic therapy—which we all assume to be partly responsible for the lack of improvement in coronary disease that has been reported in most of the large therapeutic trials—the idea of using alternative drugs seems to have awakened a great deal of interest. I would predict that, in the future, increasing numbers of patients, particularly those with mild hypertension, are going to be treated with one of the alternative drugs.

As to which alternative drug it will be, obviously we are blessed with multiple choices. Many physicians have been using beta-blocking agents. However, I believe we all harbor a certain concern about their negative effects on blood lipids, aside from the fact that probably 25 to 30% of all hypertensive patients have specific contraindications to the use of beta-blockers.

Prazosin has an additional attraction in that it does not appear to adversely affect lipid levels. In addition, it offers a theoretical advantage in that it lowers the total peripheral resistance, whereas beta-blockers increase it, at least initially. Since high peripheral resistance is the hemodynamic hallmark of most essential hypertension, everyone would prefer that it be diminished rather than increased.

Furthermore, in cold climates, many people notice cold extremities and have difficulties with their peripheral circulation while on beta-blocking therapy; that does not appear to be true with the use of prazosin.

Thus, I foresee a continued increase in the use of drugs other than diuretics for initial therapy, and s cifically I see this as a very logical place for the increa use of prazosin.

The possibility of reactive volume retention—wh can happen with any of the nondiuretic drugs and is of the reasons diuretics are often chosen first—ne to be considered. Whenever blood pressure is lower the kidney tends to retain fluid. This makes it import to institute a moderate restriction in dietary sodium the first step in therapy; if drugs need to be used moderate restriction in dietary sodium becomes e more important.

**DR. CUTLER:** I agree with what Dr. Kaplan has j said. My feeling is that some education will be nee to make physicians fully aware that other drugs do have flat response curves like the diuretics, and t need to be titrated to get maximal benefits.

**DR. GUNNELLS:** That's a good point. Diuret have always been easy to use, and we all like to do thi the easiest possible way. However, we have a respon bility, based on an examination of the available da to reeducate ourselves and other physicians. This sho be a thinking process, not a conditioned reflex.

Among the problems that everyone has mentio regarding diuretics, a frequent and difficult proble that of potassium depletion and its sequelae.

**DR. OKUN:** This is a complex issue. Let me go b a step and say that, as we have heard repeatedly, uretics have in the past been the first-line drugs. I, t think this is going to change, and that we will see a cline in the use of diuretics, particularly in view of data Dr. Ames and his co-workers have obtained. Ot studies have added to this disquieting discrepancy results between improvement in cerebrovascular dise and very little, if any, improvement in coronary dise despite blood pressure reduction. I am beginning to f rather strongly that this may be due to a less than id choice of medication.

In the past, one of my choices has often been to foll sodium restriction with the use of diuretics—prima thiazide diuretics. I will have to rethink such an proach very seriously, because the risk-benefit ratio early diuretic therapy has now shifted to the po where such therapy is no longer appropriate for a la number of patients.

One of the problems posed by diuretics is that of tassium disturbance. Much has appeared in the medi literature in the past few years regarding the risks even what was once considered modest hypokalem Some work indicates that there is indeed a signific risk of spontaneous arrhythmias in persons whose tassium levels tend to drop below 3.0 mEq/liter. Havi witnessed some of these spontaneous arrhythmi which do respond to potassium replacement, we n

initiate potassium replacement very early in patients who are beginning diuretic therapy; if they are on a digitalis preparation, we institute administration of potassium immediately. The obvious reason is to avoid potentiating the toxic effects of digitalis. However, we have problems in patient acceptance of potassium supplements. In view of the data generated recently by McMahon and his group at Tulane, it seems that many of the potassium chloride substitutes that we have been using may cause problems in the gastrointestinal tract. We will have to restrict use of some of the potassium chloride preparations, and this makes potassium replacement even more difficult. But replace potassium we must, hopefully to the point of normal total body levels, a measurement that is not available to most clinicians, but can be approximated by a serum potassium determination. The use of drugs such as prazosin will probably make treatment much easier since there is no adverse effect on potassium levels at all.

**DR. COLUCCI:** Cardiologists have always been impressed with the importance of a potassium level that is as stable (that is, free of large fluctuations) and as normal as possible, especially in patients with coronary artery disease. The data from the MRFIT study are relevant in this connection. The increased mortality rate in patients with preexisting electrocardiographic abnormalities who were aggressively treated with diuretics was impressive and reinforces the bias of many cardiologists that it is important to maintain adequate serum and total body potassium levels, especially in patients with preexisting heart disease.

**DR. GUNNELLS:** To summarize, most people would consider potassium depletion with diuretics a potential problem because hypertensive patients have an unknown amount of coronary heart disease, which places them at risk even with minor alterations in potassium levels. The usual physician is more likely than not to give potassium supplements when using diuretic agents. This adds to the expense, to the possibility of compliance problems, and to a need for more frequent laboratory tests in patients with hypertension.

In the MRFIT study, thiazides, propranolol, methyldopa, hydralazine, reserpine, and guanethidine were all used. If one looks at the conclusions on mortality from coronary heart disease, none of these drugs seemed to have much of a beneficial effect. Could it be related to the hemodynamic and metabolic actions of these drugs? Or is there something else in that study that might throw some light on this issue?

**DR. AMES:** I can only speculate in this regard. We just don't know why the patients treated with diuretics and antihypertensive therapy did not do as well as we had anticipated. Although there was an equal number of deaths in the special intervention group and the usual care group, we don't know the details. Were these sudden deaths, or were they deaths of individuals with documented myocardial infarction? This would be important to know, because if they were sudden deaths, without definite evidence of coronary disease or myocardial infarction, they might have an electrical origin rather than being due to the build-up of atherosclerotic plaque. We need more information. The changes in lipids that may have occurred during therapy have not been looked at in great detail either, so that also remains speculative. I do know that at the 4-year interval, patients in the MRFIT trial who received antihypertensive therapy, specifically diuretic therapy, did not show as large a decrease in total cholesterol or triglycerides as the patients who had not received diuretic treatment. Diuretics thus appeared to counter the reduction in cholesterol that had been anticipated. The failure of cholesterol to decrease as much as expected in the hypertensive SI group could have lessened the mortality differential in comparison with the hypertensive UC group. Still, the hypertensive SI group had, in absolute terms, both lower blood pressure and lower total cholesterol than the hypertensive UC group throughout the program. The lipid hypothesis, therefore, does not seem to explain fully the failure of SI men to do better. Perhaps differences between SI and UC men in glucose tolerance or frank diabetes related to high-dose diuretic therapy could contribute to mechanisms causing the unexpected equivalence of CHD mortality in hypertensive SI and UC men. These suggestions are interesting but remain speculative. More detailed analyses of the MRFIT data are needed.

**DR. GUNNELLS:** We have talked a great deal about lipids this afternoon. This could be an important factor in connection with the problem of coronary heart disease and atherosclerosis in all hypertensives. If we're going to embark upon drug treatment, how much of a problem are the lipid effects of diuretics and beta-blockers, and how does prazosin come out in comparison?

**DR. CUTLER:** This is obviously a controversial area. You can't get 10 physicians together who will agree on that particular point. What we've talked here is taking data that are currently extant or being developed and comparing them with data from the past, namely the Framingham study, for the purpose of risk-factor calculation. The large clinical trials that we've talked about today have given us some food for thought, but they haven't truly answered the question for us. And it's not likely we will have the answers very quickly. All we can suggest at the present time is caution, in view of the correlations that have been established in the past through epidemiologic methodology. The most we can say at this point is that antihypertensive agents that increase cholesterol and perhaps change the fractions in an adverse way by increasing the low density fractions and decreasing the high density ones may have an adverse effect on coronary heart disease. The underlying and conditional word is *may*. We won't know for sure until such studies are done. But in the meantime, as Stamler and others have said, the appropriate and prudent course of treatment is to implement dietary changes and to use drugs that do not have an adverse effect on lipid metabolism. As for a comparison between prazosin and other drugs, prazosin looks better because it doesn't seem to have any adverse effects on lipids.

Diuretics seem to be more consistent in producing adverse effects that we believe may be atherogenic.

**DR. GUNNELLS:** Another important issue is that we seem to be in an exercise-oriented society. I'm constantly dodging joggers and bicycle riders on my way to the hospital. The use of drugs, specifically the beta-blockers, as first-line therapy in the physically active patient may be limiting. These agents have been advocated for the younger hypertensive patient. In these patients, the effect of the beta-blocker on the ability to exercise can often be an important side effect.

**DR. COLUCCI:** Clearly, beta-blockers have multiple effects on the blood pressure, and the overall result is a combination of these effects. As I mentioned very briefly during my presentation, the beta-receptor in the vasculature, although frequently overlooked, is an important receptor. When it's blocked, the total peripheral resistance increases. This becomes clinically obvious when one treats a patient with Raynaud's disease or peripheral vascular occlusive disease, or just living in a cold climate. So we know that beta-blockers have an effect on total peripheral resistance that is the opposite of what we would want for an antihypertensive agent. One of the mechanisms by which beta-blockers lower blood pressure is through their reduction of renin release. They also tend to have effects on the heart. Cardiac output is diminished, and this may also contribute to their antihypertensive effect. In addition, beta-blockers seem to have a central effect, perhaps by reducing central sympathetic outflow. There may be other mechanisms, but it is somewhat paradoxical that beta-blockers were the first of the selective adrenergic antagonists to be used in hypertension, inasmuch as they do not seem to improve the main underlying problem in most primary hypertension, which is increased total peripheral resistance. The ability to exercise maximally is clearly decreased by beta-blockers. In part this is because the maximal heart rate is frequently lower, and therefore the maximal cardiac work that can be done is less. Beta-blockers may result in generalized fatigue, which may be related to this decrease in cardiac output.

**DR. OKUN:** Our experience actually goes a little beyond that. Many youngsters who had been placed on beta-blockers for borderline or very mild hypertension have come to us later for other therapy because they found they couldn't exercise even to less than maximal capacity—jogging, tennis, and so on. They found themselves in difficult straits. Some animal data indicate that propranolol in particular will strikingly decrease skeletal muscle blood flow. This may be another mechanism for the easy fatigability.

**DR. GUNNELLS:** I'd like to set forth some of the features we might all agree are useful or favorable in an antihypertensive agent and see how they fit prazosin, the diuretics, and the beta-blockers. First is effectiveness. From what we've heard here, most antihypertensive drugs have equal effectiveness. In equipotent doses, prazosin is as effective as a diuretic or a beta-blocking agent in reducing blood pressure. Second, we should look at hemodynamics and side effects: Prazosin's hemodynamic profile is a rational, reasonable, and appropriate one, relative to the underlying defect in primary hypertension, namely increased peripheral vascular resistance. Prazosin is free from the biochemical side effects that most of us have raised questions about. On the other hand, concern has been expressed about the hypokalemia induced by diuretics. Patients on prazosin do not have to worry about lowered serum potassium or increased uric acid levels. Equally important, prazosin does not appear to have any adverse effects on lipid metabolism. Another favorable feature of prazosin is its low incidence of sexual dysfunction, although some has been reported.

Having said all that, I would then conclude that prazosin, as compared with diuretics and beta blockers, is an appropriate agent for consideration as initial therapy in mild or moderate hypertension.

**DR. OKUN:** I agree with you, and I have 2 comments to make. First, I feel very strongly that correction of the pathophysiology of essential hypertension, normalization of the increased peripheral resistance, is a major benefit of prazosin and one that exists without any major counterbalancing effects in other areas. I have not seen this with any of the other drugs. That, to me, is a very positive aspect of prazosin. Second, I also feel very strongly about using prazosin more as initial therapy, along with a sodium-restricted diet. I think prazosin will be highly successful in controlling blood pressure in a great many patients without worsening risks—the other edge of the sword, so to speak.

**DR. COLUCCI:** As Dr. Kaplan pointed out, given the choice of a number of drugs which have the same endpoint, namely the lowering of hypertension, the onus is now on the physician to choose the drug that will be safest in the long run. I certainly would be careful in my choice of agent. Clearly, of the agents currently available prazosin is the most specific in terms of pathophysiologic effects. Selective alpha blockade makes more sense than beta blockade or other more generalized methods of adrenergic suppression.

A question usually arises about prazosin in regard to orthostatic hypotension and syncope. The overall incidence of syncope with the first dose of prazosin is about 0.1 to 0.2%, if one looks at a large series of patients and totals up the results. The incidence in any particular study will depend on a lot of factors. One of the factors identified as important was the dose of the drug used during the first administration. It is recommended that therapy be initiated with a 1 mg dose.

Another important factor in determining whether a patient will have a syncopal or orthostatic reaction to the first dose is volume status. Patients who are volume contracted, whether because of diuresis or other reasons, are much more sensitive. This is presumably due to a lower initial venous filling pressure in these patients. The venous dilatation effects of prazosin then may result in a further decrease in preload.

In the hypertensive patient without heart failure, when diuretics are withheld, syncope is rare. In one

ificant orthostatic symptoms after the first adminis-ation of a 2-mg dose of prazosin. When these patients ere withdrawn from prazosin for three weeks, then challenged with a lower dose (1 mg), none had severe mptoms, and only 2 had mild dizziness. Therefore, icking a low dose and avoiding diuresis are probably ie 2 major things the physician can do to prevent this roblem. In practice, good recommendations are to start ith a low dose of 1 mg preferably at bed time when the atient can remain supine. If the patient is receiving iuretics, withhold the diuretics for 1 or 2 days, to allow ie intravascular volume to reequilibrate. Diuretics can ien be readministered. That raises an interesting uestion: If prazosin were to be used as first-line ther-py, before diuretics, would we see the same incidence f syncope as when the drug is used as a Step 2 therapy? speculate that we would not, and therefore this would e another good reason to consider prazosin as initial ierapy before diuretics.

**DR. GUNNELLS:** With diuretic agents we still have ie problem of potassium depletion and other effects ot associated with prazosin. Among the antihyper-ensive drugs for which data are available, the treatment rofile of prazosin—side effects and therapeutic effec-veness—is extremely favorable. Therefore, prazosin a very reasonable and rational drug as initial therapy or hypertension. I think it is fair to say there is general greement on this among the panel members, and we ll agree it is appropriate that we reexamined past ractices and began to ask ourselves questions instead f just prescribing as a reflex.

**DR. CUTLER:** We've talked a lot about step ther-py, but we should place it in perspective. It was very good way to approach hypertension. The initial thrust in step care was provided by Wilkins many years ago with the advent of diuretics, reserpine, and vasodilators. We have now reached the point where the menu of therapeutic agents is quite large, and as when we visit a favorite restaurant, we probably need to pick and choose more appropriately, depending on the patient and the problem at hand. We can no longer deal simply with starting here and advancing to there, but rather we need to think of the clinical pharmacologic features of each agent, and use it as appropriately as we can in treating a particular patient.

**DR. GUNNELLS:** To summarize, we're not debating whether patients with mild hypertension should be treated with drug therapy, but rather what is the best way to treat them when drug therapy is chosen—how to provide the greatest benefit with the lowest risk. However, in discussing a new concept of therapy that provides an alternative to the traditional diuretic approach to initial therapy, a great deal of data are required on each specific agent. We have discussed the efficacy, hemodynamic profile, side effect profile, and effect on other risk factors for coronary heart disease (such as blood lipid levels) for at least 1 nondiuretic antihypertensive agent, namely prazosin, and it appears to fit a profile of an appropriate agent for the initial treatment of hypertension.

If we are to make significant inroads into populations with hypertension, we cannot wait until they reach the point of target organ damage or of severe degrees of blood pressure, which will require more intensive and complicated therapy with greater likelihood of side effects and less than ideal control.

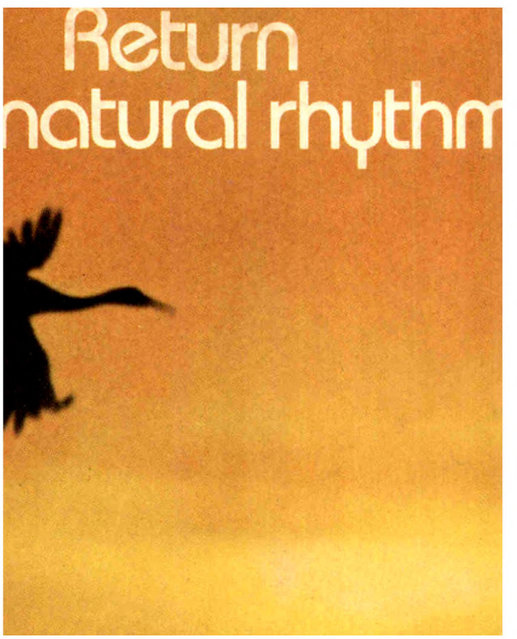
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prolonged administration of procainamide often leads to the develop- of a positive antinuclear antibody (ANA) test with or without symp- of lupus erythematosus-like syndrome. If a positive ANA titer lops, the benefit/risk ratio related to continued procainamide therapy ld be assessed. This may necessitate consideration of alternative rrhythmic therapy.

**ITIONS AND USAGE:** Oral procainamide is indicated in the treatment nature ventricular contractions and ventricular tachycardia, atrial fibril- and paroxysmal atrial tachycardia.

**RAINDICATIONS:** It has been suggested that procainamide be contra- ed in patients with myasthenia gravis. Hypersensitivity to the drug is an e contraindication; in this connection, cross-sensitivity to procaine and drugs must be borne in mind. Procainamide should not be adminis- patients with complete atrioventricular heart block. Procainamide is ntraindicated in cases of second-degree and third-degree A-V block an electrical pacemaker is operative.

**AUTIONS: General** —During administration of the drug, evidence of rd myocardial responses should be carefully watched for in all s. In the presence of an abnormal myocardium, procainamide may at roduce untoward responses. In atrial fibrillation or flutter, the ventricu- may increase suddenly as the atrial rate is slowed. Adequate digitali- educes, but does not abolish, this danger. If myocardial damage ventricular tachysystole is particularly hazardous. Correction of atrial on, with resultant forceful contractions of the atrium, may cause a dis- ent of mural thrombi and produce an embolic episode. However, it has uggested that in a patient who is already discharging emboli, pro- ide is more likely to stop than to aggravate the process.

npts to adjust the heart rate in a patient who has developed ventricular ardia during an occlusive coronary episode should be carried out with e caution. Caution is also required in marked disturbances of atrioven- conduction such as A-V block, bundle branch block, or severe digi- oxication, where the use of procainamide may result in additional sion of conduction and ventricular asystole or fibrillation.

use patients with severe organic heart disease and ventricular tachy- may also have complete heart block, which is difficult to diagnose hese circumstances, this complication should always be kept in mind eating ventricular arrhythmias with procainamide. If the ventricular rate ficantly slowed by procainamide without attainment of regular atrioven- conduction, the drug should be stopped and the patient reevaluated systole may result under these circumstances.

tients receiving normal dosage, but who have both liver and kidney e, symptoms of overdosage (principally ventricular tachycardia and hypotension) may occur due to drug accumulation.

nces of a syndrome resembling lupus erythematosus have been d in connection with maintenance procainamide therapy. The mecha- this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain mmon symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural , and pericarditis may occur. Rare cases of thrombocytopenia or s-positive hemolytic anemia have been reported which may be related syndrome.

**tory Tests**—Patients receiving procainamide for extended periods of in whom symptoms suggestive of a lupus-like reaction appear, should ntinuclear antibody titers measured at regular intervals. The drug be discontinued if there is a rising titer (antinuclear antibody) or clinical ms of LE appear. The LE syndrome may be reversible upon discontin- of the drug. If discontinuation of the drug does not cause remission of mptoms, steroid therapy may be effective. If the syndrome develops in nt with recurrent life-threatening arrhythmias not controllable by other ythmic agents, steroid suppressive therapy may be used concomi- ith procainamide. It is recommended that tests for lupus erythema- e carried out at regular intervals in patients receiving maintenance namide therapy.

ine blood counts are advisable during maintenance procainamide .

**RSE REACTIONS:** Agranulocytosis has occasionally followed the d use of the drug, and deaths have occurred. Therefore, routine blood are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS).

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

**DOSAGE AND ADMINISTRATION:** Procan SR (procainamide hydrochloride) tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every-three-hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

**Ventricular tachycardia**—Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dose of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three-hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six-hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

**Atrial fibrillation and paroxysmal atrial tachycardia**—Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dose of 0.5 to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

**HOW SUPPLIED:** Procan SR 250 mg (green, film-coated tablet, P-D 202) is available in bottles of 100 (N 0071-0202-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0202-40). Each sustained-release tablet contains 250 mg procainamide hydrochloride.

Procan SR 500 mg (yellow, scored, film-coated tablet, P-D 204) is available in bottles of 100 (N 0071-0204-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0204-40). Each sustained-release tablet contains 500 mg procainamide hydrochloride.

Procan SR 750 mg (orange, scored, film-coated tablet, P-D 205) is available in bottles of 100 (N 0071-0205-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0205-40). Each sustained-release tablet contains 750 mg procainamide hydrochloride.

**Storage—Protect from moisture. Store bottles below 86° F (30° C). Store unit-dose packages at controlled room temperature, 59°-86° F (15°-30° C).**

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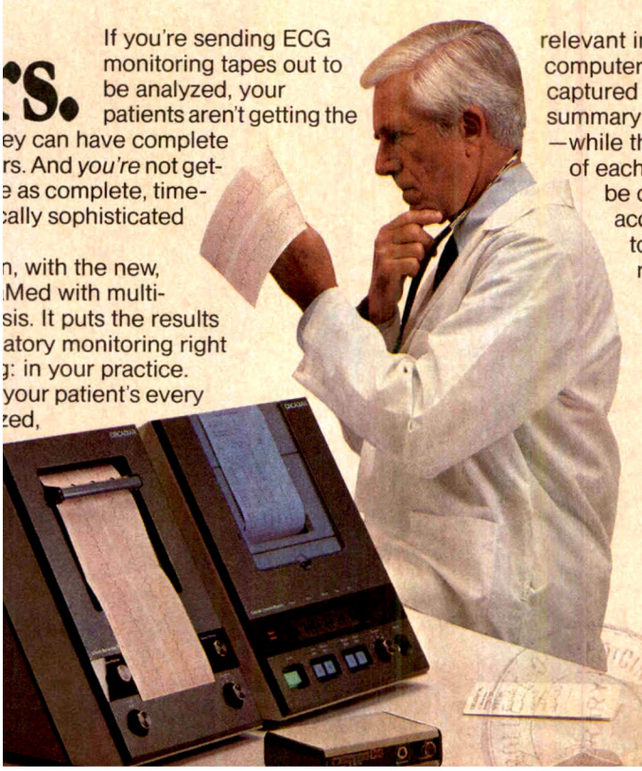


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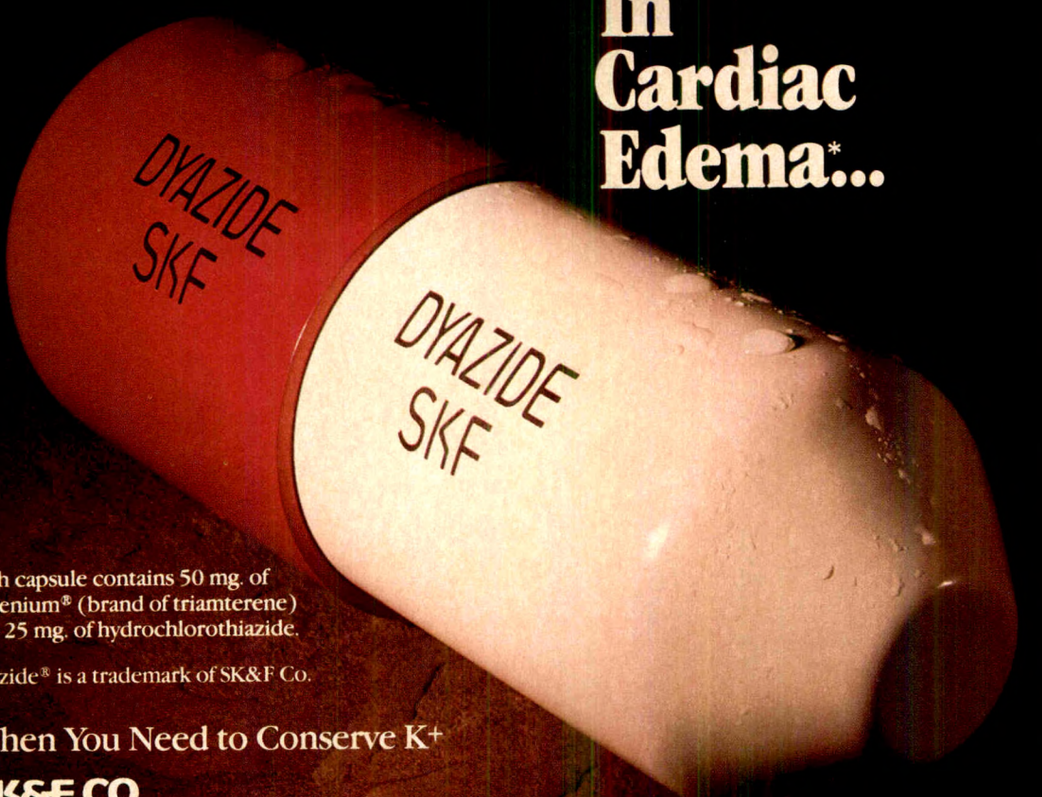
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## Serum K+ and BUN should be checked periodically (see Warnings).

**Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary:**

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

**Contraindications:** Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

**Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum $K^+$ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict $K^+$ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

**Precautions:** Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

**Adverse Reactions:** Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

**Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak® unit-of-use bottles of 100.**

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# Cordis Sequicor Technical Information.

## Sequicor, Model 233D Programmable Parameters

| | |
|---|---|
| Modes | DDD, DVI, DAD, VDD, VAT, VVI, DOO, VOO |
| Minimum Pacing Rate, (Interval) | 50 (1200), 60 (1000), 70 (857), 80 (750) |
| Maximum Pacing Rate (Interval) | 100 (600), 130 (461), 160 (375), 180 (333) |
| Atrial Sensitivity, (mV) | 0.8, 1.5, 7.0, OFF |
| Ventricular Sensitivity, (mV) | 0.8, 1.5, 2.5, OFF |
| Atrial Output Pulse Duration, (ms) | OFF, 0.5, 1.0, 1.5, |
| Ventricular Output Pulse Duration, (ms) | 0.5, 1.0, 1.5, 2.0, |
| A/V Delay (ms) | 80, 120, 165, 250 |
| Atrial Tachycardia Response | Fall Back, 2:1 Block |
| Fall Back Rate (Interval) | 55 (1.090), 65 (932), 75 (800), 85 (706) |

## Sequicor Refractory Periods

| Atrial Tachycardia Response | Maximum Rate | Total Atrial Refractory | Total Ventricular Refractory | A/V Programmed Delay | Total Atrial Refractory Following the Ventricle Pulse |
|---|---|---|---|---|---|
| 2:1 Block | 100 ppm | 600 ms | 302 ms | 80 ms | 520 ms |
| | | | | 120 | 480 |
| | | | | 165 | 435 |
| | | | | 250 | 350 |
| | 130 ppm | 461 ms | 302 ms | 80 ms | 381 ms |
| | | | | 120 | 341 |
| | | | | 165 | 296 |
| | | | | 250 | 211 |
| | 160 ppm | 375 ms | 302 ms | 80 ms | 295 ms |
| | | | | 120 | 255 |
| | | | | 165 | 210 |
| | | | | 250 | 125 |
| | 180 ppm | 333 ms | 302 ms | 80 ms | 253 ms |
| | | | | 120 | 213 |
| | | | | 165 | 168 |
| | | | | 250 | 83 |
| Any Fall Back Rate | Any Maximum Rate | 305 ms | 302 ms | 80 ms | 225 ms |
| | | | | 120 | 185 |
| | | | | 165 | 140 |
| | | | | 250 | 55 |

## Important Information — Sequicor, Models 233D and 233E

**Indications and Contraindications**
The medical literature describes currently accepted indications for various pacing modes. The physician's clinical experience and judgment must ultimately be the guide in selecting the pacing mode best suited to the patient's needs. *The physician should be thoroughly familiar with the pacing mode chosen.*

Pacing of the ventricles (VVI) is indicated for control of heart rate in patients with A-V block or sick sinus syndrome. *Asynchronous pacing is contraindicated when inherent activity is present or is likely to be present in the chamber being paced.* There are no other known contraindications for ventricular pacing to control heart rate.

Atrial-synchronized ventricular pacing (VDD) is indicated for permanent or intermittent complete heart block with normal atrial rhythm. A-V sequential (DVI) pacing is indicated for permanent sinus bradycardia with or without heart block. Automatic dual-chamber demand pacing (DDD) is indicated when there is an A-V conduction disturbance and/or sinus mode dysfunction (sinus bradycardia with A-V block or bradytachy syndrome). These atrial pacing modes are intended for patients who would benefit from the restoration of atrial contribution to cardiac output.

*Atrial-synchronized ventricular pacing and automatic dual-chamber demand pacing modes are contraindicated for use in the presence of persistent atrial flutter or atrial fibrillation.* VVI mode is recommended for these conditions.

**Precautions**
Cordis Sequicor pacers may respond to programmers of other manufacturers. Because of the unknown nature of such response, use only the Cordis Omnicor Programmer, Model 222C (with the 222C-8 control panel card), the Cordis Programmer III, Model 225A or the Cordis Interactive Programmer, Model 256A for reprogramming.

**Warnings**
None

**Adverse Effects**
The following list includes a number of complications related to pacer therapy that have been reported in the medical literature. Noninvasive techniques for assessing and managing such complications are available to the physician. Malfunctions occur randomly and may occur at any time after implant. Complications associated with pacer therapy are listed below.

*Pacer*—battery depletion, component malfunction, electromagnetic interference, decreased sensitivity.

*Lead*—unsatisfactory electrode position, fracture, displacement, penetration/perforation of heart wall, faulty connection with pacer.

*Patient*—reaction, infection/erosion, increase in stimulation threshold.

Before implantation, refer to pacer Instructions for Use supplied with the pacer.

**Caution:** Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

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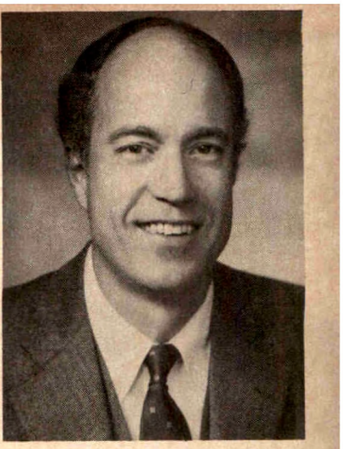
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# Author-Editor-Reviewer: How the Triumvirate Is Working at the AJC

An author submitting a manuscript to be considered for publication in a medical journal deserves to know how the manuscript will be evaluated by that journal. This piece describes the process as it now works at the AJC.

**Early decision by editor only or thorough evaluation by out-of-office reviewers:** Once logged and given a number, each manuscript is given to the Editor-in-Chief, who asks 4 basic questions as he reads it: (1) Is the subject of the manuscript appropriate at this time for the AJC? (2) Would the manuscript have wide or narrow appeal to the readers of the Journal? (3) Does the manuscript represent scientific quality? (4) Is the subject of the manuscript presented clearly and succinctly?

If the manuscript is considered inappropriate for the Journal, of insufficient interest to its readers, of obviously poor scientific quality, or poorly presented, it is returned immediately to the author with a statement that it is unacceptable for publication in the AJC. For manuscripts rejected solely on the basis of poor presentation, a request for reconsideration might be granted provided the manuscript is thoroughly revised. During my 9-month tenure as Editor, about 10% of submitted manuscripts have fallen into this immediate-reject category. This prompt decision allows the author to send his manuscript elsewhere or revise it without delay. Furthermore, it prevents having reviewers provide reviews simply to justify an editor's decision that already had been made. Although such an early decision by the editor may not engender friendship from the submitting author, it conserves the time and energy of all parties involved.

About 5% of manuscripts submitted are reviewed solely by the Editor; a rare one is accepted virtually without change, and his suggestions for improving the other manuscripts are returned to the authors immediately. If appropriate changes are made or if appropriate explanations are provided as to why changes were not made, the revised manuscript is accepted.

The remaining approximately 85% of manuscripts are sent out of office to be reviewed by 2 or more editorial board members or nonboard consultants. Some manuscripts, particularly potentially controversial ones, may be sent immediately to 3 rather than 2 reviewers.

**Selection of reviewers:** A major editorial decision in the manuscript-evaluation process is the selection of the most appropriate reviewers. Many submitting authors now participate in this decision (see the From-the-Editor column, July 1982, page A3), but the final selection is made by the Editor. When submitting authors request that their manuscript not be reviewed by a particular consultant or editorial board member or group of investigators, this request is honored by the Editor. If authors suggest 1 or more nonbiased, nonlocal reviewers for their manuscript, usually 1 author-suggested reviewer and 1 editor-selected reviewer are chosen. The Editor, of course, seeks the most objective reviewers, recognizing that this selection can predetermine the final decision regarding a manuscript.

**Evaluation of reviews by the Editor:** After reviews are returned to the Editor, the manuscript is reevaluated in light of the criticisms and recommendations of the reviewers. When both reviews are favorable, the Editor's decision is usually simple. When both reviews are negative, the Editor's decision also is usually easy. In these 2 situations the Editor's initial reaction to the manuscript is usually compatible with the reviewer's recommendations.

When 1 reviewer's recommendation is unequivocal rejection and that of the other is unequivocal acceptance, the manuscript is often sent out for a third review. Many times, however, the third reviewer is not necessary. One of the 2 reviewers may have made a far stronger case for his point of view than the other reviewer, or the Editor may feel comfortable with the subject of the manuscript and therefore can make the decision without the delay produced by seeking another out-of-office opinion. When 1 of 2 reviewers returns a manuscript unreviewed (he may be out of town, sick, or too busy), the Editor must then decide whether to seek another review or to make a decision based on

Continued on page A10

only 1 outside review and his own analysis. This decision generally depends on the quality of the single out-of-office review.

After the manuscript has been returned to the Editor after having been reviewed by 1 or more outside consultants or editorial board members and the decision is made to probably accept the manuscript, the Editor at this stage carefully examines the manuscript to suggest other alterations and to make sure that the authors have adhered to the style of the Journal. If certain changes are to be required in the manuscript for its acceptance, the authors are so informed at this stage. When a manuscript is tentatively accepted, the Editor often makes editorial changes on a xerographic copy of the manuscript containing his initials on the title page so that these changes can be considered for incorporation into the revision by the author. The Editor spends more time on a manuscript at this point than at any other stage, excluding manuscripts accepted without outside review.

**Return of the manuscript and reviews to the author:** When a manuscript is tentatively accepted pending either major or minor revision, the manuscript must be revised appropriately or the suggestions of the reviewers and the Editor must be rebutted appropriately. Authors must be careful not to be offended by criticisms of their manuscripts. Such criticism is provided by both outside reviewers and by the Editor in an attitude of genuine helpfulness. The author should evaluate critical comments carefully before discounting them as inappropriate. The revised manuscript must be retyped and resubmitted. The author also is asked to return the original version of the manuscript containing the Editor's handwritten suggestions.

**Evaluation of the revised manuscript:** The Editor evaluates the revised manuscript in light of the comments of the reviewers and the changes or rebuttals of the authors. If the changes made by the authors are considered appropriate, the manuscript at this stage is accepted without delay. Occasionally, however, the Editor considers the changes by the author inadequate or inappropriate and returns the manuscript for further changes. At times, the revised manuscript is returned to an earlier reviewer for reexamination. When this reexamination by an earlier reviewer is done, the authors usually are so advised when their manuscript was initially returned to them.

**Manuscript to the publisher:** After a final review by the Editor, the manuscript is sent to the publisher for copy editing and printing. Both the Editor and the Publisher have made strenuous efforts to diminish the lag time from acceptance to publication in the AJC. This time period is now *4 months*, and it is my intent to keep this short interval in the future. This means that manuscripts accepted in March 1983 will be scheduled for publication in July 1983.



William C. Roberts, MD
Editor-in-Chief




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**"reduction of the risk of reinfarction and cardiac mortality for many stabilized post-MI patients."**

We at MSD feel it is appropriate to bring you this definition of cardioprotective since it was MSD that brought you the impressive clinical data[1] that documented the cardioprotective benefits of BLOCADREN® (Timolol Maleate, MSD) for many stabilized patients who have survived the acute phase of a myocardial infarction.

[1]The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction, N. Engl. J. Med. 304(14):801-807, April 2, 1981.

BLOCADREN is contraindicated in patients with bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated.

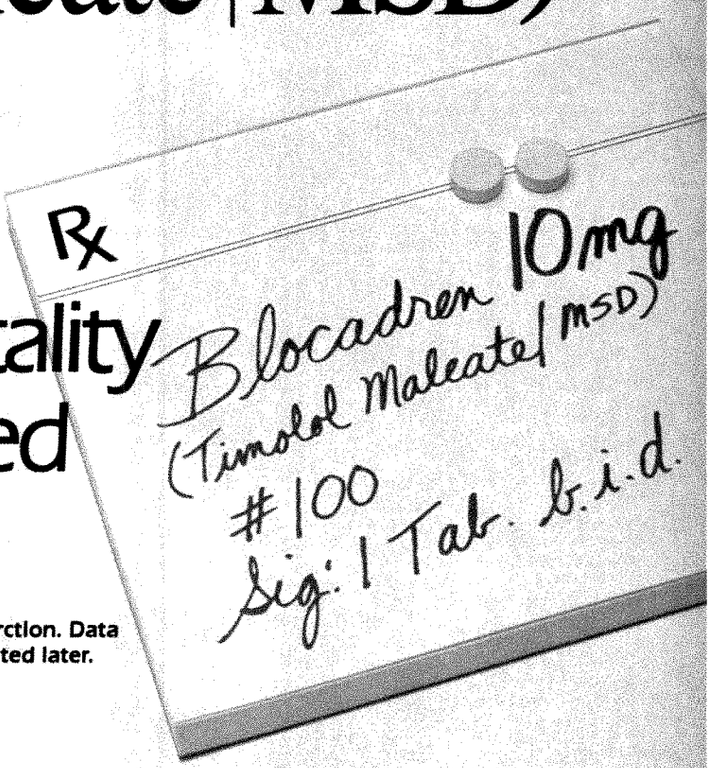
In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.

**Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal**—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after **abrupt** discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart

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**Treatment should be initiated within 1 to 4 weeks after infarction. Data are not available as to whether benefit would ensue if initiated later.**

disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

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For a Brief Summary of Prescribing Information, please see next page of this advertisement.

# BLOCADREN®
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**CONTRAINDICATIONS:**

Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

**WARNINGS:**

*Cardiac Failure*: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

*In Patients without a History of Cardiac Failure*: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

*Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal*—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

*Major Surgery*: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

*Diabetes Mellitus*: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

*Thyrotoxicosis*: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

**PRECAUTIONS:**

*General: Impaired Hepatic or Renal Function*: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

*Dosing in the Presence of Marked Renal Failure*: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

*Drug Interactions*: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

*Carcinogenesis, Mutagenesis, Impairment of Fertility*: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

*Pregnancy—Category C*: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Nursing Mothers*: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

*Pediatric Use*: Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:**

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

| | Timolol Maleate (n=176) % | Placebo (n=168) % |
|---|---|---|
| BODY AS A WHOLE | | |
| fatigue/tiredness | 3.4 | 0.6 |
| headache | 1.7 | 1.8 |
| chest pain | 0.6 | 0 |
| asthenia | 0.6 | 0 |
| CARDIOVASCULAR | | |
| bradycardia | 9.1 | 0 |
| arrhythmia | 1.1 | 0.6 |
| syncope | 0.6 | 0 |
| edema | 0.6 | 1.2 |
| DIGESTIVE | | |
| dyspepsia | 0.6 | 0.6 |
| nausea | 0.6 | 0 |
| INTEGUMENTARY | | |
| pruritus | 1.1 | 0 |
| NERVOUS SYSTEM | | |
| dizziness | 2.3 | 1.2 |
| vertigo | 0.6 | 0 |
| paresthesia | 0.6 | 0 |
| PSYCHIATRIC | | |
| decreased libido | 0.6 | 0 |
| RESPIRATORY | | |
| dyspnea | 1.7 | 0.6 |
| bronchial spasm | 0.6 | 0 |
| rales | 0.6 | 0 |
| SPECIAL SENSES | | |
| eye irritation | 1.1 | 0.6 |
| tinnitus | 0.6 | 0 |

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

| | Adverse Reaction† | | Withdrawal‡ | |
|---|---|---|---|---|
| | Timolol (n=945) % | Placebo (n=939) % | Timolol (n=945) % | Placebo (n=939) % |
| Asthenia or Fatigue | 5 | 1 | <1 | <1 |
| Heart Rate <40 beats/minute | 5 | <1 | 4 | <1 |
| Cardiac Failure—Nonfatal | 8 | 7 | 3 | 2 |
| Hypotension | 3 | 2 | 3 | 1 |
| Pulmonary Edema—Nonfatal | 2 | <1 | <1 | <1 |
| Claudication | 3 | 3 | 1 | <1 |
| AV Block 2nd or 3rd degree | <1 | <1 | <1 | <1 |
| Sinoatrial Block | <1 | <1 | <1 | <1 |
| Cold Hands and Feet | 8 | <1 | <1 | 0 |
| Nausea or Digestive Disorders | 8 | 6 | 1 | <1 |
| Dizziness | 6 | 4 | 1 | 0 |
| Bronchial Obstruction | 2 | <1 | 1 | <1 |

†When an adverse reaction recurred in a patient, it is listed only once.

‡Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

*Potential Adverse Effects*: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

*Clinical Laboratory Test Findings*: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

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The American Journal of CARDIOLOGY®

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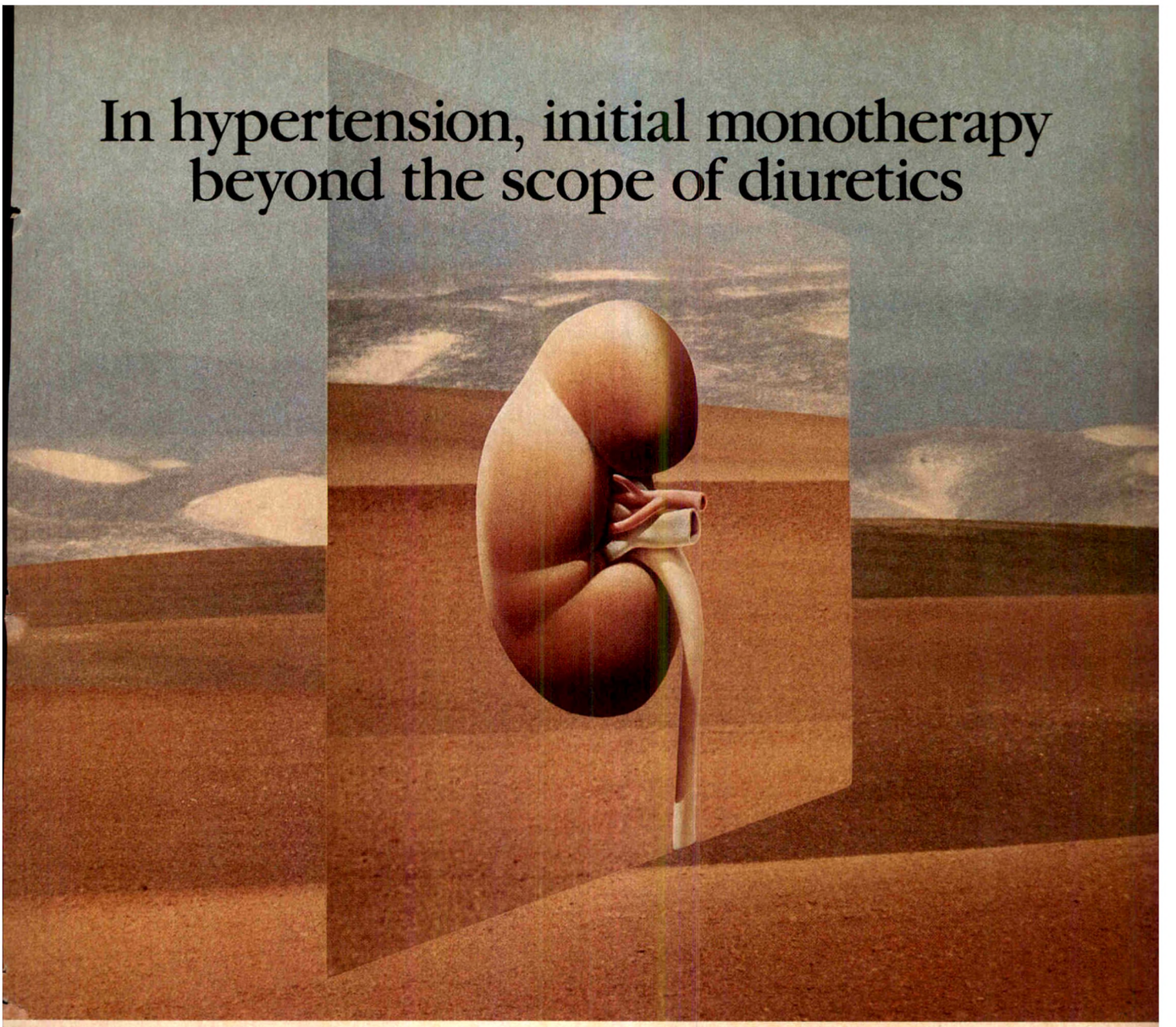
918 **LETTERS**


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**Instructions to Authors on page 740**

**Index to Advertisers on page A161**

# In hypertension, initial monotherapy beyond the scope of diuretics



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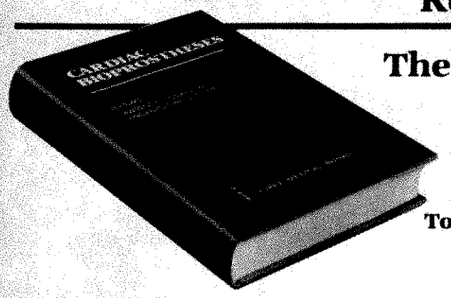
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## Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982




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## Who are the editors?

**Lawrence H. Cohn, MD,** is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

**Vincenzo Gallucci, MD,** is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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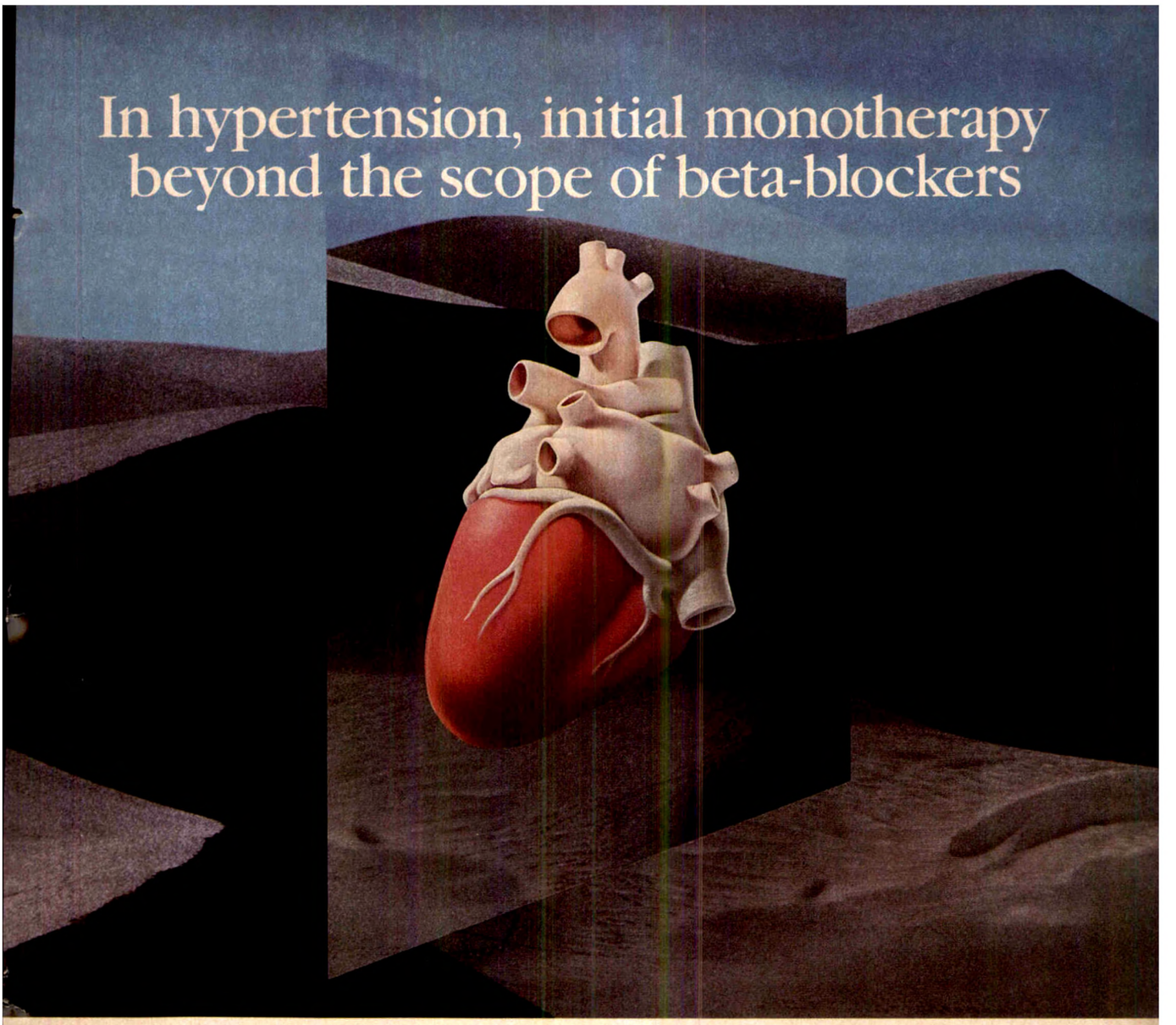
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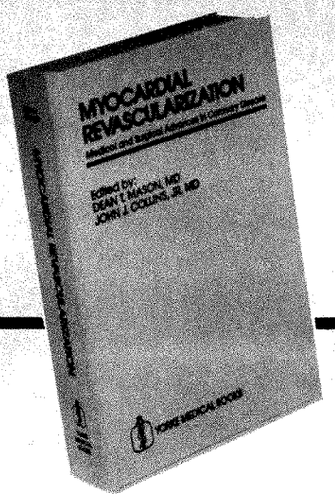
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EDITED BY

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- Coronary Bypass Surgery for Angina, Unstable Angina, AMI

## Sample Table of Contents:

**Section 1 - Stable Angina Pectoris and Asymptomatic Coronary Disease**

**Section 2 - Variant Angina Pectoris**

**Section 3 - Unstable Angina Pectoris**

**Section 4 - Acute Myocardial Infarction**

**Section 5 - Myocardial Preservation**

**Section 6 - Pharmacologic and Related Approaches to Coronary Dilatation**

**Section 7 - Percutaneous Transluminal Coronary Angioplasty**

**Section 8 - Intracoronary Thrombolysis in Evolving Myocardial Infarction**

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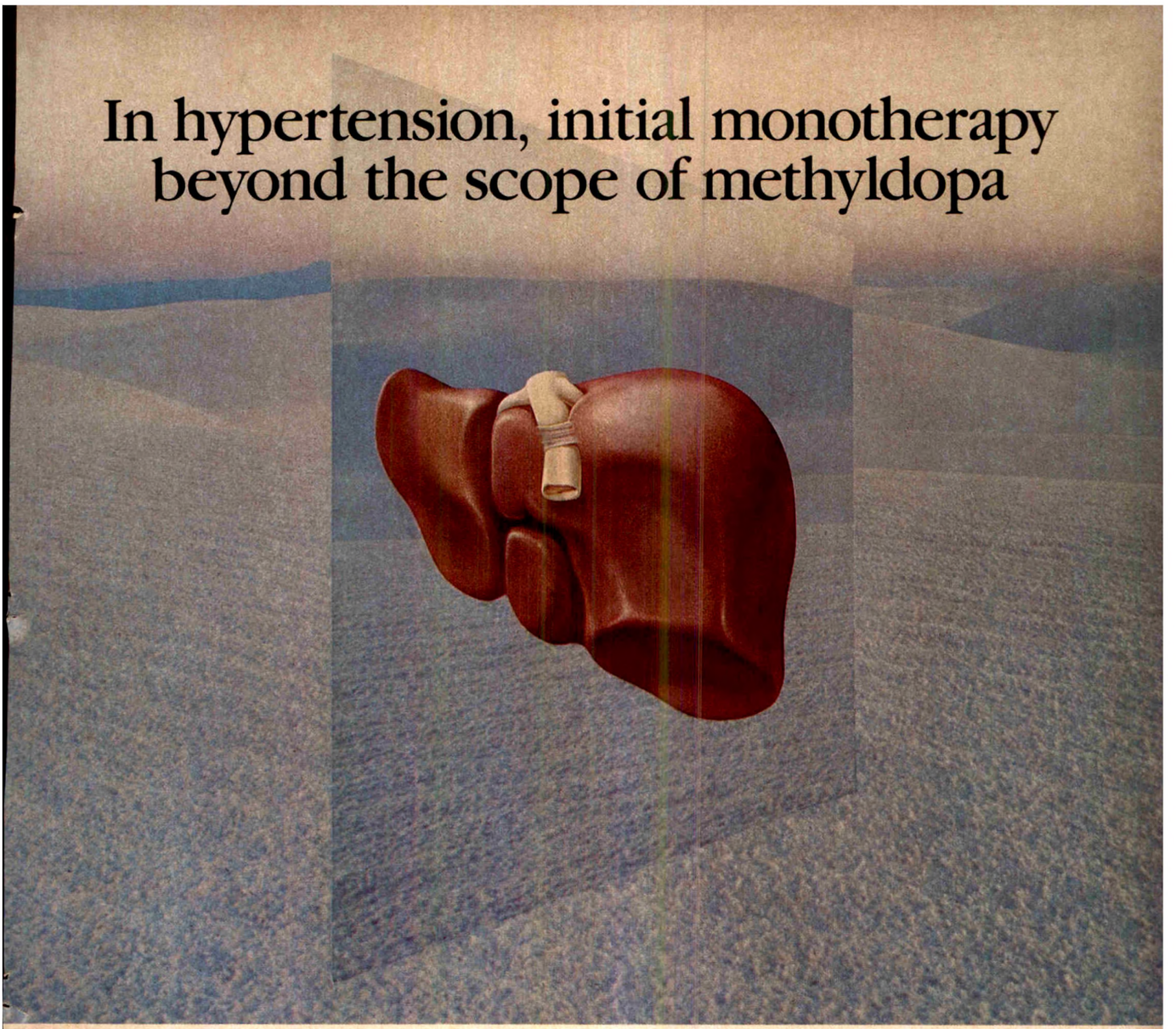
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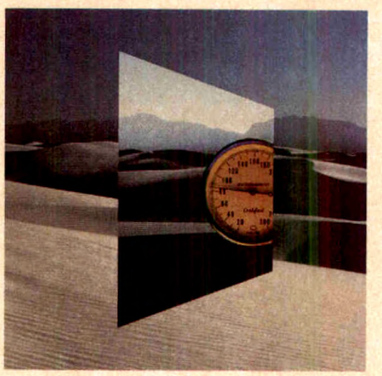
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## (guanabenz acetate)

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Wyeth

# Another dimension in the management of hypertension



No electrolyte or metabolic risk factors
No long-term cardiovascular risk factors
No immunologic disturbances
No liver damage
No contraindications except hypersensitivity

## Side effects are usually mild and transient

Patients may experience drowsiness and dry mouth early during WYTENSIN® (guanabenz acetate) therapy, but these subjective complaints are mostly mild and transient, especially when the initial dosage is *4 mg b.i.d.*, with the second dose at bedtime.

4mg b.i.d.

## New WyTensin® (guanabenz acetate)

**Brief Summary**

**Actions:**
**Wytensin®** (guanabenz acetate) is an orally active central alpha-2 adrenergic agonist. Its antihypertensive action appears to be mediated via stimulation of central alpha adrenergic receptors, resulting in a decrease of sympathetic outflow from the brain at the bulbar level to the peripheral circulatory system. The acute antihypertensive effect of **Wytensin** occurs without major changes in peripheral resistance, but its chronic effect appears to be a decrease in peripheral resistance.

**Indications and Usage:**
Treatment of hypertension, alone or in combination with a thiazide diuretic.

**Contraindication:**
Known sensitivity to the drug.

**Precautions:**
1. Sedation: Causes sedation or drowsiness in a large fraction of patients. When used with centrally active depressants, e.g., phenothiazines, barbiturates and benzodiazepines, consider potential for additive sedative effects.

2. Patients with vascular insufficiency: Like other antihypertensives use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or severe hepatic or renal failure.

3. Rebound: Sudden cessation of therapy with central alpha agonists like **Wytensin** may rarely result in "overshoot" hypertension and more commonly produces increase in serum catecholamines and subjective symptomatology.

INFORMATION FOR PATIENTS:
Advise patients on **Wytensin** to exercise caution when operating dangerous machinery or motor vehicles until it is determined they do not become drowsy or dizzy. Warn patients that tolerance for alcohol and other CNS depressants may be diminished. Advise patients not to discontinue therapy abruptly.

LAB TESTS:
In clinical trials, no clinically significant lab test abnormalities were identified during acute or chronic therapy. Tests included CBC, urinalysis, electrolytes, SGOT, bilirubin, alkaline phosphatase, uric acid, BUN, creatinine, glucose, calcium, phosphorus, total protein, and Coombs' test. During long-term use there was small decrease in serum cholesterol and total triglycerides without change in high-density lipoprotein fraction. In rare instances occasional nonprogressive increase in liver enzymes was observed, but no clinical evidence of hepatic disease.

DRUG INTERACTIONS:
**Wytensin®** was not demonstrated to cause drug interactions when given with other drugs, e.g., digitalis, diuretics, analgesics, anxiolytics, and antiinflammatory or antiinfective agents, in clinical trials. However, potential for increased sedation when given concomitantly with CNS depressants should be noted.

DRUG/LAB TEST INTERACTIONS:
No lab test abnormalities were identified with **Wytensin** use.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
No evidence of carcinogenic potential emerged in rats during a two-year oral study with **Wytensin** at up to 9.5 mg/kg/day, i.e., about 10 times maximum recommended human dose. In the Salmonella microsome mutagenicity (Ames) test system, **Wytensin** at 200-500 mcg per plate or at 30-50 mcg/ml in suspension gave dose-related increases in number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes. No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Schizosaccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those lethal to the cells in culture. In another eukaryotic system, *Saccharomyces cerevisiae*, **Wytensin** produced no activity in an assay measuring induction of repairable DNA damage. Reproductive studies showed a decreased pregnancy rate in rats given high oral doses (9.6 mg/kg), suggesting impairment of fertility. Fertility of treated males (9.6 mg/kg) may also have been affected, as suggested by decreased pregnancy rate of mates, even though females received drug only during last third of pregnancy.

PREGNANCY:
Pregnancy Category C:
WYTENSIN® MAY HAVE ADVERSE EFFECTS ON FETUS WHEN ADMINISTERED TO PREGNANT WOMEN. A teratology study in mice indicated possible increase in skeletal abnormalities when **Wytensin** is given orally at doses 3 to 6 times maximum recommended human dose of 1.0 mg/kg. These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits. However, increased fetal loss has been observed after oral **Wytensin** given to pregnant rats (14 mg/kg) and rabbits (20 mg/kg). Reproductive studies in rats have shown slightly decreased live-birth-indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6.4 and 9.6 mg/kg. There are no adequate, well-controlled studies in pregnant women. **Wytensin®** should be used during pregnancy only if potential benefit justifies potential risk to fetus.

NURSING MOTHERS:
Because no information is available on **Wytensin** excretion in human milk, it should not be given to nursing mothers.

PEDIATRIC USE:
Safety and effectiveness in children less than 12 years of age have not been demonstrated; use in this age group cannot be recommended.

**Adverse Reactions:**
Incidence of adverse effects was ascertained from controlled clinical studies in U.S. and is based on data from 859 patients on **Wytensin** for up to 3 years. There is some evidence that side effects are dose-related.

Following table shows incidence of adverse effects in at least 5% of patients in study comparing **Wytensin** to placebo, at starting dose of 8 mg b.i.d.

| Adverse Effect | Placebo (%) n = 102 | Wytensin (%) n = 109 |
|---|---|---|
| Dry mouth | 7 | 28 |
| Drowsiness or sedation | 12 | 39 |
| Dizziness | 7 | 17 |
| Weakness | 7 | 10 |
| Headache | 6 | 5 |

In other controlled clinical trials at starting dose of 16 mg/day in 476 patients, incidence of dry mouth was slightly higher (38%) and dizziness was slightly lower (12%), but incidence of most frequent adverse effects was similar to placebo-controlled trial. Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time. In more recent studies using an initial dose of 8 mg/day in 274 patients, incidence of drowsiness or sedation was lower, about 20%.

Other adverse effects reported during clinical trials but not clearly distinguishable from placebo effects and occurring with frequency of 3% or less: Cardiovascular—chest pain, edema, arrhythmias, palpitations. Gastrointestinal—nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort. Central nervous system—anxiety, ataxia, depression, sleep disturbances. ENT disorders—nasal congestion. Eye disorders—blurring of vision. Musculoskeletal—aches in extremities, muscle aches. Respiratory—dyspnea. Dermatologic—rash, pruritus. Urogenital—urinary frequency, disturbances of sexual function. Other—gynecomastia, taste disorders.

**Drug Abuse and Dependence:**
No dependence or abuse has been reported.

**Overdosage:**
Accidental ingestion caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two children aged one and three years. Gastric lavage and pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both. Since experience with accidental overdosage is limited, suggested treatment is mainly supportive while drug is being eliminated and until patient is no longer symptomatic. Vital signs and fluid balance should be carefully monitored. Adequate airway should be maintained and, if indicated, assisted respiration instituted. No data are available on **Wytensin** dialyzability.

**Dosage and Administration:**
Individualize dosage. A starting dose of 4 mg b.i.d. is recommended, whether used alone or with a thiazide diuretic. Dosage may be increased in increments of 4 to 8 mg/day every one to two weeks, depending on response. Maximum dose studied has been 32 mg b.i.d., but doses this high are rarely needed.

**How Supplied:**
**Wytensin®** (guanabenz acetate) Tablets, 4 mg and 8 mg, bottles of 100.

CI 3046-1 8/17/82

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MARCH 1, 1983

# The American Journal of CARDIOLOGY®

VOLUME 51

NUMBER 5

## CONTENTS

A note from the Editor-in-Chief, William C. Roberts, MD, appears on pages A9 and A10 of this issue.

Coming March 15th: our second March issue.

### CORONARY HEART DISEASE

**661 Influence of Partial Sympathetic Denervation on the Results of Myocardial Revascularization in Variant Angina**

AMADEO BETRIU, JOSE LUIS POMAR, MARTIAL G. BOURASSA, and CLAUDE M. GRONDIN

Thirty-one patients with variant angina and severe coronary artery disease underwent myocardial revascularization; in 14 patients partial sympathetic denervation was performed in addition to coronary artery grafting. The average follow-up was just under 2 years. Actuarial curves showed the probability of recurrence of variant angina to be significantly lower in the 14 who had partial sympathetic denervation ($p < 0.05$ and $p < 0.001$ at 6 and 10 months, respectively).

**668 Digital Angiography in Assessment of Ventricular Function and Wall Motion During Pacing in Patients With Coronary Artery Disease**

JONATHAN TOBIS, ORHAN NALCIOGLU, WARREN D. JOHNSTON, ANTHONY SEIBERT, LLOYD T. ISERI, WERNER ROECK, and WALTER L. HENRY

Using digital subtraction angiography, left ventriculograms were obtained with 10 ml of iodinated contrast material in 21 patients both at rest and during atrial pacing. In 15 patients with significant coronary artery lesions, the ejection fraction decreased during atrial pacing from a mean of 62.1 + 14.4% to 50.7 + 15.2% ($p > 0.001$). In 6 patients with chest pain but normal coronary arteries, the ejection fraction increased from a mean of 66.4 + 8.6% at rest to 71.6 + 5.7% during atrial pacing ($p < 0.01$). The digital ventriculograms demonstrated new or increased wall motion abnormalities during atrial pacing in 12 of 15 patients with coronary artery disease. Because digital subtraction angiography allows multiple left ventriculograms to be obtained during routine cardiac catheterization, intervention studies such as atrial pacing can be used to obtain a functional assessment of the severity of coronary artery lesions.

**676 Angiographic Changes Produced by Percutaneous Transluminal Coronary Angioplasty**

DAVID R. HOLMES, Jr., RONALD E. VLIETSTRA, MICHAEL B. MOCK, GUY S. REEDER, HUGH C. SMITH, ALFRED A. BOVE, JOHN F. BRESNAHAN, JEFFREY M. PIEHLER, HARTZELL V. SCHAFF, and THOMAS A. ORSZULAK

Percutaneous transluminal coronary angioplasty (PTCA) is being used with increasing frequency in the treatment of patients with symptomatic coronary artery disease. After dilatation, a range of angiographic findings may be seen which reflect, in part, the anatomic and pathologic changes produced by PTCA. The long-term effects of PTCA may depend on these anatomic and pathologic changes. Recognition and classification of these findings will become increasingly important in the evaluation of the long-term effect of coronary angioplasty and in developing new approaches for avoiding adverse effects. To facilitate communication and evaluation of the results of PTCA, a classification of the angiographic findings and potential mechanisms is presented.

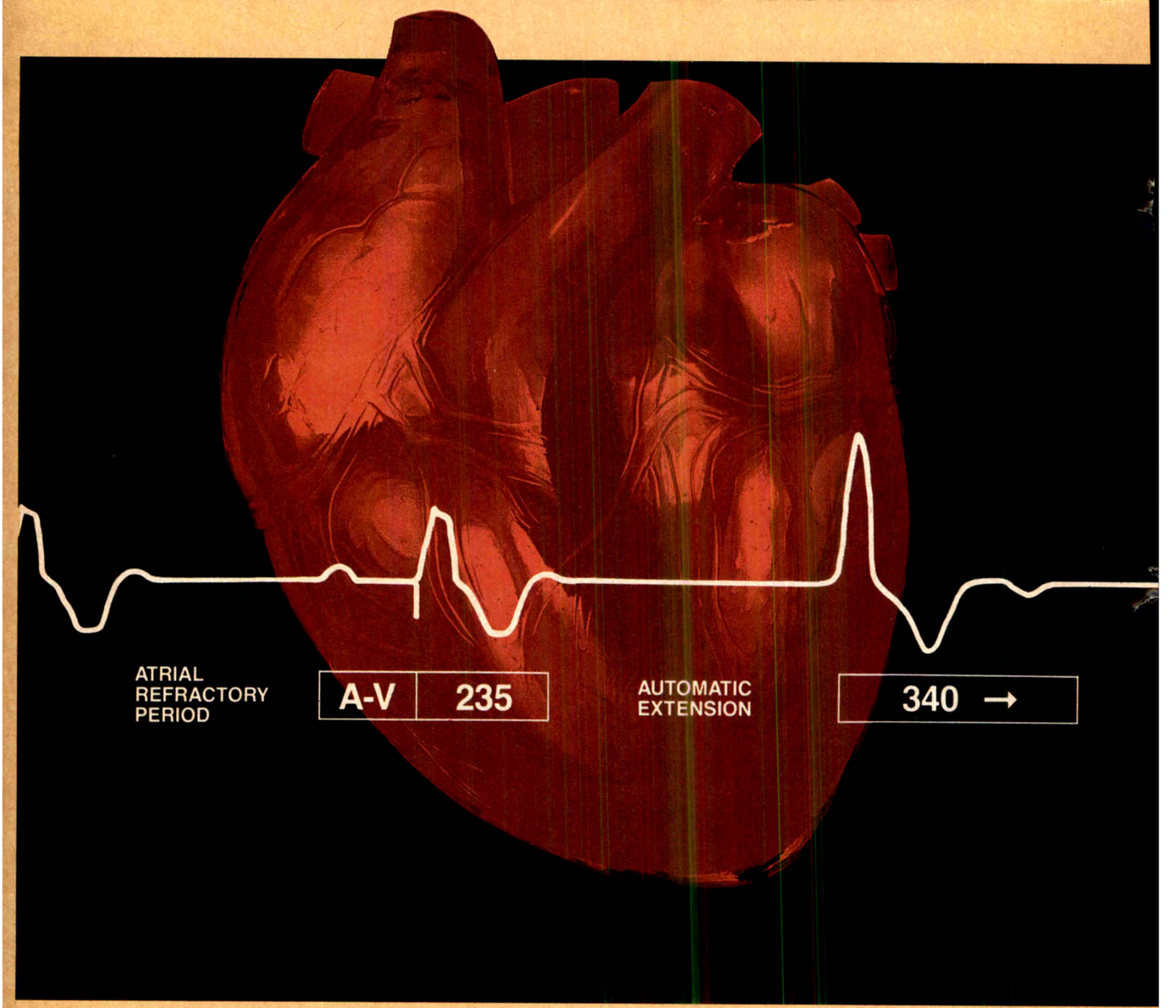
**684 Ergonovine Provocation to Assess Efficacy of Long-Term Therapy With Calcium Antagonists in Prinzmetal's Variant Angina**

MICHAEL D. WINNIFORD, STACEY M. JOHNSON, DAVID R. MAURITSON, and L. DAVID HILLIS

This study was performed to compare ergonovine responsiveness with clinical and electrocardiographic evidence of disease activity in patients with Prinzmetal's angina during chronic therapy with placebo, verapamil, and nifedipine. Twenty-seven patients with variant angina received placebo and verapamil for 2 months each, after which 23 also received nifedipine for 2 months. All patients kept a diary of chest pains, all had weekly 24-

Continued on Page A27

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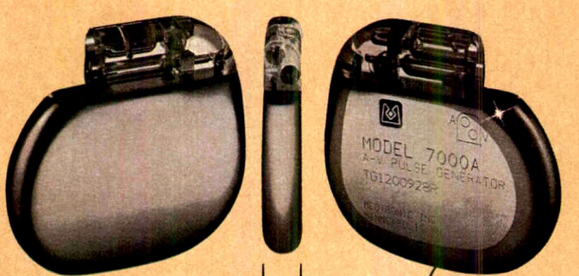



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With the Model 7000A programmed in the A-V universal (DDD) mode, indications may include:

- Some of the sick sinus syndrome conditions such as intermittent sinus bradycardia, sinus arrest or SA block.
- Intermittent or complete atrioventricular block with normal sinus activity.
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V interval settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

In the A-V sequential (DVI) mode, the Model 7000A may have application in the following:

- Sick Sinus Syndrome (sinus bradycardia, sinus arrest, SA block, and the brady-tachy syndrome).
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V delay settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

At any time, the Model 7000A can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry (e.g., atrial lead malfunction).

**NOTE:** The Medtronic® Model 7000A universal A-V pulse generator is under clinical investigation in the U.S. The procedures for using this pulse generator, as well as its safety and efficacy, will be evaluated during this investigational study according to the Clinical Investigation Protocol. Therefore, the "Intended Uses" section is based on Medtronic's experience with other physiologic pulse generators. No claims for safety and efficacy can be made for the Model 7000A pulse generator during its clinical investigation. Patients should be advised that the Model 7000A pulse generator is under clinical investigation.

**Contraindications**

*General:* There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician.

*DDD Mode:* The DDD mode is contraindicated in the presence of atrial fibrillation, atrial flutter and rapid atrial rhythms or slow retrograde conduction.

*DVI Mode:* In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation or flutter.

**Warnings**

*Diathermy:* Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site.

*Electrosurgical Units:* Electrosurgical units should never be used in the vicinity of unipolar pulse generators because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead.

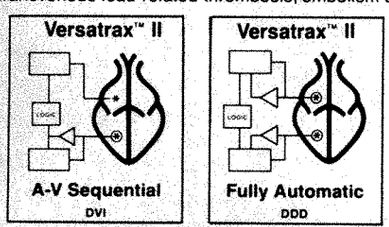
*Defibrillation:* Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. Positioning a magnet or the programming head over the pulse generator makes it subject to programming. A nominal vertical magnetic field strength of 90 Gauss (in a field measured 1½ inches from the magnet's surface) from a magnet at 1¼ inches from the reed switch is required to initiate asynchronous pacing. Do not use electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programming head has been positioned over the pulse generator. If an electrocautery unit is used, the physician may prefer to program the pacemaker to asynchronous pacing prior to the procedure.

**Precautions**

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

**Side Effects**

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.




**KEY TO SYMBOLS**

◁ = Sensing Circuit
□ = Output Circuit
○ = Sensing
* = Stimulation

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hour Holter monitoring, and all had ergonovine testing during therapy with each agent. Of the 74 tests, 59 were negative; 6 of the negative tests occurred when the patient was having >10 chest pains/week and >25 episodes/week of S-T segment deviation. Of the 15 positive tests, 5 occurred when the patient was having no angina or S-T deviation. Thus, in the patient with variant angina, disease activity cannot be monitored reliably by ergonovine provocation, since some patients have negative ergonovine tests at a time of marked disease activity, whereas others have positive tests at a time of little (or no) disease activity.

**689 Frequency in Nonangioplasty Patients of Morphologic Findings Reported in Coronary Arteries Treated With Transluminal Angioplasty**

JEFFREY M. ISNER and ROBERTA V. FORTIN

In 33 (49%) of 70 patients in whom percutaneous transluminal angioplasty (PTA) had *not* been performed during life, necropsy examination disclosed 1 or more findings identical to those observed in necropsy studies of PTA-treated arteries. These findings included "plaque fractures" in 31 (or 44%), "dissection clefts" in 26 (33%), and medial thinning in 40 (57%). Observations in these 70 patients indicate that findings previously described in PTA-treated patients cannot necessarily be assumed to represent the result of PTA.

**694 Intravenous Nitroglycerin for the Treatment of Angina at Rest Unresponsive to Standard Nitrate Therapy**

KERRY KAPLAN, RICHARD DAVISON, MICHELE PARKER, JEAN PRZYBYLEK, J. RUSSELL TEAGARDEN, and MICHAEL LESCH

Thirty-five patients who had angina at rest unresponsive to standard therapy comprised of oral and topical nitrates and beta-blocking drugs were treated with a continuous infusion of intravenous nitroglycerin. The average infusion rate was 140 ± 15 μg/min. With intravenous nitroglycerin therapy the number of episodes of angina at rest decreased from 3.5 ± 0.4 to 0.3 ± 0.1, sublingual nitroglycerin use decreased from 1.9 ± 0.3 to 0.4 ± 0.1 mg/day, and morphine sulfate administration decreased from 5.5 ± 1.3 to 0.4 ± 0.2 mg/day (all $p < 0.001$). When each patient's response on the endpoint day was analyzed, 25 were defined as complete (no rest angina), 8 as partial (>50% decrease in number of episodes per day from control) and 2 as nonresponders. No significant drug-induced side effects occurred. Intravenous nitroglycerin appears to be effective therapy for angina at rest refractory to standard oral and topical medications.

**699 Effects of Verapamil on Coronary Hemodynamic Function and Vasomobility Relative to Its Mechanism of Antianginal Action**

CHRISTOPHER Y. C. CHEW, B. GREGORY BROWN, BRAMAH N. SINGH, MAYLENE M. WONG, CINDY PIERCE, and ROBERT PETERSEN

Intravenously administered verapamil (0.145 mg/kg followed by 0.005 mg/kg/min infusion) during cardiac catheterization in patients with coronary artery disease reduced mean arterial pressure (−14%, $p < 0.001$,) systemic vascular resistance (−27%, $p < 0.01$) with a small, insignificant (+13%) increase in coronary sinus flow and no change in myocardial oxygen consumption. A computer-assisted angiographic technique showed that the drug dilated normal as well as stenotic segments of epicardial coronary vessels, producing a mean reduction of 14% ($p < 0.01$) of estimated stenosis flow resistance; nitroglycerin produced a 28% reduction ($p < 0.01$) under comparable conditions. The data suggest that intravenously, verapamil dilates normal as well as narrowed atherosclerotic segments of coronary arteries without a change in oxygen demand. The reduction in stenosis flow resistance may contribute to its antianginal actions.

**706 Nifedipine in Chronic Stable Angina: A Double-Blind Placebo-Controlled Crossover Trial**

LON G. SHERMAN and CHANG-SENG LIANG

Thirty patients with chronic stable argina pectoris were randomized in a double-blind prospective placebo-controlled crossover trial to assess the efficacy of nifedipine in controlling symptoms and objective signs of myocardial ischemia using a symptom-limited treadmill exercise test. Adverse effects that occurred during both nifedipine and placebo treatment were minor and generally well tolerated. Twenty-three patients were analyzed from the crossover phase of the study. Nifedipine significantly reduced the frequency of angina and nitroglycerin consumption, and increased exercise time. These changes were significantly greater than those in the placebo group. Hemodynamic evaluation during exercise revealed a significant reduction in systolic and diastolic blood pressures in the nifedipine group at the onset of angina and at maximal exercise without significant differences in heart rate responses in the nifedipine and placebo groups. The pressure-rate product during submaximal exercise was significantly smaller in the nifedipine group than in the placebo group, but did not differ significantly in the 2 groups at the onset of angina or on maximal exercise. Furthermore, S-T segment depressions that occurred during exercise at the same pressure-rate products were smaller in the nifedipine period than in the placebo period. Thus, it appears that the antianginal effects of nifedipine are caused by a reduced myocardial oxygen demand for a specific work load and possibly by an increased blood supply to ischemic myocardium.

Continued on Page A32


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REFERENCE: 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS and Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833

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**712 Effect of Intravenous and Intracoronary Nifedipine on Coronary Blood Flow and Myocardial Oxygen Consumption**

PETER SCHANZENBÄCHER, GERHART LIEBAU, PETER DEEG, and KURT KOCHSIEK

The effect of intravenous and intracoronary nifedipine on coronary sinus blood flow, coronary vascular resistance, and myocardial oxygen consumption was studied in 20 patients with coronary artery disease. Intravenous infusion of 1.0 mg of nifedipine resulted in a decrease in mean aortic pressure, an increase in heart rate and coronary blood flow, and no significant change in myocardial oxygen consumption. In contrast, intracoronary injection of 0.1 mg of nifedipine led to a moderate reduction in mean aortic pressure, no change in heart rate, an increase in coronary blood flow, and a significant reduction in myocardial oxygen consumption. During rapid atrial pacing before and approximately 6 minutes after the intracoronary nifedipine injection, coronary blood flow and myocardial oxygen consumption reached identical levels. Thus, only intracoronary injection of nifedipine increases coronary flow in the presence of reduced myocardial oxygen consumption. After intravenous administration, reflex tachycardia counteracts the direct myocardial effect of nifedipine and the potential oxygen-saving effect of afterload reduction. There is no evidence of a prolonged oxygen-sparing effect after cessation of the immediate effects.

**718 Electrocardiographic Criteria for the Diagnosis of Combined Inferior Myocardial Infarction and Left Anterior Hemiblock**

ROBERT A. WARNER, NORMA E. HILL, SAKTI MOOKHERJEE, and HAROLD SMULYAN

New electrocardiographic criteria based on vectorcardiographic principles for diagnosing the combination of inferior infarction and left anterior hemiblock are proposed. The proposed criteria can be applied to tracings obtained with 3-channel electrocardiographic machines and are as follows: (1) leads aVR and aVL both end in R waves, with the peak of the terminal R wave in lead aVR occurring later than the peak of a terminal R wave in lead aVL, and (2) a Q wave of any magnitude is present in lead II. The performance of the proposed criteria is statistically superior to that of each of 10 sets of traditional electrocardiographic criteria for the diagnosis.

**723 Improved Electrocardiographic Criteria for the Diagnosis of Left Anterior Hemiblock**

ROBERT A. WARNER, NORMA E. HILL, SAKTI MOOKHERJEE, and HAROLD SMULYAN

New electrocardiographic criteria for diagnosing left anterior hemiblock are proposed. The proposed criteria are based on a method of analysis that permits diagnostically important features of the vectorcardiographic frontal plane QRS loop to be inferred from the electrocardiogram. The proposed criteria can be applied to tracings obtained with 3-channel electrocardiographic machines and are as follows: (1) the QRS complexes in leads aVR and aVL each end in R waves (terminal R waves), and (2) the peak of the terminal R wave in lead aVR occurs later than the peak of the terminal R wave in lead aVL. The performance of the proposed criteria is statistically superior to each of 2 sets of traditional QRS axis criteria for the diagnosis.

**727 Effects of Provocation on Transcardiac Thromboxane in Patients With Coronary Artery Disease**

PAUL D. HIRSH, BRIAN G. FIRTH, WILLIAM B. CAMPBELL, GREGORY J. DEHMER, JAMES T. WILLERSON, and L. DAVID HILLIS

Simultaneous ascending aortic and coronary sinus blood samples were obtained for quantitation of thromboxane $B_2$ in 52 patients provoked with rapid cardiac pacing, cold pressor stress, or sustained isometric exertion. Five had a >3-fold increase in coronary sinus thromboxane $B_2$: 1 had unstable angina and chest pain during the previous 48 hours and 4 had a myocardial infarction within the previous 6 weeks. Similarly, 7 had a >3-fold increase in the coronary sinus/aortic thromboxane $B_2$ ratio: 1 had unstable angina and recent chest pain, 5 had a recent myocardial infarction, and 1 had both. The remaining patients with similar diagnoses did not have a marked increase in thromboxane $B_2$. None of the 35 patients with stable ischemic heart disease or nonischemic chest pain syndromes had a substantial increase in thromboxane $B_2$ ($p < 0.001$). Thus, generous amounts of thromboxane $B_2$ are released into the coronary circulation after provocation in some patients with unstable angina or recent myocardial infarction but not in those with stable ischemic heart disease or nonischemic chest pain syndromes.

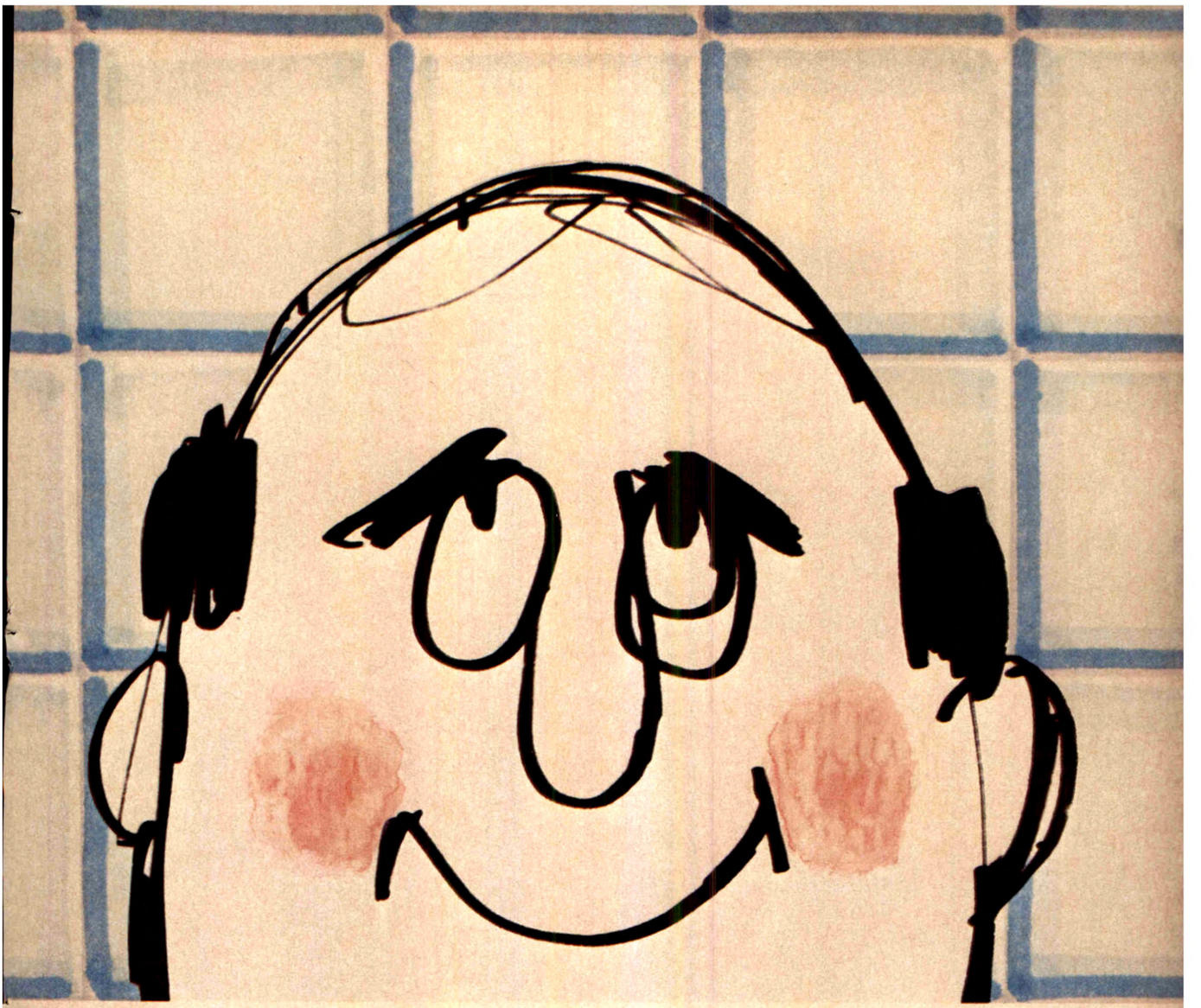
**734 Precordial S-T Segment Depression in Inferior Myocardial Infarction. Evaluation by Quantitative Thallium-201 Scintigraphy and Technetium-99m Ventriculography**

LAWRENCE ONG, BENILDA VALDELLON, JAMES COROMILAS, ROBERT BRODY, PETER REISER, and JOHN MORRISON

Seventy patients with acute inferior myocardial infarction were studied with early thallium-201 scintigraphy and technetium-99m ventriculography. Patients with precordial S-T segment depression did not have significantly more anteroseptal hypokinesia, anterior thallium-201 perfusion defects, or thallium-201 redistribution abnormalities. They did have a lower mean ejection fraction, greater inferoposterior hypokinesia, and larger inferoposterior perfusion defects, indicating the presence of larger infarcts. Compared with other variables reflecting




Continued on Page A36



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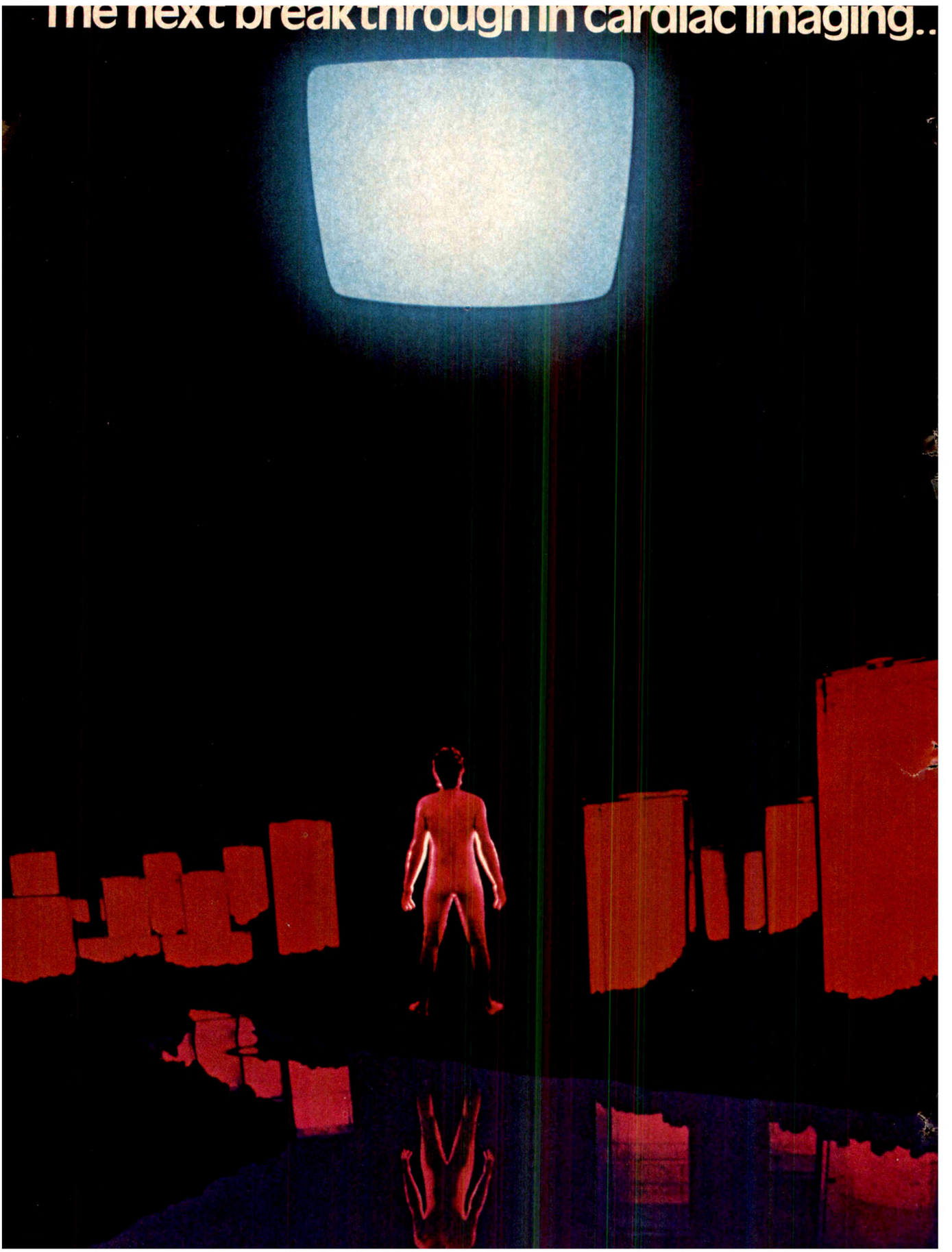
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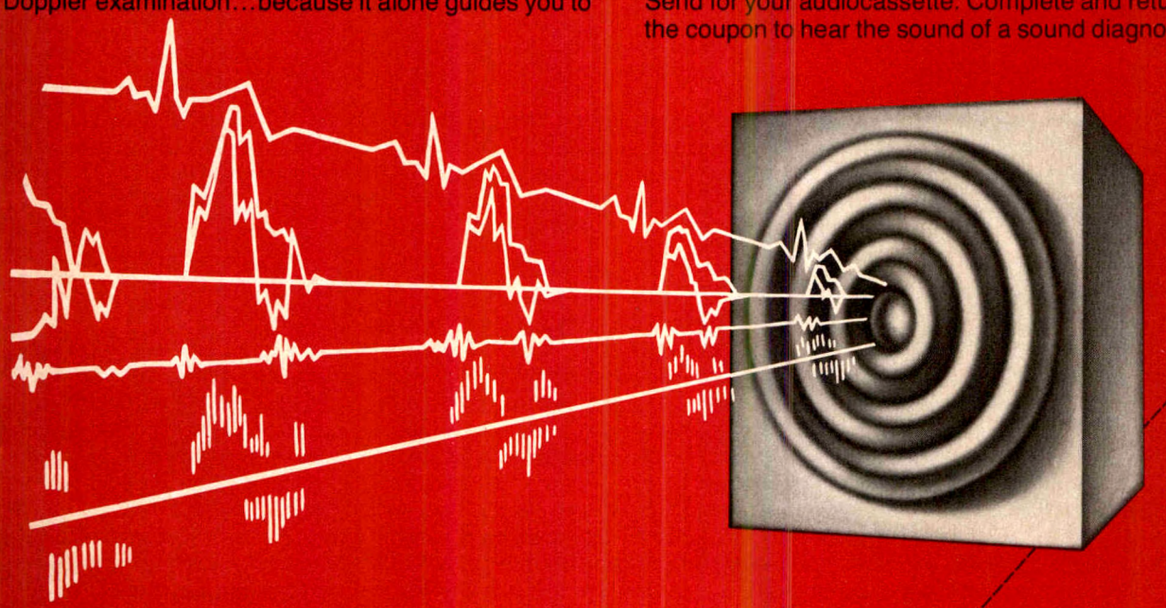
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AJC 3/83

left ventricular dysfunction and infarct size in a multivariate analysis, the presence of precordial S-T segment depression did not have independent prognostic value. Significant independent prognostic variables were Killip class, initial left ventricular ejection fraction <40%, and pulmonary vascular congestion on admission chest radiography.

**741 Radionuclide-Determined Changes in Pulmonary Blood Volume and Thallium Lung Uptake in Patients With Coronary Artery Disease**

RICHARD A. WILSON, ROBERT D. OKADA, CHARLES A. BOUCHER, H. WILLIAM STRAUSS, and GERALD M. POHOST

Exercise-induced increases in radionuclide-determined pulmonary blood volume (PBV) and thallium lung uptake have been described in patients with coronary artery disease (CAD) and have been shown to correlate with transient exercise-induced left ventricular dysfunction. To compare these 2 techniques in the same patients, 74 patients (59 with and 15 without significant CAD) underwent supine bicycle exercise twice on the same day—first for thallium myocardial and lung imaging and then for technetium-99m gated blood pool imaging for the PBV ratio determination. Thallium activity of lung and myocardium was determined to calculate the thallium lung/heart ratio. Relative changes in PBV from rest to exercise were expressed as a ratio of pulmonary counts (exercise/rest). The results indicate the following conclusions: (1) the prevalence of an abnormal thallium lung/heart ratio is smaller than that of the PBV ratio in patients with CAD; (2) both tests are normal in normal control subjects; (3) propranolol does not cause abnormal results in normal control subjects; however, propranolol may influence lung thallium uptake in patients with CAD; and (4) when both tests are abnormal, there is a high likelihood of multivessel disease.

**749 Sinus Node Coronary Arteries Studied With Angiography**

MICHAEL K. KYRIAKIDIS, COSTAS B. KOUROUKLIS, JOHN T. PAPAIOANNOU, STAMATIS G. CHRISTAKOS, GEORGE P. SPANOS, and DIMITRIS G. AVGOUSTAKIS

Coronary angiograms of 309 consecutive patients undergoing coronary angiography were reviewed to investigate the blood supply to the sinus node area. Blood was supplied from the right coronary artery in 59% of cases, from the left coronary artery in 38%, and from both coronary arteries in 3%. The posterior sinus node artery was demonstrated in 32 patients (27% of the 119 patients with the sinus node artery originating from the left circumflex and 10.5% of all patients).

**751 Beneficial Effects of Ibuprofen in Pacing-Induced Myocardial Ischemia**

PAUL WALINSKY, J. BRYAN SMITH, ALLAN M. LEFER, and LESLIE WIENER

The effect of ibuprofen on cathepsin D, a marker of lysosomal membrane leakiness, and on thromboxane $B_2$, a marker of platelet activation, was evaluated in 44 patients with angina pectoris. Coronary sinus and systemic arterial blood were analyzed for cathepsin D, thromboxane $B_2$ and lactate before and after atrial pacing to 140 beats/min for 4 minutes. Ibuprofen (800 mg) or placebo was administered orally 2 hours before catheterization. There were 4 subgroups based on administration of ibuprofen or placebo and based on demonstration of lactate extraction or production. Patients with lactate production given placebo had a significant increase in thromboxane $B_2$ level and in cathepsin D activities after atrial pacing. In contrast, patients with lactate production given ibuprofen and patients with lactate extraction had no significant efflux of either thromboxane $B_2$ or cathepsin D after pacing. These findings suggest that ibuprofen stabilizes lysosomal membranes and prevents platelet activated release of thromboxane $A_2$ in pacing-induced myocardial ischemia.

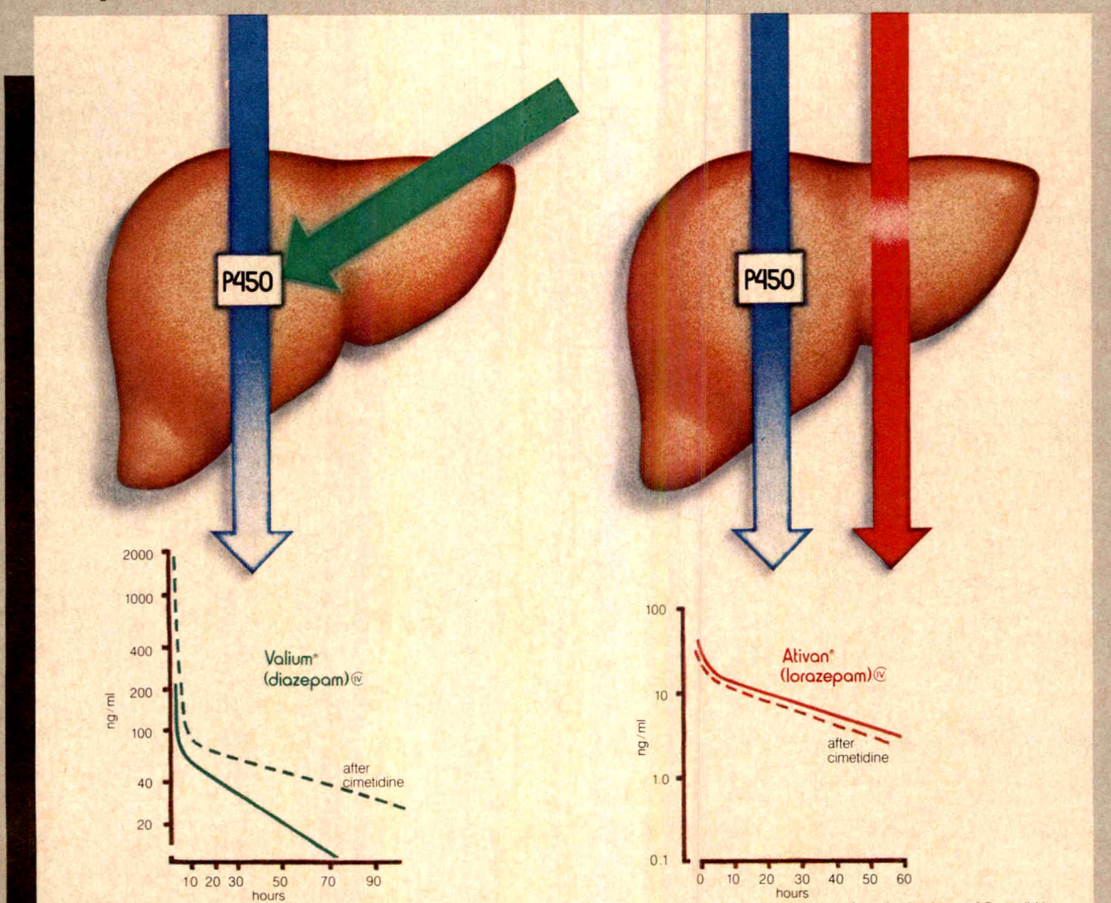
**755 Improved Exercise Ventilatory Responses After Training in Coronary Heart Disease During Long-Term Beta-Adrenergic Blockade**

NEIL F. GORDON, PIETER E. KRÜGER, and JONES F. CILLIERS

Exercise ventilatory responses of 7 men with well-documented myocardial infarction receiving long-term beta-adrenergic blockade were studied before and after 4 months of endurance training. Observations were obtained during graded levels of upright treadmill exercise continued until 85% of the predetermined symptom-limited heart rate (working heart frequency limit) was obtained. This submaximal testing procedure revealed a significant slowing of the heart rate ($p < 0.005$) together with an increased oxygen pulse ($p < 0.05$) after training, for what was previously a maximal work load for the working heart frequency limit. In addition, all patients achieved an increased exercise duration and work load, accompanied by significant increases in maximal oxygen uptake ($p < 0.01$), oxygen pulse ($p < 0.025$), and respiratory exchange ratio, for their working heart frequency limit after exercise conditioning. These results show that prolonged physical training results in physiologic adaptations to cardiac rehabilitation in the presence of long-term beta-adrenergic blockade.

Continued on Page A40

# Ativan®. Agent of Change
(lorazepam)




Plasma concentration of diazepam after a single dose of 0.1 mg/kg IV to a single subject administered before (—) and after (---) pretreatment with cimetidine—5 X 200 mg orally q6h. (Adapted from Klotz U, Reimann I: N Engl J Med *302*:1012-1014, 1980.)

Plasma concentration of lorazepam after single dose of 2 mg IV in 8 normal subjects before (—) and after (---) 7 days of treatment with cimetidine, 300 mg orally qid. (Adapted from Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980.)

## because it doesn't utilize the P450 system

All drugs inactivated by oxidative metabolism, including cimetidine and most benzodiazepines, utilize the cytochrome P450 oxidase enzyme system and, therefore, compete for it when given concomitantly. Patients on cimetidine, for example, are apt to experience excessive drowsiness when taking a benzodiazepine dependent on this system—because benzodiazepine clearance is delayed and plasma levels increase.

Ativan® (lorazepam) is inactivated by simple, one-step glucuronidation and is not subject to N-dealkylation or hydroxylation by the P450 system—unlike diazepam, chlordiazepoxide, clorazepate and prazepam, all CIV.

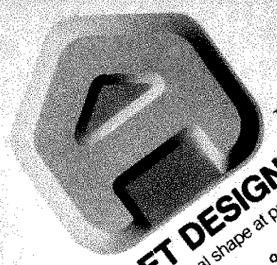
And, since Ativan does not compete for the P450 system, its elimination is not appreciably affected by concomitant use of cimetidine... one more reason why Ativan is becoming the anxiolytic of choice for an increasing number of physicians.

See important information on following page.

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Philadelphia, PA 19101

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**for** (lorazepam)IV
**Anxiety**



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**NEW TABLET DESIGN 0.5 mg and 1 mg**

(2 mg tablet retains original oval shape at present)

**Brief Summary of Prescribing Information.**

**Indications and Usage:** Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

**Contraindications:** Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

**Warnings:** Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

**Precautions:** In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

**Adverse Reactions,** if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

**Overdosage:** In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

**Ativan® (IV) for (lorazepam) Anxiety**

**DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

**HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.**

**Wyeth Laboratories**
Philadelphia, PA 19101

## NOTICE OF PUBLIC SALE

NOTICE is hereby given that JOHN and LINDA VALENTINE as the secured party in possession of their collateral furnished to them by their debtor, Bomed Medical Manufacturing, Ltd., will sell that collateral, for cash, at public sale on Tuesday, April 5, 1983, at 10:00 A.M. at the offices of Drummy Garrett King & Harrison at 3200 Park Center Drive, Suite 1000, Costa Mesa, California. The collateral is generally described in the Financing Statement filed with the Office of the California Secretary of State as "(a) all of Debtor's right to manufacture, sell and license others to manufacture and sell three devices (the "devices") developed by Debtor commonly known as (1) the Heart Rate Monitor, (2) the Depil-X, and (3) the Bioimpedance Analyzer; (b) that certain Patent for Accelerated Electrolysis issued June 11, 1974, being Patent No. 3815603 relating to the Depil-X; and (c) all proceeds of the foregoing Collateral."

This personal property is owned by Bomed Medical Manufacturing, Ltd. and is located at 130 McCormick Avenue, Suite 109, Costa Mesa, California and is subject to that certain Security Agreement dated June 23, 1982 between it and JOHN and LINDA VALENTINE, that certain Financing Statement dated June 23, 1982 filed in the Office of the Secretary of State of the State of California on June 28, 1982, and that certain Notice of Assignment and Assignment of Patent for Security Purposes Only dated June 23, 1982 and filed in the office of the Commissioner of Patents and Trademarks in Washington, D.C., on June 28, 1982.

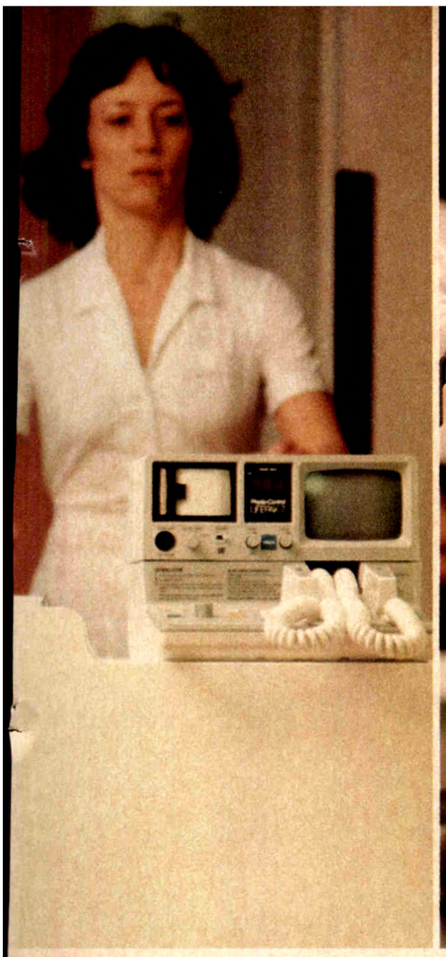
The sale is being held to enforce the rights of JOHN and LINDA VALENTINE as secured party in possession of their collateral under and pursuant to the above-mentioned Security Agreement, Financing Statement, Notice of Assignment and the California Uniform Commercial Code.

For additional information concerning the above sale, and the Heart Rate Monitor, Depil-X, and Bioimpedance Analyzer, please contact Alan I. White of Drummy Garrett King & Harrison, attorneys for JOHN and LINDA VALENTINE, at P.O. Box 5080, Costa Mesa, CA 92626, or at the following telephone number: (714) 850-1800.

**CARDIOLOGIST**—IMMEDIATE OPENING FOR A BOARD CERTIFIED OR ELIGIBLE CANDIDATE AT THE KING-DREW MEDICAL CENTER, LOS ANGELES. MUST QUALIFY FOR ACADEMIC APPOINTMENT AT UCLA AT ASSISTANT OR ASSOCIATE PROFESSOR LEVEL. CALL AND SEND RESUME TO: Dr. Ravi Prakash, Professor and Chief of Cardiology, 12021 S. Wilmington Ave., Los Angeles, CA 90059 213/603-4567.

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# CONTENTS

## ARRHYTHMIAS AND CONDUCTION DISTURBANCES


**759 Disopyramide: Evaluation of Electrophysiologic Effects and Clinical Efficacy in Patients With Sustained Ventricular Tachycardia or Ventricular Fibrillation**

BRUCE B. LERMAN, HARVEY L. WAXMAN, ALFRED E. BUXTON, and MARK E. JOSEPHSON

The efficacy of disopyramide was evaluated by programmed ventricular stimulation in 50 patients who had a history of sustained ventricular tachyarrhythmias. Disopyramide prevented induction of sustained ventricular tachycardia in one third of patients studied and remained effective therapy in 80% of those discharged on the drug. Regardless of response to disopyramide, plasma levels, ventricular refractory periods, QRS and Q-Tc durations did not differ significantly. Although minor side effects developed in 20% of patients receiving disopyramide, the major factor limiting its use was myocardial depression. This occurred only in patients with preexisting ventricular dysfunction.

**765 Effects of Oral Digoxin on Ventricular Ectopy and Its Relation to Left Ventricular Function**

ALAN H. GRADMAN, MOIRA CUNNINGHAM, MARY A. HARBISON, HARVEY J. BERGER, and BARRY L. ZARET

The ventricular antiarrhythmic properties of oral digoxin were examined in 13 patients with chronic ventricular ectopy using serial 24-hour electrocardiographic monitoring. For the group as a whole, mean premature ventricular contraction frequency (per 1,000 normal beats) decreased from 56.1 ± 46.6 during the placebo period to 40.0 ± 27.2 (difference not significant) and 24.8 ± 17 ($p < 0.05$) during daily administration of digoxin, 0.25 and 0.375 mg, respectively. Radionuclide left ventricular ejection fraction was measured during the placebo period. Both mean premature ventricular contraction and couplet frequency decreased significantly in the 7 patients with normal left ventricular performance, while the patients with abnormal resting ejection fractions showed no significant reduction in arrhythmia occurrence after digoxin administration. This study indicates that digoxin is a moderately effective ventricular antiarrhythmic agent, and that its effects are greatest in patients with normal overall left ventricular function.

**770 Cardiac Electrophysiologic Effects of Flecainide Acetate for Paroxysmal Reentrant Junctional Tachycardias**

KEVIN J. HELLESTRAND, ANTHONY W. NATHAN, RODNEY S. BEXTON, ROWORTH A. J. SPURRELL, and A. JOHN CAMM

Intravenous flecainide acetate was administered to 18 patients with a direct accessory atrioventricular (AV) pathway and 15 patients with functional longitudinal A-H dissociation (dual A-H pathways). Flecainide was given to 14 patients during sustained AV reentrant tachycardia and to 9 patients during sustained intra-AV nodal reentrant tachycardia. AV reentrant tachycardia was successfully terminated in 12 patients, due to retrograde accessory pathway block in 11 and AV nodal block in 1. Tachycardia reinitiation was not possible in 6 patients. Flecainide significantly increased both anterograde and retrograde accessory pathway effective refractory periods. Intra-AV nodal reentrant tachycardia was successfully terminated in 8 patients, due to retrograde "fast" A-H pathway block in 7 patients and anterograde "slow" A-H pathway block in 1. Reinitiation was not possible in 4 patients. Flecainide selectively prolonged the retrograde effective refractory period of the fast A-H pathway only. Flecainide acetate effectively terminates reentrant junctional tachycardias by increasing accessory AV pathway and retrograde fast A-H pathway refractoriness.

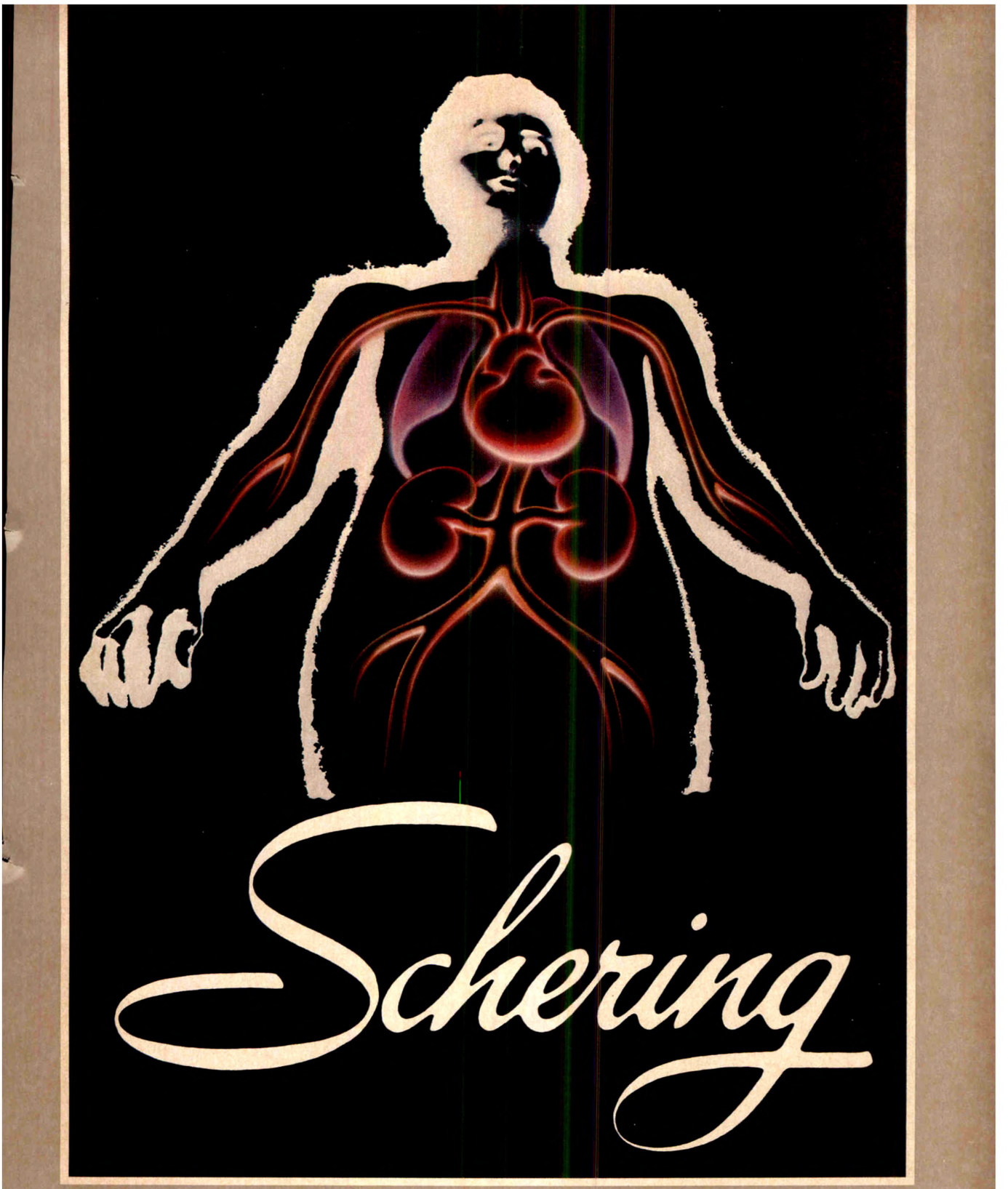
**777 Cardiac Effects of Treatment With Quinidine and Digoxin, Alone and in Combination**

KARIN SCHENCK-GUSTAFSSON, TOMAS JOGESTRAND, LARS-ÅKE BRODIN, ROLF NORDLANDER, and RUNE DAHLQVIST

Systolic time intervals ($QS_2$-I and LVET-I) and echocardiographically determined ejection fraction and velocity of circumferential fiber shortening were recorded in 10 healthy volunteers, as measures of inotropic effect during sequential maintenance treatment with the following drug regimens: (1) quinidine alone, 1,200 mg daily, (2) digoxin alone, (3) combined treatment with quinidine and digoxin, (4) digoxin alone with increased dose to produce the same steady-state level as during the combined quinidine-digoxin treatment. Quinidine prolonged while digoxin caused a dose-related shortening of systolic time intervals. The addition of quinidine to digoxin treatment further shortened $QS_2$-I. By correcting for the negative inotropic effect of quinidine itself, the molar effect of digoxin on systolic time intervals was the same, irrespective of absence or presence of quinidine. Drug effects on echocardiographic measurements were less marked but followed the same directions as the systolic time intervals. This study performed under steady-state conditions demonstrates that the quinidine-induced increase in steady-state serum digoxin concentration will, with due consideration to quinidine's own pharmacodynamic properties, be accompanied by increased cardiac effects. This indicates that quinidine is not interfering with active receptor sites in the heart for digoxin.

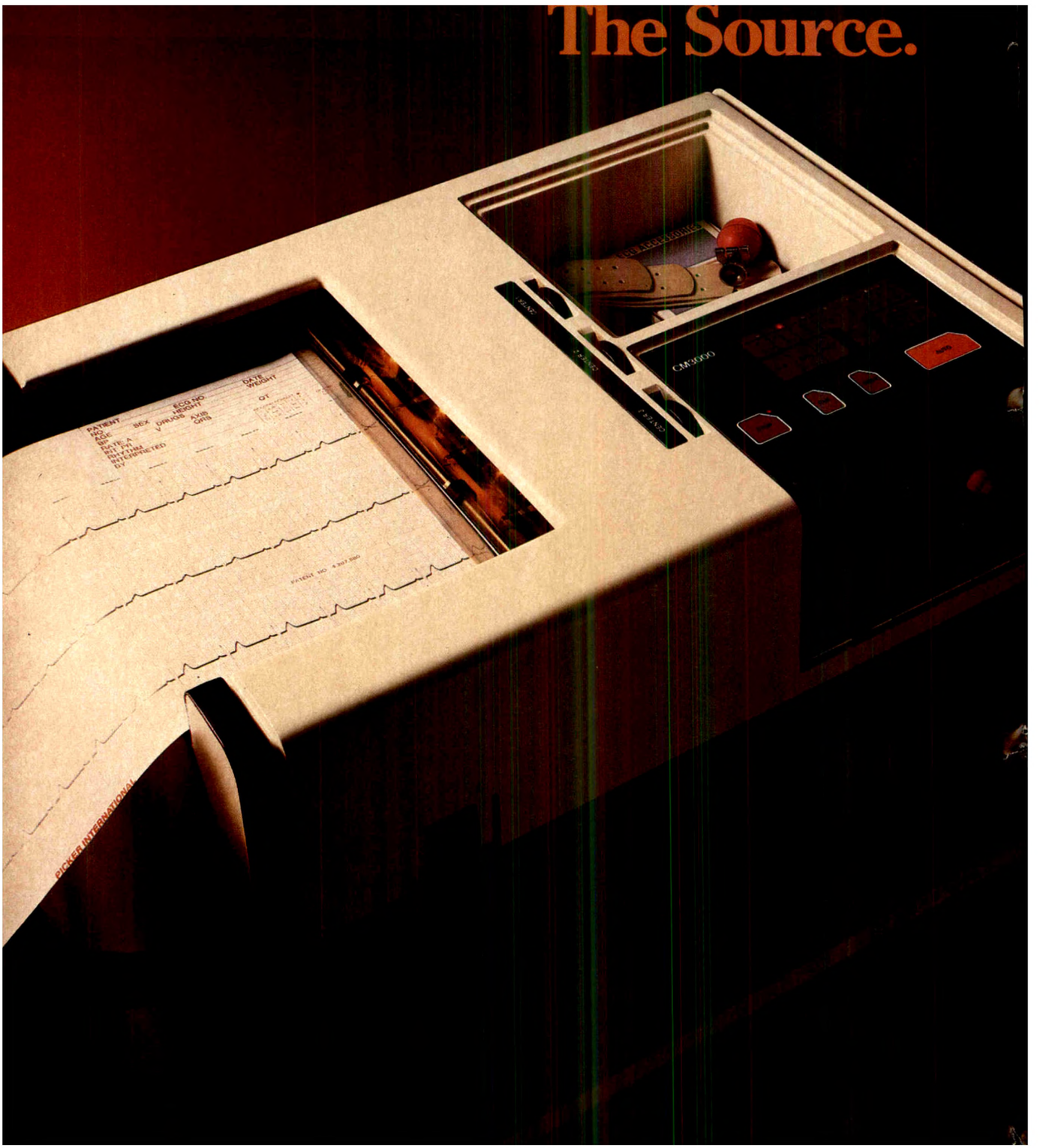



Continued on Page A44




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# CONTENTS


## SYSTEMIC HYPERTENSION

**783 Immediate Hemodynamic Effect of a New Calcium-Channel Blocking Agent (Nitrendipine) in Essential Hypertension**

HECTOR O. VENTURA, FRANZ H. MESSERLI, WILLIE OIGMAN, FRANCIS G. DUNN, EFRAIN REISIN, and EDWARD D. FROHLICH

The immediate hemodynamic effects of nitrendipine were studied in 12 patients with mild essential hypertension. Patients were classified as responders (decrease ≥ 10 mm Hg, 7 patients) or nonresponders (≤ 10 mm Hg, 5 patients) according to the observed decreases in mean arterial pressure. The decrease in arterial pressure in responders was associated with a significant decrease in total peripheral resistance and a significant increase in heart rate, cardiac index, and left ventricular ejection rate. Plasma norepinephrine was significantly increased in the responders. It is concluded that nitrendipine lowered arterial pressure as a result of arteriolar dilatation associated with a reflexive increase in heart rate and cardiac index. Furthermore, nitrendipine combined with beta-blockers would be beneficial for the treatment of arterial hypertension.

**787 Predictability of Blood Pressure Response to Isometric Stress**

ROBERT H. CHANEY and STEPHAN ARNDT

Since there is marked individual variation in blood pressure (BP) response to isometric stress, a study was designed to determine whether such response could be predicted by readily measured clinical variables. BP, heart rate (HR), electrocardiographic findings, and symptoms were recorded during maximal isometric as well as dynamic exercise in 270 office patients. Multiple regression analyses of several potential predictors demonstrated that isometric systolic BP was best predicted by resting systolic BP, and this in combination with age, sex, and maximal treadmill systolic BP yielded 70% predictability. Isometric diastolic BP was best predicted by resting diastolic BP, and this with handgrip strength, treadmill HR, systolic BP, and diastolic BP allowed 66% prediction. Isometric testing was also found safe and practical if monitored for electrocardiogram, symptoms, and BP.

## CONGESTIVE HEART FAILURE

**791 Clonidine in Congestive Heart Failure: A Vasodilator With Negative Inotropic Effects**

JAMES B. HERMILLER, RAYMOND D. MAGORIEN, MARK E. LEITHE, DONALD V. UNVERFERTH, and CARL V. LEIER

Fourteen patients with moderately severe congestive heart failure were given oral clonidine (0.2 and 0.4 mg doses) in order to determine the hemodynamic effects of a typical central-acting vasodilator. The 0.2 mg dose significantly reduced systemic (15%), pulmonary (20%), and pulmonary capillary wedge pressures (27%). The reductions in systemic and pulmonary vascular resistance were comparatively modest secondary to a diminished cardiac output. Heart rate decreased 11% and stroke volume remained unchanged. The 0.4 mg dose augmented these reductions but increased stroke volume modestly (15%). After both doses, isovolumic developed pressure/duration of isovolumic contraction decreased dramatically (≥23%) and the preejection period increased substantially (≥18%). Compared with currently employed vasodilators, the central-acting agent clonidine appears unique in that drug-induced reductions of afterload are not accompanied by a commensurate improvement in ventricular function. This lack of improvement appears to be secondary to negative inotropic effects.

## CARDIOVASCULAR PHARMACOLOGY

**796 In Vivo Quantitation of Platelet Deposition on Human Peripheral Arterial Bypass Grafts Using Indium-111–Labeled Platelets. Effect of Dipyridamole and Aspirin**

CHARLES W. PUMPHREY, JAMES H. CHESEBRO, MRINAL K. DEWANJEE, HEINZ W. WAHNER, LARRY H. HOLLIER, PETER C. PAIROLERO, and VALENTIN FUSTER

Indium-111–labeled, autologous platelets injected 48 hours after operation were used to quantitate platelet deposition in vivo and to assess the effect of platelet-inhibitor therapy. Dacron® double-velour (Microvel®) aortobifemoral artery grafts were placed in 16 patients and unilateral polytetrafluorethylene femoropopliteal grafts were placed in 10 patients. Half of the patients in each group received dipyridamole before and dipyridamole plus aspirin after operation; the rest of the patients served as controls. Scintigrams of the graft region were taken with a gamma camera interfaced with a computer 48, 72, and 96 hours after injection of the labeled platelets. Platelet deposition was estimated from the radioactivities of the grafts and expressed as counts per 100 pixels per microcurie injected. Platelet deposition on vascular grafts can be quantitated in vivo by noninvasive methods. Therapy with dipyridamole and aspirin significantly reduced platelet deposition on Dacron aortofemoral artery grafts. Platelet deposition was low on polytetrafluoroethylene grafts in the femoropopliteal position.


Continued on Page A49

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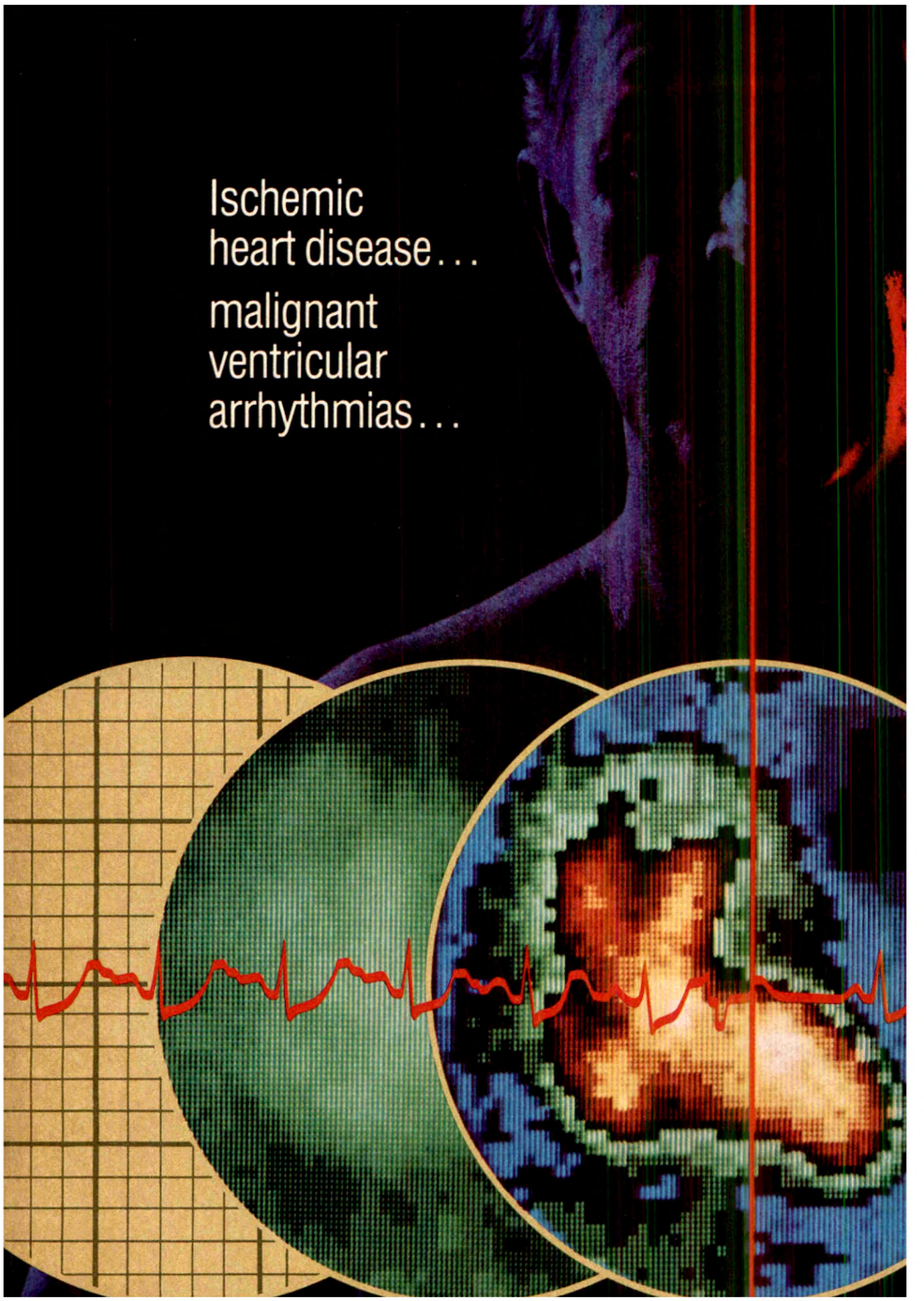
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- BID or TID dosage helps improve compliance while providing 24-hour antiarrhythmic activity.
- "As a rule, GI toxicity associated with quinidine gluconate is less frequent and less severe than that associated with quinidine sulfate."[5]

References: **1.** Lown B, Podrid PJ, Graboys TB, et al: *Curr Probl Cardiol* 4:13-14, 1980. **2.** Schulze RA Jr, Strauss HW, Pitt B: *Am J Med* 62:192-199, 1977. **3.** Pine MB, Aronow WS: *Ration Drug Ther* 14:1-5, 1980. **4.** Kastor JA, Horowitz LN, Harken AH, et al: *N Engl J Med* 304: 1004-1020, 1981. **5.** Podrid PJ: *Patient Care* 15:100-132, 1981.

Please turn page for brief summary of prescribing information.

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**QUINAGLUTE® (quinidine gluconate) DURA-TABS®**

**INDICATIONS AND USAGE:** Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:

**1. Ventricular arrhythmias:** Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).

**2. Junctional (nodal) arrhythmias:** A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).

**CONTRAINDICATIONS:** 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.

**WARNINGS:** 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.

3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.

7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

**PRECAUTIONS: General:** The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.

**Drug Interactions:**

| *Drug* | *Effect* |
|---|---|
| Quinidine with anticholinergic drugs | Additive vagolytic effect |
| Quinidine with cholinergic drugs | Antagonism of cholinergic effects |
| Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics | Alkalinization of urine resulting in decreased excretion of quinidine |
| Quinidine with coumarin anticoagulants | Reduction of clotting factor concentrations |
| Quinidine with tubocurare, succinylcholine and decamethonium | Potentiation of neuromuscular blockade |
| Quinidine with phenothiazines and reserpine | Additive cardiac depressive effects |
| Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin) | Decreased plasma half-life of quinidine |
| Quinidine with digoxin | Increased plasma concentrations of digoxin (see WARNINGS) |

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.

**Pregnancy:** *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

**Nursing Mothers:** Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.

**Pediatric Use:** There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.

**ADVERSE REACTIONS:** Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.

Less frequently encountered adverse reactions:

**Cardiovascular:** Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.

**Hematologic:** Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.

**Central Nervous System:** Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.

**Dermatologic:** Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.

**Hypersensitivity Reactions:** Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.

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# CONTENTS


**802 Cardiovascular Effects of a Newly Synthesized Cardiotonic Agent (TA-064) on Normal and Diseased Hearts**

MASAYA KINO, YUZO HIROTA, SHOJI YAMAMOTO, KENICHI SAWADA, MASATOMO MORIGUCHI, MASAHIRO KOTAKA, SHINICHIRO KUBO, and KEISHIRO KAWAMURA

A positive inotropic effect was confirmed echocardiographically in both healthy volunteers (n = 8) and patients with congestive heart failure (CHF) (n = 9) who were on a maximal medical regimen. Mean velocity of circumferential fiber shortening increased (healthy, 1.29 ± 0.05 to 1.60 ± 0.11 circ/s [$p < 0.05$]; patients with CHF, 0.69 ± 0.08 to 0.93 ± 0.09 circ/s [$p < 0.01$]) and ejection fraction increased (healthy, 68 ± 2 to 75 ± 2% [$p < 0.05$]; patients with CHF, 37 ± 4 to 45 ± 5% [$p < 0.01$]) without change in heart rate.

## CARDIOMYOPATHY

**811 Vulnerability of Patients With Obstructive Hypertrophic Cardiomyopathy to Ventricular Arrhythmia Induction in the Operating Room. Analysis of 17 Patients**

KELLEY P. ANDERSON, EDWARD B. STINSON, GERALDINE C. DERBY, PHILIP E. OYER, and JAY W. MASON

Seventeen patients with obstructive hypertrophic cardiomyopathy (HC) and 5 control patients underwent programmed electrical stimulation in the operating room. Of the 17 patients with HC, 14 had inducible sustained ventricular tachycardia or ventricular fibrillation, whereas none of the control patients had an inducible sustained ventricular arrhythmia. Unsustained ventricular tachycardia was induced in 1 patient in each group. The differences in the 2 groups with respect to ventricular tachyarrhythmia induction was significant ($p < 0.001$). Patients with obstructive HC are unusually vulnerable to ventricular tachyarrhythmia induction which may, in part, account for their propensity for sudden death.

**817 Myocardial Texture Characterization by Two-Dimensional Echocardiography**

ANIL K. BHANDARI and NAVIN C. NANDA

Twenty-four normal subjects and 181 patients with various cardiac disorders (36 autopsies) were studied by 2-dimensional echocardiography. All patients with infiltrative disorders (amyloidosis and Pompe's disease) showed multiple, discrete, and small highly refractile echoes (HREs) in the myocardium. However, this finding was nonspecific and was observed in many other conditions. In the noninfiltrative group, HREs in the autopsied cases were shown to result from gross fibrosis/endocardiofibroelastosis utilizing in vitro echocardiographic studies and metallic probe guided biopsies, whereas HREs in the autopsied cases with cardiac amyloidosis could be correlated only with amyloid deposits since fibrosis was absent. Larger HREs presenting as broad patches or long linear echoes in the myocardium were seen in old myocardial infarctions and congestive cardiomyopathy and were correlated with large areas of myocardial fibrosis.

**826 Sensitivity of Technetium-99m–Pyrophosphate Scintigraphy in Diagnosing Cardiac Amyloidosis**

RODNEY H. FALK, VICTOR W. LEE, ALAN RUBINOW, WILLIAM B. HOOD, Jr., and ALAN S. COHEN

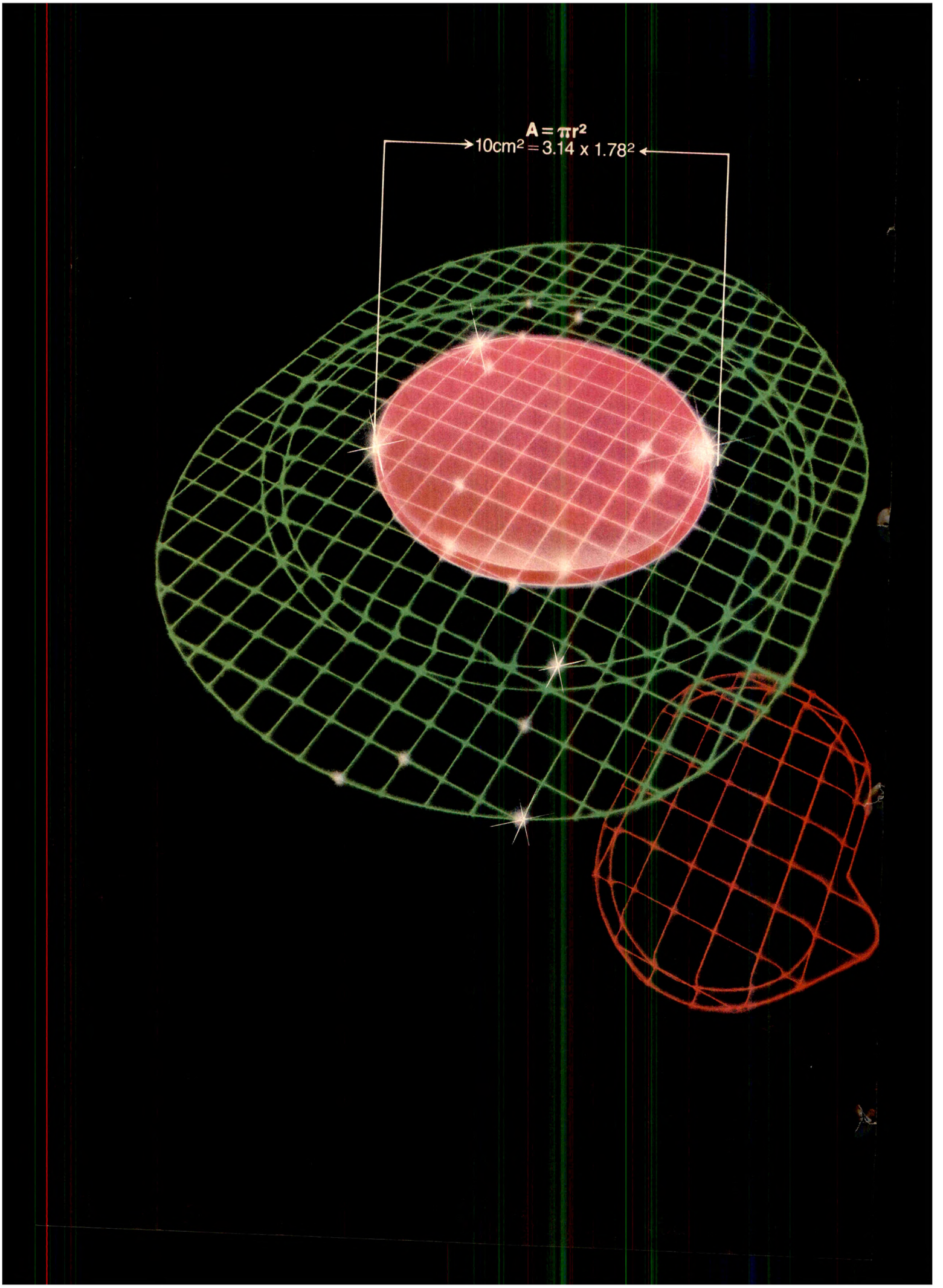
Technetium pyrophosphate scintigraphy, performed prospectively in 20 patients with systemic primary amyloidosis, demonstrated myocardial uptake of equal or greater intensity than that of the ribs in 8 of 9 subjects with heart failure and 9 of 11 with abnormal echocardiograms. None of 10 control patients with nonamyloid, nonischemic heart failure had positive findings on scintigraphy. Increased left ventricular wall thickness measured by M-mode echocardiography correlated with myocardial pyrophosphate uptake. In the presence of an abnormal echocardiogram, technetium pyrophosphate scintigraphy is a sensitive and specific test in the diagnosis of cardiac amyloidosis.

**831 Survival in Men With Severe Chronic Left Ventricular Failure Due to Either Coronary Heart Disease or Idiopathic Dilated Cardiomyopathy**

JOSEPH A. FRANCIOSA, MARY WILEN, SUSAN ZIESCHE, and JAY N. COHN

A greater misunderstanding of the course of congestive heart failure (CHF) is needed. In this study 182 patients with refractory CHF due to coronary artery disease (95 patients) or idiopathic dilated cardiomyopathy (87 patients) were followed up. Total mortality was 34% at 1 year, 59% at 2 years, and 76% at 3 years. The incidence of sudden death was 45%, and did not differ between groups. Mortality was worse in coronary artery disease than idiopathic dilated cardiomyopathy (46 versus 23% at 1 year, and 69 versus 48% at 2 years, $p < 0.01$). At entry hemodynamic abnormalities were more severe in patients who did not survive.


Continued on Page A53


$A = \pi r^2$
$10cm^2 = 3.14 \times 1.78^2$

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**CLINICAL PHARMACOLOGY:** When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies[2] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

**INDICATIONS AND USAGE:** Prevention and treatment of angina pectoris due to coronary artery disease.

**CONTRAINDICATIONS:** Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

**WARNINGS:** The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

**PRECAUTIONS:** Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

**ADVERSE REACTIONS:** Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

**HOW SUPPLIED:** Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28.

**CAUTION:** Federal law prohibits dispensing without a prescription.

**PATIENT INSTRUCTIONS FOR APPLICATION:** Patient instructions are furnished with each unit dose package.

*For complete prescribing information, please see package insert.*

1082

**References**


1. Pharmacy acquisition cost (AWP), *Drug Topics Red Book*, 1982 (assuming a 50% markup).
2. Data on file: Key Pharmaceuticals, Inc.


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## METHODS

**837 Evaluation of Left Ventricular Performance Using Digital Subtraction Angiography**

MARVIN W. KRONENBERG, RONALD R. PRICE, CLYDE W. SMITH, ROSE MARIE ROBERTSON, JAMES M. PERRY, DAVID R. PICKENS, MICHAEL J. DOMANSKI, C. LEON PARTAIN, and GOTTLIEB C. FRIESINGER

Cardiac applications for digital subtraction angiography appear promising. Thus, left ventricular volume, ejection fraction, and regional wall motion by digital subtraction angiography were evaluated after intravenous injection of 40 ml of iodinated contrast medium and after left ventricular injection of 5 to 10 ml. A film-based system of the authors' own design was used. Results were compared with those after 40 ml direct left ventricular contrast injection. The ventriculograms after intravenous injection showed close correlation with direct left ventricular injections for ejection fraction, volume, and regional wall motion. After small-volume left ventricular injections, the ventricular image was enhanced markedly by digital subtraction, and correlations between small and large volume ventriculograms were close for left ventricular ejection fraction, volume, and regional wall motion. Thus, digital subtraction angiography improves the visibility of the left ventricle after either intravenous or small-volume direct left ventricular injection. Digital images produce excellent estimates of left ventricular volume and should have considerable usefulness for the study of cardiac performance and anatomy.

**843 Evaluation of Intracardiac Thrombus With Computed Tomography**

HARUO TOMODA, MITSUMOTO HOSHIAI, HIDEO FURUYA, SACHIO KURIBAYASHI, MAKOTO OOTAKI, SEIYA MATSUYAMA, SHIROSAKU KOIDE, SHIAKI KAWADA, and AKIRA SHOTSU

Left atrial and left ventricular thrombus was evaluated by computed tomography in 56 patients: Group I, 28 patients with mitral valve disease; and Group II, 28 patients with myocardial infarction. Computed tomography, 2-dimensional echocardiography, angiocardiography, and open-heart surgery or autopsy were performed in these patients. The sensitivity in detecting left atrial thrombus was 100% with computed tomography, 60% with 2-dimensional echocardiography, and 70% with angiocardiography. The specificity in detecting left atrial thrombus was 91% with computed tomography, 86% with 2-dimensional echocardiography, and 88% with angiocardiography. Left ventricular thrombus was visualized by computed tomography with similar or greater accuracy than other diagnostic methods, although the sensitivity and specificity were not ascertained because surgery or autopsy was performed in only a minority of Group II patients.

**853 Absolute Left Ventricular Volume From Gated Blood Pool Imaging With Use of Esophageal Transmission Measurement**

ALAN H. MAURER, JEFFRY A. SIEGEL, BARRY S. DENENBERG, BLASE A. CARABELLO, ARNOLD K. GASH, JAMES F. SPANN, and LEON S. MALMUD

A new method for determining absolute left ventricular volume from equilibrium gated blood pool images was validated by comparing gated blood pool imaging with contrast ventriculography. The technique is geometry-independent and is the first to correct for tissue attenuation utilizing an in vivo point source. An orally administered capsule containing 1 to 2 mCi of technetium-99m sulfur colloid is used for this purpose. Left ventricular volumes are determined by dividing attenuation- and background-corrected count rates obtained from semiautomated left ventricular regions of interest by the count rate per milliliter from a blood sample.

**859 Effect of Exercise Protocol on the Left Ventricular Response to Exercise**

CARL FOSTER, DUNCAN S. DYMOND, JAMES D. ANHOLM, MICHAEL L. POLLOCK, and DONALD H. SCHMIDT, *With the technical assistance of* JOHN G. CARPENTER

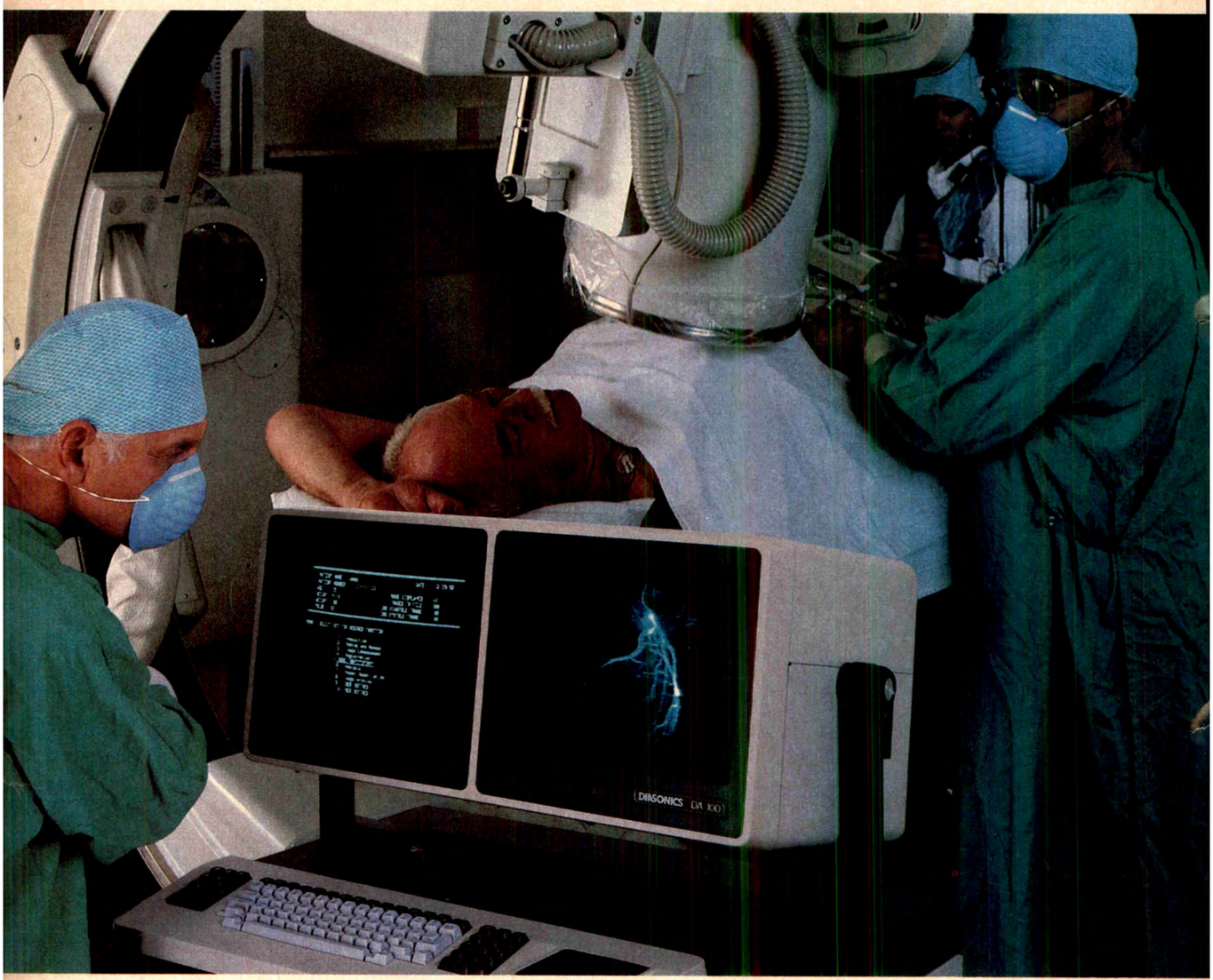
The effect of exercise protocol on the left ventricular ejection fraction response to exercise was evaluated in a sample of 120 healthy male volunteers. When first-pass radionuclide angiograms were obtained during peak upright graded bicycle exercise with >85% of age-predicted maximal heart rate attained, there was no net change in ejection fraction from rest to exercise. When exercise was submaximal, either through failure to attain at least 85% of the age-predicted maximal heart rate or through the use of postexercise imaging, the ejection fraction increased significantly from rest to exercise. If exercise was supermaximal and was presented abruptly, either with or without warm-up, the ejection fraction decreased from rest to exercise. The results suggest that interpretation of exercise radionuclide angiograms on the basis of reported values for normal and abnormal responses is dependent on careful replication of exercise protocol.

Continued on Page A57

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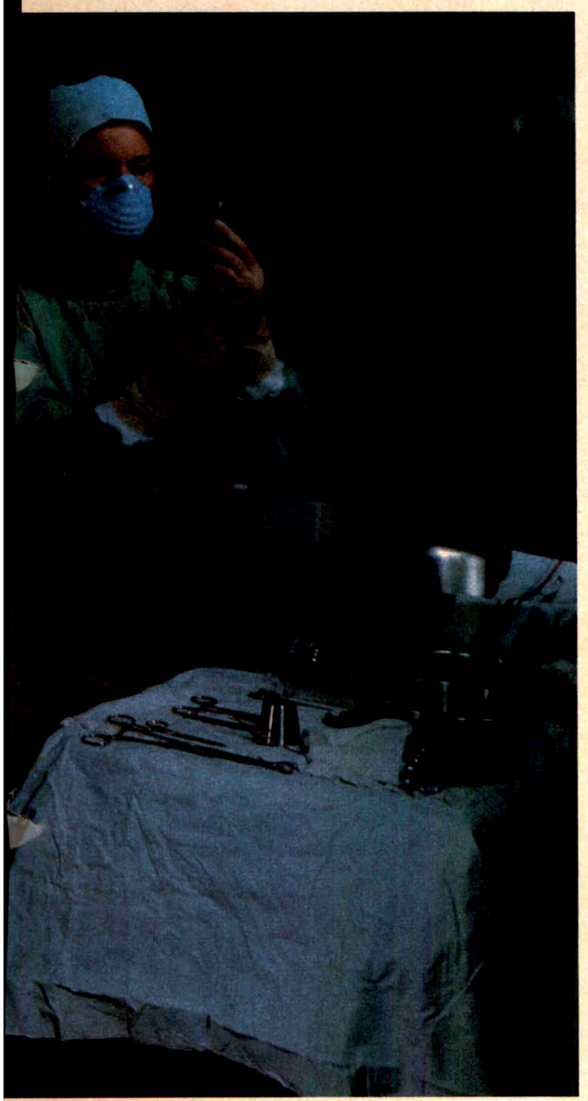
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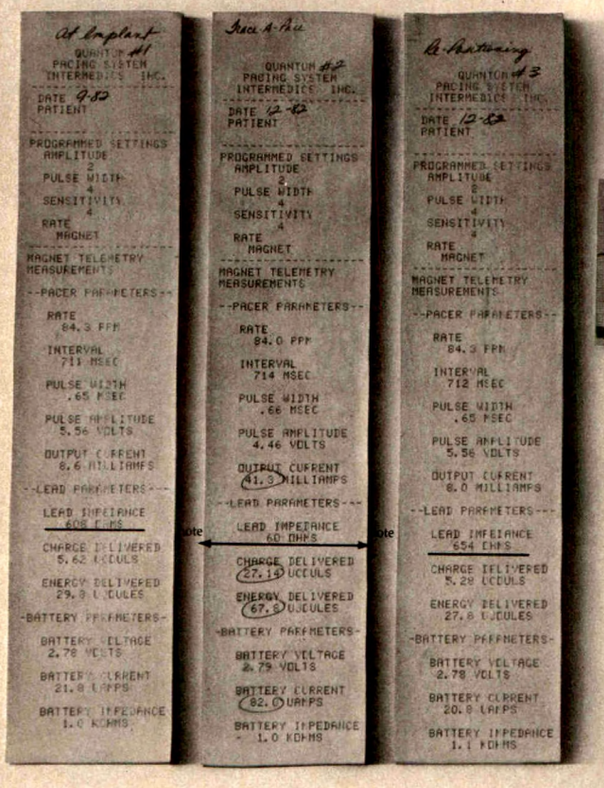
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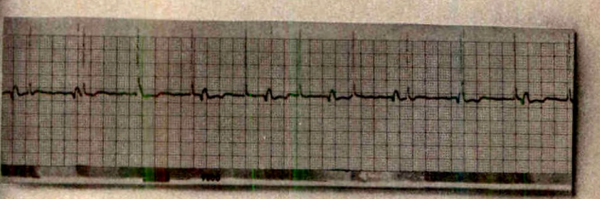
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# #2

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# CONTENTS

## EXPERIMENTAL STUDIES


**865 Influence of Aortic Stenosis on the Hemodynamic Importance of Coronary Artery Narrowing in Dogs Without Left Ventricular Hypertrophy**

ROBERT L. FELDMAN, WILMER W. NICHOLS, JAMES R. EDGERTON, C. RICHARD CONTI, and CARL J. PEPINE

This study evaluated coronary hemodynamic effects of both controlled left ventricular outflow obstruction simulating aortic valve stenosis and graded coronary artery diameter narrowing in open-chest dogs without left ventricular hypertrophy. Mean coronary flow during aortic stenosis increased an average of 17%, as did the percentage of flow occurring during diastole. However, there was a concomitant decrease in the endocardial/epicardial ratio. During reactive hyperemia, values with no coronary narrowing during aortic stenosis were similar to peak hyperemic flows with 60% coronary narrowing during control. With coronary narrowings estimated at 90%, mean coronary flow decreased with or without aortic stenosis. At this time transmural flow distribution also decreased but was consistently lower during aortic stenosis. These data suggest that in a model of aortic stenosis without left ventricular hypertrophy, the changes in aortic and left ventricular pressures during aortic stenosis periods were sufficient to influence total coronary flow and transmural distribution. The addition of a coronary narrowing produced further coronary effects.

**872 Topographic Changes in the Left Ventricle After Experimentally Induced Myocardial Infarction in the Rat**

CHARLES S. ROBERTS, DEREK MACLEAN, EUGENE BRAUNWALD, PETER R. MAROKO, and ROBERT A. KLONER

The factors which determine the thickness of transmural myocardial infarctions are unknown. Therefore, the relation between size and thickness of transmural infarcts was studied in 67 rats 21 days after occlusion of the left main coronary artery. Septal wall thickness was similar in rats with transmural infarcts and in sham-operated rats. There was no significant correlation between infarct size and thickness ($r = 0.10$) or circumferential length of infarct ($r = 0.17$). Large infarcts resulted in a 23% greater loss of myocardial tissue ($p < 0.001$), greater expansion of the left ventricular (LV) cavity area ($18 \pm 9$ mm$^2$ compared with $14 \pm 1$ mm$^2$ in small infarcts, $p < 0.005$), and lengthening of the noninfarcted septal wall ($7.2 \pm 1.1$ mm and $6.7 \pm 1.0$ mm in large and small infarcts, respectively [$p < 0.05$], and $6.3 \pm 0.1$ mm in shams). Increase in cavity area and noninfarcted septal length in infarcted ventricles suggested a volume overload hypertrophy, which at 3 weeks was nonetheless inadequate to provide as much normal muscle as was present in sham-operated rats. In an additional 9 rats with subendocardial infarctions (involving <75% of the LV wall from endo- to epicardium), the LV walls were thicker ($94 \pm 5$% of septal wall thickness, compared with $35 \pm 1$% for transmural infarcts, $p < 0.001$), and there was an inverse correlation between infarct size and thickness.

**877 Scar Thinning Due to Ibuprofen Administration After Experimental Myocardial Infarction**

EDWARD J. BROWN, Jr., ROBERT A. KLONER, FREDERICK J. SCHOEN, HAIM HAMMERMAN, SHARON HALE, and EUGENE BRAUNWALD

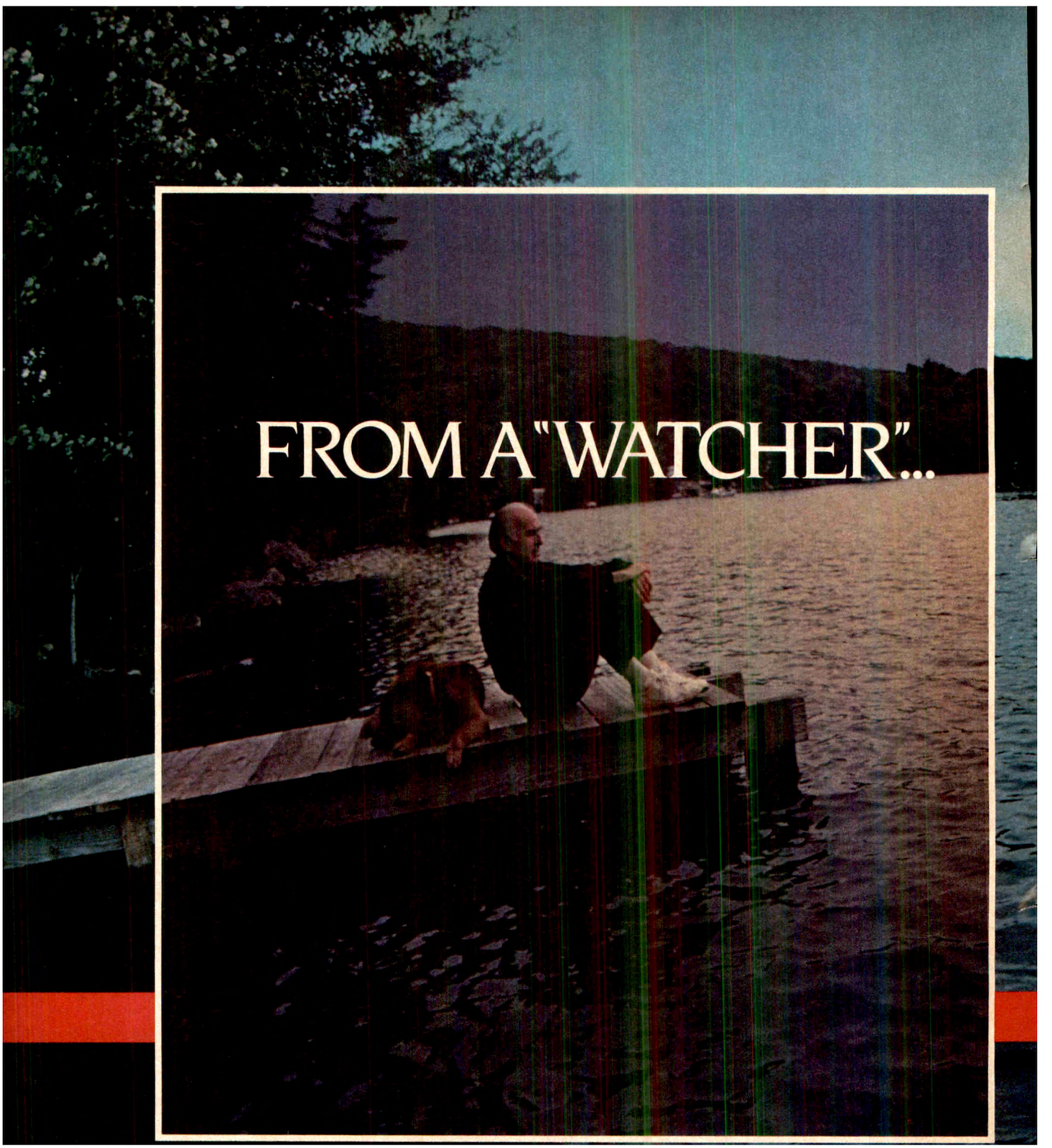
While much attention has been directed toward interventions which reduce myocardial infarct size, the effect of such agents on the healing phase of myocardial infarction is largely unknown. The effect of ibuprofen and aspirin on the healing of experimental canine myocardial infarctions was investigated. After coronary artery ligation, dogs received either saline solution, aspirin, high-dose ibuprofen or low-dose ibuprofen. Six weeks after coronary artery ligation the animals were killed and the hearts were removed for analysis of scar thickness. The myocardial infarct scars of the animals receiving ibuprofen were thinned compared with those of the control animals. Animals receiving aspirin demonstrated no scar thinning. Thus, ibuprofen increases the incidence of scar thinning after myocardial infarction.

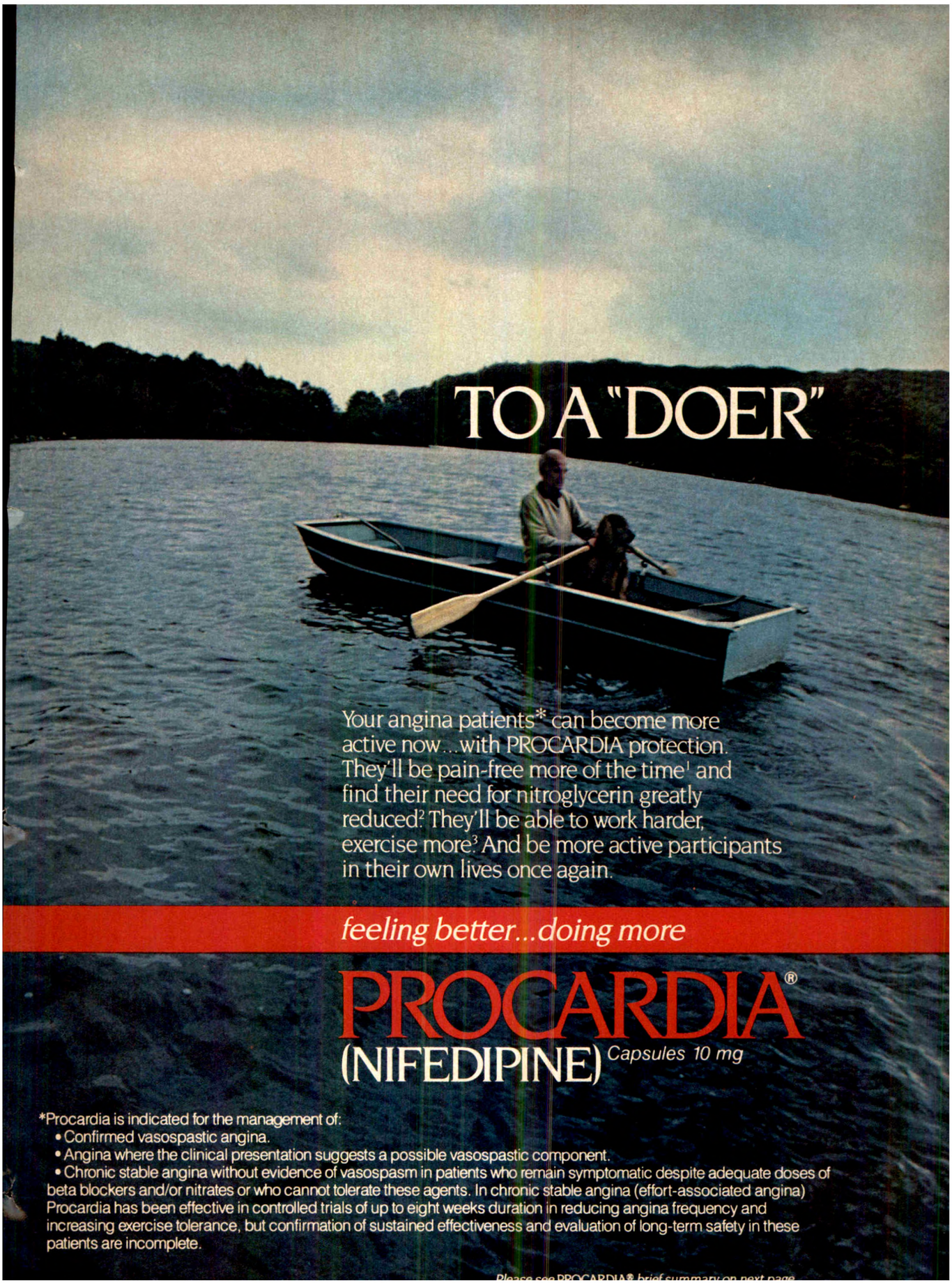
**884 Effects of Flurbiprofen in Altering the Size of Myocardial Infarcts in Dogs: Reduction or Delay?**

DAVID E. CHAMBERS, DEREK M. YELLON, DAVID J. HEARSE, and JAMES M. DOWNEY

Anti-inflammatory agents such as flurbiprofen have been reported to reduce myocardial infarct size. In the present study, a closed-chest model of permanent coronary occlusion was used. Groups of dogs were subjected to either 6 or 24 hours of elapsed ischemia. Flurbiprofen (1 mg/kg) was given immediately after occlusion and thereafter every 6 hours. Risk zone to infarct size ratios for the 24 hour group revealed that flurbiprofen treatment had no effect on infarct size. In contrast, when hearts were examined after only 6 hours of ischemia, infarct size was considerably reduced in the flurbiprofen-treated group. These results indicate that during myocardial ischemia, flurbiprofen may delay but not prevent tissue injury.


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Your angina patients* can become more active now...with PROCARDIA protection. They'll be pain-free more of the time[1] and find their need for nitroglycerin greatly reduced.[2] They'll be able to work harder, exercise more.[3] And be more active participants in their own lives once again.

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## (NIFEDIPINE) *Capsules 10 mg*

*Procardia is indicated for the management of:

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- Angina where the clinical presentation suggests a possible vasospastic component.
- Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) Procardia has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

*Please see PROCARDIA® brief summary on next page*

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# PROCARDIA®
# (NIFEDIPINE) *Capsules 10 mg*

## *–Usual effective dosage is 30-60 mg/day*

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because Procardia decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration is suggested. Close observation is especially recommended for patients taking medication known to lower blood pressure.

## *–Offers a favorable safety profile*

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.


**References:**

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Eng J Med* 302:1269-1273, June 5, 1980.
3. De Ponti C, De Biase AM, Pirelli S, et al: Effects of nifedipine, acebutolol, and their association on exercise tolerance in patients with effort angina. *Cardiology* 68 (suppl 2): 195-199, 1981.


**BRIEF SUMMARY**
**PROCARDIA® CAPSULES** For Oral Use
(nifedipine)

**INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA** (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

**II. Chronic Stable Angina (Classical Effort-Associated Angina):** PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

**CONTRAINDICATIONS:** Known hypersensitivity reaction to PROCARDIA.

**WARNINGS: Excessive Hypotension:** Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out.

**Increased Angina:** Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

**Beta Blocker Withdrawal:** Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

**Congestive Heart Failure:** Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

**PRECAUTIONS: General: Hypotension:** Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

**Peripheral edema:** Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

**Drug interactions:** Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

**ADVERSE REACTIONS:** The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

**Laboratory Tests:** Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

**HOW SUPPLIED:** Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

*More detailed professional information available on request.*


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To study the relation between myocardial thallium-201 uptake, thallium-201 release, and reduced coronary flow, isolated Langendorff rat hours (n = 8) were perfused for 3 hours at constant flows ranging from physiologic (12 ml/min) to severely ischemic (1.5 ml/min); thallium activity was monitoring with a scintillation probe. Each heart was perfused for 1 hour with thallium buffer, followed by 2 hours with thallium-free buffer at the same flow rate. Accumulation curves for all 4 flows were monoexponential. However, release curves during the 2 hours of washout with thallium-free buffer demonstrated a biexponential configuration. The early fast release component decreased with reductions in coronary flow, and the later slow release component did not vary significantly with flow. These data show that thallium clearance has at least 2 components: a rapid (possibly extracellular) component related to coronary flow and a slow (possibly intracellular) component independent of coronary flow. These findings should be useful in providing a better understanding of thallium redistribution observed clinically.

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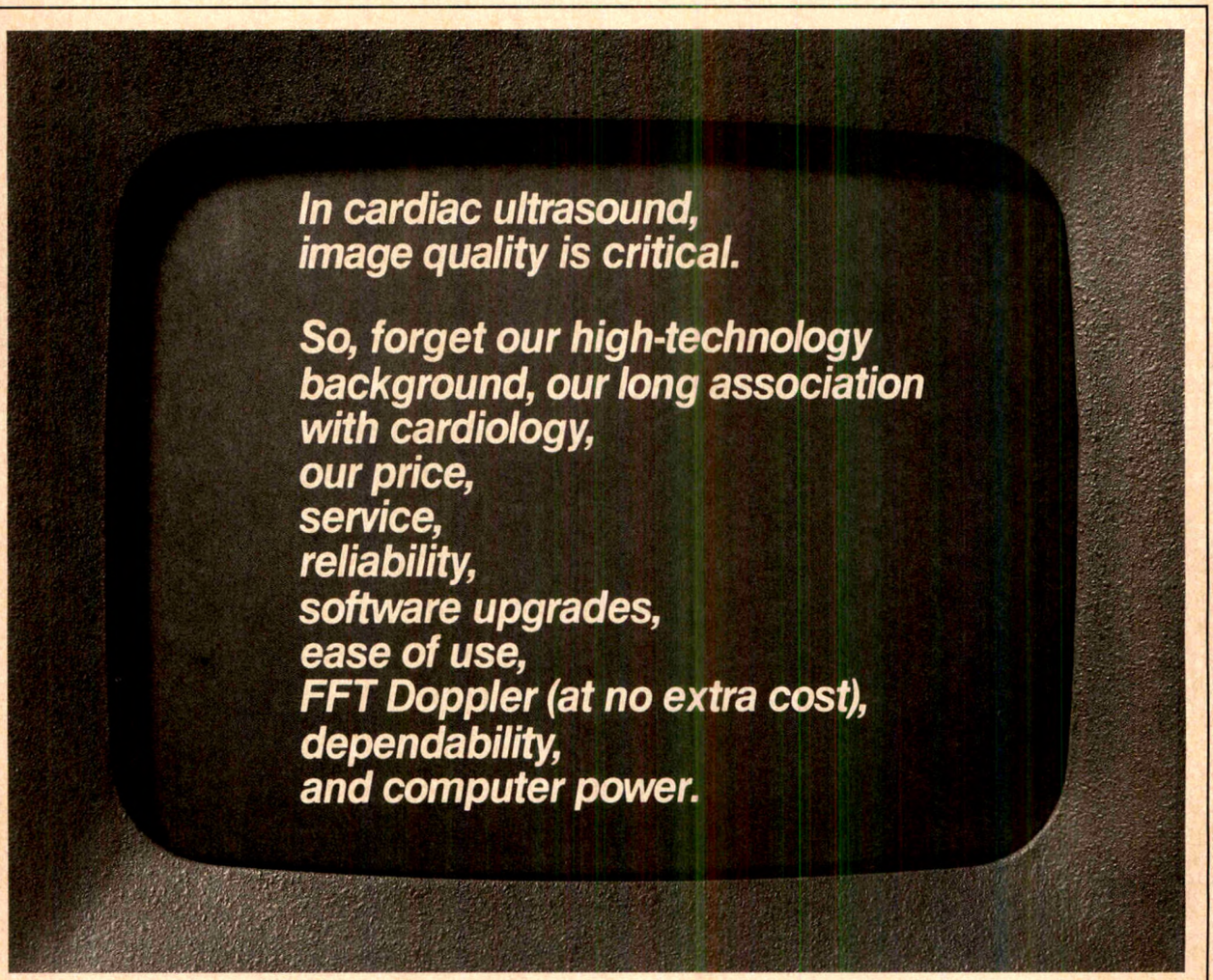
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VOLUME 51

NUMBER 5

CORONARY HEART DISEASE

# Influence of Partial Sympathetic Denervation on the Results Of Myocardial Revascularization in Variant Angina

AMADEO BETRIU, MD, JOSE LUIS POMAR, MD, MARTIAL G. BOURASSA, MD, and CLAUDE M. GRONDIN, MD

**Poor results of the aortocoronary bypass graft operation in the treatment of variant angina have been ascribed to recurrent vasospastic activity due to autonomic imbalance. Cardiac sympathetic denervation (plexectomy) may represent a rational approach in the prevention of vasospasm. To test the value of plexectomy in the treatment of variant angina, 31 patients were studied, 17 of whom (Group 1) underwent conventional coronary artery grafting whereas the remaining 14 (Group 2) underwent cardiac sympathetic denervation also. The 2 groups were similar with respect to age (54 ± 8 versus 50 ± 7 years), sex distribution (male/female ratio 12/5 versus 9/5), prevalence of coexisting effort angina (10 versus 12 patients), previous myocardial infarction (7 versus 4 patients), and duration of variant angina (3.3 ± 5.4 versus 2.4 ± 2.7 months). The left ventricular ejection fraction was comparable in both groups (60 ± 11 versus 60 ± 4%) as were left ventricular end-diastolic pressure (15 ± 4 versus 13 ± 5 mm Hg) and extent of coronary artery disease (65 versus 71% prevalence of multivessel disease).**

**The average duration of follow-up was 23 ± 15 months in Group 1 and 22 ± 18 months in Group 2 (p = not significant [NS]). There were no operative deaths. Four patients, 2 in each group, had a perioperative myocardial infarction. Seven patients in Group 1 and 1 patient in Group 2 had recurrent variant angina. There was sudden death and 2 infarcts in Group 1. Actuarial curves showed the cumulative probability of recurrent variant angina to be significantly lower ($p < 0.05$ and $p < 0.001$ at 6 and 10 months, respectively) in Group 2. This study suggests that cardiac sympathetic denervation may prevent recurrent vasospastic activity in variant angina.**

Calcium channel-blocking agents provide effective control of symptoms in most patients with the variant form of angina pectoris.[1–8] Nevertheless, coronary artery grafting is currently offered to a subset of patients with variant angina who present with fixed severe coronary artery stenoses and show poor response to medical treatment. Unfortunately, aortocoronary bypass grafting appears less successful in the variant form than in the classic form of angina,[9–11] as evidenced by a higher rate of graft occlusion[9,12–15] and of recurrence of symptoms despite graft patency.[1] Coronary artery spasm, the primary pathogenetic mechanism in variant angina[16–18] has been held responsible for the surgical failures.[1,9–11] Recent studies suggest that coronary artery spasm develops by activation of alpha receptors as a result of increased sympathetic activity.[19–21] Thus, the association of sympathetic denervation (plexectomy)

From the Department of Surgery, Montreal Heart Institute and the University of Montreal Medical School, Montreal, Quebec, Canada. Dr. Betriu was a visiting scientist at the Montreal Heart Institute at the time this study was performed. Manuscript received June 28, 1982; revised manuscript received November 22, 1982, accepted November 24, 1982.

Address for reprints: Claude M. Grondin, MD, Montreal Heart Institute, Department of Surgery, 5000 East Belanger Street, Montreal, Quebec, Canada, H1T 1C8.

**TABLE I Clinical, Catheterization, and Follow-Up Data**

| Case | Age (yr) & Sex | Duration of VA (mo) | Effort Angina | Prior MI | Drug and Daily Dose (mg) | LVEDP (mm Hg) | EF (%) | % of CA Stenosis | | | | ACBG (n) | Extent of Follow-Up (mo) | Follow-Up Events |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | ML | LAD | RCA | LCx | | | |
| | | | | | | Group 1 | | | | | | | | |
| 1 | 51M | 1 | 0 | 0 | N40 | 12 | 60 | | 70 | | | 2 | 36 VA at 5 mo | |
| 2 | 60F | 18 | + | 0 | P360, I80 | 14 | 62 | | 75 | | | 1 | 45 | VA at 1 week and at 10 mo |
| 3 | 56M | 2 | 0 | 0 | P320, I60 | 16 | 75 | | 70 | 70 | 70 | 3 | 48 | VA at 1 week |
| 4 | 64M | 2 | 0 | 0 | D360 | 18 | 60 | | 90 | | | 1 | 7 | Va immediate postop |
| 5 | 40F | 3 | 0 | 0 | P360, I80 | 14 | 62 | 60 | | | | 1 | 48 | Periop MI, VA at 3 mo |
| 6 | 55M | 1 | 0 | 0 | D360 | 12 | 64 | | 99 | | | 2 | 9 | Periop MI |
| 7 | 42M | 1 | + | + | N80 | 14 | 41 | | 80 | 99 | 70 | 5 | 10 | |
| 8 | 65M | 5 | + | + | N80, D360 | 10 | 57 | | 90 | | 90 | 2 | 10 | |
| 9 | 44M | 2 | + | 0 | V480 | 14 | 70 | 50 | | 50 | | 2 | 13 | MI at 3 mo |
| 10 | 56M | 1 | + | + | N80 | 12 | 45 | | 100 | 80 | 90 | 5 | 18 | |
| 11 | 45M | 1 | + | + | N80 | 16 | 48 | | 80 | 95 | 80 | 2 | 20 | Sudden death at 20 mo |
| 12 | 62M | 1 | + | 0 | D360 | 11 | 69 | | | 80 | | 1 | 24 | |
| 13 | 54M | 1 | 0 | 0 | V480 | 11 | 73 | | 60 | | 50 | 1 | 18 | VA at 9 mo |
| 14 | 50M | 1 | + | + | N80, D360 | 12 | | | 80 | 70 | 70 | 3 | 18 | VA at immediate postop at 6 mo MI at 14 mo |
| 15 | 66F | 1 | 0 | + | N80 | 18 | 62 | | | 95 | | 1 | 26 | |
| 16 | 53F | 16 | + | + | PH400 | 23 | 41 | | 90 | 90 | 90 | 3 | 42 | |
| 17 | 56F | 2 | + | 0 | D360 | 25 | 73 | 75 | 75 | 99 | 99 | 6 | 1 | |
| Mean ±SD | 54 ± 8 | 3.3 ±5.4 | | | | 14.8 ±4.2 | 60.1 ±11.1 | | | | | 2.4 ±1.5 | 23.12 ±15.2 | |
| | | | | | | Group 2 | | | | | | | | |
| 18 | 50M | 3 | + | 0 | D360 | 8 | 66 | | 85 | 60 | 50 | 3 | 8 | Periop MI |
| 19 | 54M | 2 | + | 0 | N80, D360 | 14 | 64 | | 99 | | 90 | 2 | 9 | |
| 20 | 47F | 2 | + | 0 | D360 | 20 | 67 | | 70 | | 90 | 2 | 9 | |
| 21 | 50M | 3 | + | 0 | V480 | 12 | 70 | 75 | 75 | | | 2 | 11 | Periop MI |
| 22 | 44M | 1 | 0 | + | N80 | 14 | 55 | | 90 | 90 | | 1 | 14 | |
| 23 | 56M | 2 | + | + | D360 | 10 | 69 | | 80 | | | 2 | 18 | |
| 24 | 44M | 1 | + | 0 | N80, D360 | 8 | 58 | | 80 | | | 2 | 14 | Acute liver failure and death |
| 25 | 64F | 9 | + | 0 | V480 | 10 | 57 | | 90 | | | 1 | 24 | VA (immediate postop S-T↑) |
| 26 | 35F | 1 | + | 0 | D360 | 12 | 65 | | 60 | | | 1 | 26 | |
| 27 | 47F | 2 | + | + | N80 | 20 | 57 | | 90 | 90 | 90 | 2 | 30 | |
| 28 | 47F | 1 | + | 0 | D360 | 7 | 57 | | 60 | | 90 | 2 | 30 | |
| 29 | 47M | 7 | + | 0 | PH400 | 18 | 54 | | 80 | | | 2 | 60 | |
| 30 | 54M | 1 | 0 | 0 | P320, I40 | 10 | 60 | | 80 | | 50 | 1 | 60 | |
| 31 | 62M | 1 | + | + | D360 | 22 | 45 | | | 90 | | 1 | 1 | |
| Mean ±SD | 50 ± 7 | 2.4 ±2.7 | | | | 13.2 ±4.9 | 60.2 ±4.2 | | | | | 1.7 ±0.6 | 22.43 ±18.3 | |

**TABLE I (Continued)**

| | Age | Sex | Duration of VA (mo) | Effort Angina | Prior MI | Drug and Daily Dose (mg) | LVEDP (mm Hg) | EF (%) | % of CA Stenosis | | | | ACBG (n) | Extent of Follow-Up (mo) | Follow-Up Events |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | ML | LAD | RCA | LCx | | | |
| Group 1 Versus Group 2 | | | | | | | | | | | | | | | |
| Tests | | | | | | | | | | | | | | | |
| $t$ | 1.42 | ... | 0.61 | ... | ... | ... | 0.98 | 0.05 | ... | ... | ... | ... | 1.55 | 0.11 | ... |
| $\chi^2$ | ... | 0.14 | ... | 2.69 | 0.53 | ... | ... | ... | ... | 0.01* | 2.37* | 2.69* | ... | ... | ... |
| p | 0.2 | 0.7 | 0.6 | 0.2 | 0.5 | ... | 0.4 | 0.9 | ... | 0.7 | 0.2 | 0.1 | 0.2 | 0.9 | ... |
| | NS | NS | NS | NS | NS | | NS | NS | | NS | NS | NS | NS | NS | |

* Values refer to the presence of 1-, 2-, and 3-vessel disease, respectively.

ACBG = aortocoronary bypass graft; CA = coronary artery; D = diltiazem; EF = ejection fraction; I = isosorbide dinitrate; LAD = left anterior descending artery; LCx = left circumflex artery; LVEDP = left ventricular end-distolic pressure; MI = myocardial infarction; ML = main left; N = nifedipine; NS = not significant; P = propranolol; Periop = perioperative; PH = perhexiline maleate; Postop = postoperative; RCA = right coronary artery; S-T↑ = elevated S-T segment; $t$ = Student's $t$ test; V = verapamil; VA = variant angina; $\chi^2$ = chi-square.

and coronary artery grafting may represent a reasonable surgical approach for patients with variant angina and obstructive coronary artery lesions.

Plexectomy in the treatment of variant angina was introduced in 1977.[10] Recently, Bertrand et al[11] reported on 22 patients undergoing combined plexectomy and coronary artery bypass grafting. To our knowledge no other clinical study dealing with cardiac denervation in the management of variant angina has been reported. To further elucidate the possible advantages of myocardial revascularization associated with plexectomy over the former procedure alone we studied 31 consecutive patients, 14 of whom had combined coronary artery bypass grafting and partial sympathetic denervation.

## Methods

**Patient group:** During a 5-year period ending in December 1981, 31 patients presenting with the variant form of angina underwent myocardial revascularization at the Montreal Heart Institute. Variant angina was defined as that occurring at rest and associated with a transient elevation of the S-T segment of ≥0.2 mV and no subsequent evidence of myocardial infarction. Surgery was performed because of failure of medical treatment to control the chest pain or because of the severity and location of coronary artery lesions, or both. Seventeen patients (Group 1) underwent aortocoronary bypass operation alone; the remaining 14 (Group 2) underwent, in addition to coronary artery grafting, partial sympathetic denervation.

**Clinical characterization (Table I):** The mean age of Group 1 was 54 years (range 42 to 66) and that of group 2 was 50 years (range 35 to 64). There were 12 men and 5 women in Group 1 and 9 men and 5 women in Group 2. Differences in age and sex distribution between the 2 groups were not statistically significant. Coexisting angina on effort was present in 10 patients in Group 1 and in 12 in Group 2 (NS). The prevalence of previous myocardial infarction (7 patients in Group 1 and 4 patients in Group 2) was similar in both groups. Recent onset variant angina (≤1 month in duration) was found in 9 patients in Group 1 and 6 in Group 2 (NS). Three patients in Group 1 and 2 in Group 2 were treated with long-acting nitrates and propranolol, whereas the remaining 26 patients (14 in Group 1 and 12 in Group 2) received calcium antagonists. The choice of a particular calcium-channel blocking agent depended on its availability at the time.

**Hemodynamic and angiographic data:** Left ventricular end-diastolic pressures were comparable in both groups (14.8 ± 4.2 mm Hg in Group 1 and 13.2 ± 4.5 mm Hg in Group 2) as were the left ventricular ejection fractions (60.1 ± 11.1% in Group 1 and 60.2 ± 4.2% in Group 2). Coronary artery disease was considered significant when the luminal diameter was narrowed by ≥50%. Stenoses of the diagonal or the marginal branches were considered lesions of the left anterior descending or the circumflex coronary artery.

Single-vessel disease was present in 7 patients (41%) in Group 1 and 6 patients (43%) in Group 2, whereas double- and triple-vessel disease, respectively, were found in 3 (18%) and 6 (35%) patients in Group 1 and in 7 (50%) and 2 (14%) patients in Group 2. Three patients in Group 1 and 1 in Group 2 had left main coronary artery stenosis, associated in 3 instances with lesions in other coronary arteries. Differences in the incidence of single-, double-, and triple-vessel disease and those found between single- and multiple-vessel involvement did not reach statistical significance.

**Surgical procedures:** The electrocardiogram (lead $CM_5$) was monitored throughout the procedure. A nitroglycerin drip infusion was started at induction of anesthesia and continued for at least 24 hours postoperatively. Standard cardiopulmonary bypass and systemic hypothermia (24°C) was used. Intermittent crystalloid cold cardioplegia and topical hypothermia were used for myocardial protection. Distal anastomoses were performed first through a single aortic cross clamping. A mean of 2.3 grafts per patient was inserted in Group 1, whereas an average of 1.7 ± 0.6 grafts were inserted in patients in Group 2 (NS). Partial sympathetic denervation was carried out after completion of the proximal anastomosis, with the heart fibrillating and the aorta unclamped, according to a technique previously described.[10] Briefly, the procedure involves removal of the adventitia of the ascending aorta, of the anterior and superior aspect of the main pulmonary artery and its right and left branches, and the inferior aspect of the aortic arch including the triangle of tissue overlying the carina and left main bronchus underneath the aortic arch. Histologic examination showed the presence of ganglion cells and nerve fibers in all instances.

Perioperative myocardial infarction was diagnosed when both enzymatic (myocardial-specific creatine kinase [CK-MB]) and electrocardiographic criteria were present. Serial blood samples for enzyme determination were withdrawn the day before operation, at the beginning of cardiopulmonary bypass, 6 and 8 hours postoperatively, and daily for the 5 following days. The upper limit of normally expected postoperative CK-MB activity was considered 120 IU/liter. This corresponds to the 95% confidence limits of the mean peak CK-MB activity (61.18 ± 28.41 IU/liter) of a series of 79 patients undergoing uneventful simple coronary artery bypass grafting in our institution. Standard 12-lead electrocardiograms were obtained the day before and immediately after operation, daily for 5 days, and before hospital discharge. Electrocardiograms were also obtained as deemed clinically appropriate. The electrocardiographic criterion for a new infarction was the appearance of a Q wave of at least 0.04 second in duration in 2 or more adjacent leads.

**Follow-up:** After discharge, each patient returned to the outpatient clinic at 1 month, 3 months, and every 6 months thereafter. On each visit a standardized questionnaire, physical examination, and electrocardiogram were recorded. Mean follow-up was 23.12 ± 15.2 months in Group 1 and 22.43 ± 18.3 months in Group 2 (NS). Two patients in Group 1 were lost to follow-up at 9 and 18 months.

**Statistical analysis:** Data are expressed as mean ± standard deviation. Clinical and angiographic data were compared by using the unpaired $t$ test or the chi-square test when appropriate. Actuarial curves were plotted with the follow-up data. Cardiac death, myocardial infarction, and variant angina were considered endpoints. The difference between groups was assessed by the Mantel-Haenszel test.[22] A probability (p) value $<0.05$ was considered significant.

## Results

**Group 1:** There were no surgical deaths. In 2 patients (Cases 5 and 6) a perioperative anterior myocardial infarction developed. Patient 5, who had a single bypass to the left anterior descending coronary artery for a 60% stenosis of the main left stem, again underwent cardiac catheterization 3 weeks after the infarct. His bypass graft was occluded and he underwent a second operation in which a double graft to the left anterior descending and to the circumflex coronary artery was constructed. Three months later, chest pain with transient S-T segment elevation at rest recurred and a second postoperative angiogram was obtained. The bypass graft to the left anterior descending artery was occluded and that of the circumflex was patent. The patient was given nifedipine (20 mg, 4 times a day) and has remained asymptomatic. Patient 6 has been free of symptoms since his perioperative infarct. There were 2 other infarcts in this group, at 3 and 14 months (Cases 9 and 14, respectively) and 1 sudden cardiac death at 20 months (Case 11).

Spontaneous transient S-T segment elevation without further evidence of infarction was documented in 4 patients (Cases 2, 3, 4, and 14) during hospitalization. Patients 4 and 14 showed the electrocardiographic changes shortly after their arrival in the recovery room, whereas Patients 2 and 3 had the attack 1 week after the operation. In all instances the S-T segment elevation occurred in the same leads as in those preoperatively (precordial in Patients 2, 3, and 4 and in the inferior leads in Patient 14) and disappeared after the administration of a bolus dose of nitroglycerin. These patients were given calcium-channel blocking agents for 3 months after discharge from the hospital.

Five patients (Cases 1, 2, 5, 13, and 14) had recurrent chest pain at rest which developed at variable intervals after operation (at 3, 5, 6, 9, and 10 months). All 5 patients were off medication at the time of recurrence and all but 1 (Case 6) were relieved of angina with the use of calcium-channel blocking drugs. Patient 2, who showed both early and late recurrent variant angina, underwent a repeat angiographic study. Although his bypass graft to the left anterior descending coronary artery was patent, a transient occlusion of the distal vessel was elicited by administration of ergonovine. In Patient 13, angiographic evaluation performed shortly after onset of recurrent angina showed patency of the graft and an unchanged coronary anatomy.

**Group 2:** All patients survived the operation. There were 2 perioperative infarctions, anterior in Patient 18 and inferior in Patient 21. Both patients have remained symptom-free. Patient 25 presented with several episodes of S-T segment elevation within the first 48 hours. The first of these episodes occurred in the operating room and subsided after administration of papaverine into the graft to the left anterior descending coronary artery. Subsequent attacks required repeat intravenous bolus doses of nitroglycerin in addition to the permanent drip infusion. Control of these episodes was achieved by the use of calcium-channel blocking agents (through the nasogastric tubing during the first 12 hours). Both diltiazem and nifedipine were administered to this patient until the 7th postoperative day, when unexpected left ventricular failure occurred. The latter responded after several hours to infusion of calcium and dopamine. This patient has been well after cessation of calcium blocking agents.

There was 1 noncardiac death (Patient 24) caused by Australia antigen hepatitis 14 months after operation. No late myocardial infarction or recurrent variant angina was documented in this group. Two asymptomatic patients (Cases 26 and 30) underwent angiography, which demonstrated patent bypasses and no significant change in the coronary arteries.

**Comparison of the 2 groups:** The chi-square test disclosed significant differences between the 2 groups with respect to the overall prevalence of new coronary events ($p < 0.05$), but no difference was found when prevalence of recurrent variant angina or that of peri- and postoperative myocardial infarction and cardiac death were analyzed separately.

Actuarial curves showed the cumulative probability of new coronary events to be significantly different in the 2 groups ($p < 0.01$ at 6 months and $p < 0.001$ at 10 months). Cumulative probability or recurrent variant angina was also different in each group ($p < 0.05$ at 6 months and $p < 0.001$ at 10 months). When only myocardial infarction and death were selected as endpoints, the actuarial analysis failed to show differences between the study groups (Fig. 1).

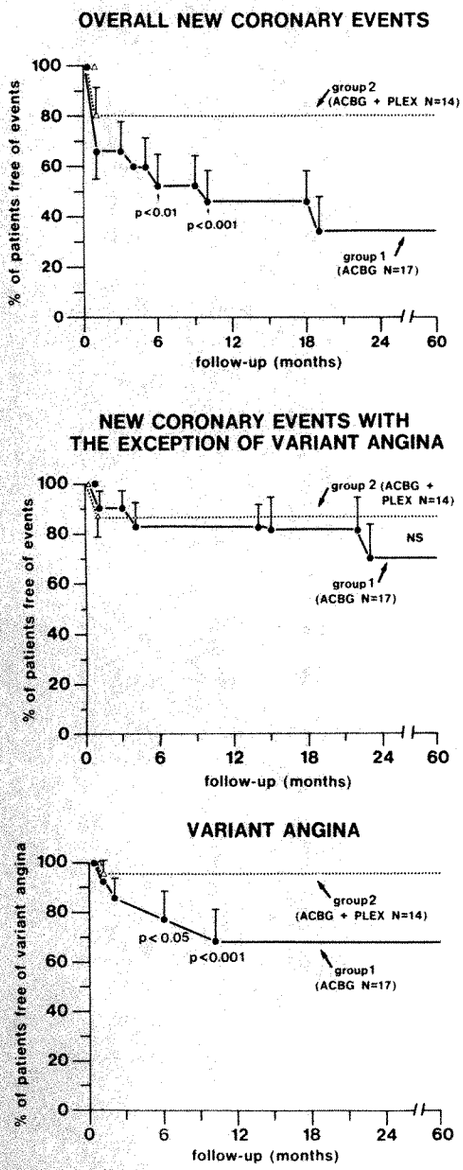



**FIGURE 1.** Actuarial curves with standard error of the mean showing the cumulative probability of overall new coronary events (**top**), that of new coronary events with the exception of variant angina (**middle**), and that of variant angina (**bottom**). Note that when only myocardial infarction and death were selected as endpoints, actuarial analysis failed to show differences in the 2 groups. The differences reach significance at the 6- and 10-month points (**arrow**). ACBG = aortocoronary bypass graft; PLEX = plexectomy.

## Discussion

The cyclic nature of variant angina that includes long asymptomatic time intervals and spontaneous remissions makes assessment of the effectiveness of any treatment quite difficult.[23–25] Recently, calcium-channel blocking agents have proved the therapy of choice in this condition.[3,7,26] Patients in whom spasm and severe coronary artery stenoses coexist are still considered surgical candidates. The results of coronary artery bypass surgery in variant angina are not as gratifying as those obtained in conventional effort angina, as evidenced by the lower patency rate and higher recurrence of symptoms.[9,12–15] In addition, a higher incidence of perioperative myocardial infarction has been reported.[9] Coronary artery spasm, the underlying mechanism of variant angina,[16–18,27–30] conceivably may occur distal to a patent graft and jeopardize the results of an otherwise successful operation. Prevention of coronary spasm therefore appears to be a logical complement to revascularization procedures in the treatment of variant angina. Although the mechanism for coronary spasm remains largely unknown, the autonomic nervous system appears to play an important role. Yasue et al[19] suggested that attacks of variant angina are initiated by enhanced parasympathetic activity, although the parasympathetic neurotransmitter, acetylcholine, causes direct coronary vasodilatation. Acetylcholine also induces release of norepinephrine from the postganglionic sympathetic nerve terminals in the heart which, in turn, causes vasoconstriction of large coronary arteries by activating alpha receptors. Thus, cardiac sympathetic denervation might be a valid approach in the prevention of coronary artery spasm.

Permanent and complete cardiac denervation is difficult to achieve short of allotransplantation. Denervation obtained by autotransplantation[31] is complete, but temporary as fibers ultimately regenerate and cross the suture lines. The heart receives its sympathetic innervation mainly from the cervical ganglia. It has not been clearly demonstrated that the sympathetic system below the stellate ganglion participates in the cardiac innervation. Nonetheless, the sympathetic fibers originating from the lower cervical and upper thoracic ganglia merge with vagal fibers to form cardiac plexuses. The major plexuses are located anterior to the aorta and trachea and behind the left atrium near the interatrial septum. The pretracheal plexus contains several ganglia, including the large and inconsistent ganglion of Wrisberg. Section of the preaortic fibers and removal of the pretracheal plexus may be sufficient to sever connections with the coronary plexus.

Although sympathetic cardiac denervation was used initially to interrupt pain fibers in patients with angina pectoris,[32,33] its use in the treatment of variant angina is recent.[10] It was first performed in 2 patients who

presented with variant angina associated with organic coronary artery lesions. Both remained free of symptoms 12 and 18 months after operation.[10] More recently, Bertrand et al[11] compared the results in 22 patients undergoing combined plexectomy and coronary artery bypass grafting with those obtained in 13 patients who had isolated revascularization procedures. They observed a 5% recurrence rate of variant angina in the former group, versus 18% in the latter. Although these figures suggest that associated plexectomy improves the results of the aortocoronary bypass operation in variant angina, the significance of their findings remains unsettled because no statistical analysis was applied to their data. However, the extent of follow-up was longer in the series of patients without plexectomy, and that may account—at least in part—for the higher rate of recurrent angina observed in this group.

In contrast, the present study concerns only patients whose operations were performed during the same time frame. Because the choice of plexectomy was a medical decision, our study may be regarded as an open-label trial and thus subject to bias. However, the 2 groups were homogeneous with regard to age and sex distribution, prevalence of coexistent effort angina and previous myocardial infarction, and time of onset of variant angina. In addition, left ventricular function, as assessed by left ventricular end-diastolic pressure and ejection fraction, was similar in both groups. As for the extent of coronary artery lesions, no significant differences were found in the 2 study groups, although the incidence of 3-vessel involvement was greater in Group 1 (35% versus 14%); this difference failed to reach statistical significance because of the small sample size. Furthermore, it is not likely that the results could be influenced seriously by differences in the severity of coronary artery disease as the outcome of the 2 groups appears related only to recurrences in variant angina.

Our series did not show an increased operative mortality in variant angina. In 1974, Gaasch et al[9] reported from the literature a 12.5% rate of operative deaths. Composite results from 17 series[10] totaling 126 patients showed an operative mortality of 10%, higher than that generally observed. There was no operative death in the current series, a fact that may be related to improved intraoperative myocardial protection as well as the routine use of intravenous nitroglycerin during operation and the first postoperative day.

The rate of perioperative myocardial infarction in this study (13%) is comparable with that observed in patients undergoing coronary artery grafting before the use of cardioplegia but superior to the current rate with cardioplegia.[34] These findings differ from those of previous reports showing a high incidence of perioperative myocardial infarction in variant angina.[14,15,35] However, the value of these reports is limited as they deal with small population samples. The composite results from 17 series[10] show a perioperative infarction rate of 15%, comparable with that in the current study.

No myocardial infarction was demonstrated in the patient with repeated episodes of S-T segment elevation within 48 hours after plexectomy. Although variant angina could not be demonstrated on long-term follow-up, the early electrocardiographic changes indicate that vasospastic activity could not be prevented by plexectomy. Whether partial sympathetic denervation was adequately achieved or not in this patient is difficult to assess. However, because autonomic dysfunction is certainly not the only cause of spasm, an increase in circulating catecholamines or changes in the coronary vessel walls themselves could account for the recurrent vasospasm.

Although the hypothesis that plexectomy is effective in preventing recurrent vasospastic activity is supported by our data, these must be interpreted with caution. Several methodologic difficulties arise in assessing therapeutic efficacy in the setting of coronary artery spasm. As mentioned earlier, the cyclic nature of the disease is a confounding factor that often magnifies the apparent benefits of any therapeutic intervention. Because patients tend to present to physicians at peak of disease activity, improvement may occur regardless of the therapy used. It should be stressed in this respect that 40% of patients in Group 1 have not manifested evidence of recurrent vasospasm since operation. We did not attempt to elicit vasospasm by ergonovine injection. This test may be negative in asymptomatic patients.[25,26] Because recurrence of pain was the only clinical variable separating the 2 groups of patients, it is conceivable that plexectomy, in fact, leads to interruption of pain fibers rather than to abolition of spasm. Effort angina did occur in both groups, however, which suggests that interruption of afferent pain fibers was not the primary mechanism for the relief of variant angina. Larger series, perhaps with pre- and postoperative ergonovine tests and a longer follow-up, will be required to validate our data. Nonetheless, as plexectomy does not increase the surgical risk, the association of this procedure with aortocoronary bypass grafting may be considered in the management of patients presenting with refractory variant angina. At present, plexectomy is not advocated for patients with variant angina who have no significant obstructive coronary disease.

## References


1. **Endo M, Kanda I, Hosoda S, Hayashi H, Hirosawa K, Konno S.** Prinzmetal's variant form of angina pectoris: re-evaluation of mechanisms. Circulation 1975;52:33–37.
2. **Raabe DS.** Treatment of angina pectoris with perhexiline maleate. Chest 1979;75:152–156.
3. **Antman E, Muller J, Goldberg S, MacAlpin R, Rubenfire M, Tabatznic B, Liang C, Heupler F, Achuff S, Reichek N, Geltman E, Kerin N, Neff RK, Braunwald E.** Nifedipine therapy for coronary spasm: experience in 127 patients. N Engl J Med 1980;302:1269–1273.
4. **Raizner AE, Gaston W, Chahine RA, Fulweber R, Rochelle D, Miller RR, Luchi RJ.** The effectiveness of combined verapamil and nitrate therapy in Prinzmetal's variant angina (abstr). Am J Cardiol 1980;45:439.
5. **Théroux P, Waters DD, Affaki GS, Crittin J, Bonan R, Mizgala HF.** Provocative testing with ergonovine to evaluate the efficacy of treatment with calcium antagonists in variant angina. Circulation 1979;60:504–510.
6. **Rosenthal SJ, Ginsberg R, Lamb IH, Baim DS, Schroeder JS.** Efficacy of diltiazem for control of symptoms of coronary artery spasm. Am J Cardiol 1980;46:1027–1032.
7. **Kishida H.** Application of calcium antagonists in patients with Prinzmetal angina pectoris. In: Fleckenstein A, Roskamm H, eds. Calcium Antagonism. Heidelberg: Springer Verlag, 1980;246–251.
8. **Johnson SM, Mauritson DR, Willerson JT, Hillis LD.** A controlled trial of verapamil for Prinzmetal's variant angina. N Engl J Med 1981;304:862–866.
9. **Gaasch WH, Lufschanowski R, Leachman RD, Alexander JK.** Surgical management of Prinzmetal's variant angina. Chest 1974;66:614–621.
10. **Grondin CM, Limet R.** Sympathetic denervation in association with coronary artery grafting in patients with Prinzmetal's angina. Ann Thorac Surg

1977;23:111–117.
11. **Bertrand ME, Lablanche JM, Rousseau MF, Warembourg HH, Stankowtak C, Soots G.** Surgical treatment of variant angina: use of plexectomy with aortocoronary bypass. Circulation 1980;61:877–882.
12. **Buonanno C, Manucuso M, Zanini S.** Diagnosi e triattamento dell'insufficienza coronarica acuta: A proposito di sei casi. G Ital Cardiol 1972;2: 893–906.
13. **Bolooki H, Vargas A, Ghahramani A, Sommer LS, Orvald T, Jude JR.** Aortocoronary bypass graft for preinfarction angina. Chest 1972;61: 247–252.
14. **Betriu A, Solignac A, Bourassa MG.** The variant form of angina: diagnostic and therapeutic implications. Am Heart J 1974;87:272–278.
15. **Bodenheimer M, Lipski J, Donoso E, Dack S.** Prinzmetal's variant angina: a clinical and electrocardiographic study. Am Heart J 1974;87:304–313.
16. **Oliva PB, Potts DE, Pluss RG.** Coronary arterial spasm in Prinzmetal angina. Documentation by coronary arteriography. N Engl J Med 1973;288:745–751.
17. **Dhurandar RW, Watt DL, Silver MD, Trimble AS, Adelman AG.** Prinzmetal's variant form of angina with arteriographic evidence of coronary arterial spasm. Am J Cardiol 1972;30:902–905.
18. **Maseri A, Mimmo R, Chierchia S, Marchesi C, Pesola A, L'Abbate A.** Coronary artery spasm as a cause of acute myocardial ischemia in man. Chest 1975;68:625–633.
19. **Yasue H, Touyama M, Shimamoto M, Kato H, Tanaka S, Akiyama F.** Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. Circulation 1974;50:534–539.
20. **Robertson D, Robertson RM, Nies AS, Oates JA, Friesinger GC.** Variant angina pectoris: investigation of indexes of sympathetic nervous system function. Am J Cardiol 1979;43:1080–1085.
21. **Ricci DR, Orlick AE, Cipriano PR, Guthaner DF, Harrison DC.** Altered adrenergic activity in coronary arterial spasm: insight into the mechanism based on study of coronary hemodynamics and the electrocardiogram. Am J Cardiol 1979;43:1073–1079.
22. **Kalbfleisch JD, Prentice RL.** The statistical analysis of failure time data. New York: John Wiley, 1980:70–86.
23. **Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N.** Angina pectoris. I. A variant form of angina pectoris. Am J Med 1959;27:375–388.
24. **Yasue H, Omote S, Takizawa A, Nagao M, Miwa K, Tanaka S.** Circadian variation of exercise capacity in patients with Prinzmetal's variant angina: role of exercise-induced coronary artery spasm. Circulation 1979;59: 938–954.
25. **Waters DD, Szlachcic J, Théroux P, Dauwe F, Mizgala HF.** Ergonovine testing to detect spontaneous remissions of variant angina during long-term treatment with calcium antagonist drugs. Am J Cardiol 1981;47:179–84.
26. **Waters DD, Théroux P, Szlachcic J, Dauwe F.** Provocative testing with ergonovine to assess the efficacy of treatment with nifedipine, diltiazem and verapamil in variant angina. Am J Cardiol 1981;48:123–130.
27. **Berman MD, McLaughlin PR, Huckell VF, Mahon WA, Morch JE, Adelman AG.** Prinzmetal's angina with coronary artery spasm: angiographic, pharmacologic, metabolic and radionuclide perfusion studies. Am J Med 1975;60:727–732.
28. **Maseri A, Parodi O, Severi S, Pesola A.** Transient transmural reduction of myocardial blood flow, demonstrated by thallium-201 scintigraphy as a cause of variant angina. Circulation 1975;54:280–288.
29. **McLaughlin PR, Doherty PW, Martin RP, Goris ML, Harrison DC.** Myocardial imaging in a patient with reproducible variant angina. Am J Cardiol 1977; 39:126–129.
30. **Ricci DR, Orlick AE, Doherty PW, Cipriano PR, Harrison DC.** Reduction of coronary blood flow during coronary artery spasm occurring spontaneously and after provocation by ergonovine maleate. Circulation 1978; 57:392–395.
31. **Clark DA, Quint RA, Mitchell RL, Angell WW.** Coronary artery spasm. Medical management, surgical denervation and autotransplantation. J Thorac Cardiovasc Surg 1977;73:332–339.
32. **Arnulf G.** De la section du plexus préaortique: justification et technique. Presse Med 1939;94:1635–1641.
33. **Lindgren I, Olivecrona H.** Surgical treatment of angina pectoris. J Neurosurg 1947;4:19–23.
34. **Berger RL, Davis KB, Kaiser GC, Foster ED, Hammond GL, Tong TGL, Kennedy W.** Preservation of the myocardium during CABG (abstr). Circulation 1980;62:Suppl III:III-40.
35. **Gaasch WH, Adyanthaya AJ, Wang JH, Pickering E, Quinones MA, Alexander JK.** Prinzmetal's variant angina: hemodynamic and angiographic observations during pain. Am J Cardiol 1975;35:683–690.

# Digital Angiography in Assessment of Ventricular Function And Wall Motion During Pacing in Patients With Coronary Artery Disease

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**Using digital subtraction angiography, left ventriculograms were obtained with 10 ml of iodinated contrast material in 21 patients both at rest and during atrial pacing. In 15 patients with significant coronary artery lesions (CAD) (>50% diameter narrowing in at least 1 major artery), ejection fraction decreased during atrial pacing from a mean of 62 ± 14% to 51 ± 15% ($p < 0.001$). In 14 (93%) of 15 patients, ejection fraction decreased or was unchanged during pacing. In 6 patients with chest pain but normal coronary arteries, ejection fraction increased from a mean of 66 ± 9% at rest to 72 ± 6% during atrial pacing ($p < 0.01$). Ejection fraction increased by ≥5% during pacing in 5 of 6 patients with normal coronary arteries. Patients with CAD also had an abnormal response in end-systolic volume during atrial pacing (50 ± 31 ml at rest versus 47 ± 24 ml during pacing) compared with patients with normal coronary arteries (46 ± 16 ml at rest versus 26 ± 9 ml during pacing; $p < 0.01$). The digital ventriculograms demonstrated new or increased wall motion abnormalities during atrial pacing in 4 of 5 patients with CAD who had wall motion abnormalities at rest and in 8 of 10 patients with CAD who had normal wall motion at rest. Moreover, these wall motion abnormalities occurred in myocardial wall segments that were supplied by coronary arteries with significant lesions.**

**Thus, because digital subtraction angiography allows multiple left ventriculograms to be obtained during routine cardiac catheterization, intervention studies such as atrial pacing can be used to obtain a functional assessment of the severity of coronary arterial lesions.**

Digital subtraction angiography enhances standard angiographic images by processing the radiographic images through a high-speed digital computer. The enhancement is such that adequate visualization of major arterial systems can be obtained with low concentrations of iodinated contrast material.[1] Because lower concentration provides adequate visualization, standard doses (30 to 40 ml) of contrast material can be injected intravenously, which is different from traditional angiography in which the same amount of contrast material must be injected directly into the arterial circulation. Several investigators have reported their results with digital angiographic imaging of carotid, renal, and other peripheral arteries,[2–5] whereas others have actively been employing this technology in cardiac imaging.[6–9] We recently reported our results comparing digital first-pass left ventriculograms obtained after intravenous administration of 30 to 40 ml of contrast material with standard left ventriculograms obtained during cardiac catheterization with intraventricular injection of the same amount of contrast material.[10] There were close correlations between the 2 techniques for ventricular volume and ejection fraction.

Another potential application of this technology is to use the digital subtraction technique to process images so that less contrast material is needed for each intraventricular injection during routine cardiac catheterization. For example, it is possible to use digital

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angiography to obtain left ventriculograms with one fourth the usual amount of contrast material. Therefore, 4 times as many digital left ventriculograms can be performed compared with standard cineangiograms without increasing either the total amount of contrast material or the radiation exposure to the patient.[6] This capability of obtaining additional left ventriculograms might permit the angiographer to assess the functional capacity of myocardial segments supplied from specific coronary arteries by performing ventriculography before and after a stressful intervention during routine cardiac catheterization.

This study assesses whether small-dose left ventriculograms obtained with digital angiography at the time of routine cardiac catheterization could be used before and during atrial pacing to determine the functional significance of coronary artery disease (CAD) as defined by changes in ejection fraction and the development of wall motion abnormalities.

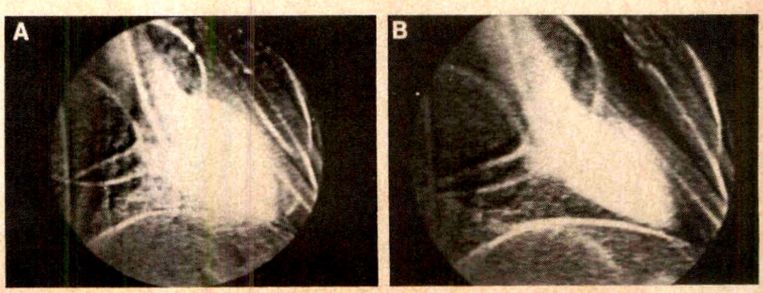
## Methods

**Digital angiographic technique:** Digital angiography was performed using the method of mask mode subtraction.[11,12] This technique involved the acquisition of fluoroscopic images of the heart before and during contrast injection. Each 1/30 second fluoroscopic image was digitized by an image processing computer (Cardiac 1000, American Edwards Laboratories, Irvine, California) into a 512 by 512 by 8 bit matrix. Each picture element (pixel) in the matrix was capable of differentiating 256 shades of gray. Because the memory of the image processing computer was large enough to allow computer storage of a 512 by 512 by 12 bit matrix, 16 frames of the 512 by 512 by 8 bit images were summated and stored in memory for the mask. This mask image contained data about the soft tissues and bone structures of the chest. After the mask was obtained, each new 1/30 second video fluoroscopic image was digitized and the stored mask was subtracted from it in real time. If perfect subtraction occurred, the resultant image signals would cancel out and not reveal any soft tissue or bone structures. If iodinated contrast media were injected after the mask was obtained and during fluoroscopy, the soft tissues and bones would be subtracted but the iodine signal would be maintained so that low concentrations of contrast material in the heart could be visualized more clearly.

Our catheterization laboratory is equipped with a Siemens Cardioskop U-arm x-ray unit. Images were focused on a 7-inch cesium iodide image intensifier and the images were converted into an electrical signal by a Plumbicon television camera. The video output signal from the television camera was connected to the image processing computer where it was logarithmically amplified before computer digitization. The subtracted images were processed in real time and displayed on television monitors in the catheterization laboratory. For this study, the fluoroscopic exposure level was set at 8 mA and 70 to 90 kVp depending on the size of the subject. The 8 mA setting is 2 to 3 times the electrical current typically used in fluoroscopy. A 5-mm thick aluminum filter was used to eliminate low-energy radiation. The measured incident exposure rate on the image intensifier was 2 to 17 $\mu$R/frame depending on the kVp. After mask mode subtraction processing, the images were reconverted to analog format for storage on videotape (Sony Betamax, model SL0323MD, 1/2-inch recorder) (Fig. 1). After the study, analog images could be replayed through the computer and the image redigitized. This postprocessing of the images permitted manipulation of the contrast and gray scale levels through the computer to enhance visualization and boundary detection. The computer contained software programs to calculate left ventricular volume and ejection fraction using the area-length method.[13] A more comprehensive description of our imaging system is presented in a previous report.[10]

**Clinical studies:** Patients undergoing left ventriculography during routine cardiac catheterization for clinically indicated reasons were asked to participate in this study. Patients with left main coronary artery obstruction and those with unstable angina were excluded from the study. Informed consent was obtained for each patient who agreed to participate. Drugs such as long-acting nitrates and beta-adrenergic antagonists were withheld for 24 hours before the study. Twenty-one patients (14 men and 7 women) who had a clinical history of chest pain were evaluated by atrial pacing. The mean age was 54.3 years (range 38 to 70) and the mean weight was 82.4 kg (range 54.5 to 120.5). Fifteen patients had at least 1 anatomically significant coronary artery lesion. Significant coronary artery stenosis was defined as $\geq$50% diameter narrowing of the coronary artery in at least 1 projection. Two or more projections were obtained for each coronary artery in standard and caudocranial views. At least 2 of these projections were orthogonal. The lesions were as follows: 9 in the left anterior descending artery, 8 in the circumflex system, and 11 in the right coronary artery. Six patients had normal coronary arteries as defined by <25% diameter narrowing of all coronary branches. Percent coronary artery stenoses in each patient are presented in Table I.

After coronary angiography was completed, a 7-French Cordis pigtail catheter was passed retrograde across the aortic valve into the left ventricle. A digital left ventriculogram was taken at rest in the 30° right anterior oblique position by injecting 10 ml of Vascoray® or Hypaque® 75 at a rate of 5 ml/s. A 6-French Cordis bipolar temporary pacemaker wire was passed from the right femoral vein under fluoroscopic control and placed against the lateral border of the right atrium. The pacemaker wire was connected to a Medtronic external pulse generator (model 5375). The right atrium was stimulated at




REAL TIME SUBTRACTION

**FIGURE 1.** End-diastolic (**A**) and end-systolic (**B**) images obtained by injecting 10 ml of contrast material over 2 seconds into the left ventricle. The video signals are processed in real time by the method of mask mode subtraction. Images are recorded on videotape and displayed in real time on a television monitor.

**TABLE I Effect of Atrial Pacing on Ejection Fraction, Wall Motion, and Left Ventricular End-Diastolic Pressure (LVEDP)**

| Pt | Diameter Stenosis (%) | | | | Abnormal ECG During Pacing | Chest Pain During Pacing | Wall Motion | | Heart Rate (beats/min) | | Ejection Fraction (%) | | LVEDP | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LAD | CX | RCA | Diag | | | Rest | Paced | | | | | Baseline (mm Hg) | Resting 10 ml Dig Angio (mm Hg) | Paced 10 ml Dig Angio (mm Hg) |
| **Abnormal Coronary Arteries** | | | | | | | | | | | | | | | |
| 1 | 80 | ... | ... | ... | ... | ... | N | Ant Hypo | 83 | 140 | 0.80 | 0.70 | 11 | 12 | ... |
| 2 | 60 | 100 | 50 | ... | ... | + | N | Ant-Inf Hypo | 62 | 110 | 0.66 | 0.46 | 18 | 16 | ... |
| 3 | 85 | 85 | 95 | 50 | ... | + | Anti-Api Ak | Anti-Api Ak | 62 | 110 | 0.32 | 0.31 | 40 | 41 | 40 |
| 4 | 60 | 50 | ... | 100 | ... | + | N | N | 58 | 110 | 0.66 | 0.71 | 8 | 9 | 10 |
| 5 | 50 | 65 | 95 | ... | + | + | Inf Ak | Inf Ak | 60 | 120 | 0.43 | 0.31 | 14 | 16 | 20 |
| 6 | 25 | 60 | 25 | ... | ... | + | N | N | 50 | 108 | 0.82 | 0.70 | 19 | 16 | 18 |
| 7 | 50 | ... | 100 | 60 | ... | ... | Inf Hypo | Inf Ak, Ant Hypo | 73 | 135 | 0.57 | 0.27 | 17 | 20 | 20 |
| 8 | 90 | 75 | 65 | 55 | + | + | N | Ant-Api Hypo | 54 | 110 | 0.63 | 0.44 | 16 | 16 | 32 |
| 9 | 70 | ... | 100 | 50 | ... | ... | N | Ant Hypo | 50 | 120 | 0.76 | 0.61 | ... | ... | ... |
| 10 | ... | ... | 70 | ... | ... | ... | Inf Hypo | Inf Dys | 68 | 140 | 0.53 | 0.44 | 22 | 22 | 22 |
| 11 | ... | ... | 65 | ... | ... | ... | Inf-Bas Hypo | Inf Dys | 72 | 146 | 0.47 | 0.44 | 20 | 20 | 24 |
| 12 | 40 | 40 | 100 | 35 | + | + | N | Inf Hypo | 85 | 110 | 0.56 | 0.53 | 10 | 10 | 15 |
| 13 | ... | 80 | ... | 65 | ... | ... | N | Api Ak | 78 | 150 | 0.60 | 0.53 | 24 | 24 | 24 |
| 14 | ... | ... | 95 | ... | ... | ... | N | inf Hypo | 62 | 130 | 0.79 | 0.71 | 16 | 16 | 24 |
| 15 | 75 | 60 | 70 | ... | ... | + | N | Ant-Bas Hypo; Inf Hypo | 68 | 120 | 0.72 | 0.45 | 14 | 15 | 15 |
| Mean ± SD | | | | | | | | | 65.7 ±11.0 | 123.9 ±14.9 | 0.62 ±0.14 | 0.51 ±0.15 | 17.8 ±7.8 | 18.1 ±7.8 | 22.0 ±8.0 |
| **Normal Coronary Arteries** | | | | | | | | | | | | | | | |
| 16 | | | | | ... | ... | N | N | 74 | 140 | 0.60 | 0.66 | 18 | 19 | 22 |
| 17 | | | | | ... | ... | N | N | 90 | 150 | 80 | 75 | 20 | 20 | 20 |
| 18 | | | | | ... | ... | N | N | 68 | 135 | 0.63 | 0.72 | 21 | 21 | 23 |
| 19 | | | | | ... | + | N | N | 74 | 120 | 0.62 | 0.72 | 16 | 16 | 22 |
| 20 | | | | | ... | ... | N | N | 55 | 140 | 0.61 | 0.66 | 13 | 13 | 15 |
| 21 | | | | | ... | + | N | N | 66 | 110 | 0.74 | 0.80 | 16 | 18 | ... |
| Mean ± SD | | | | | | | | | 71.2 ±11.6 | 132.5 ±14.8 | 0.66 ±0.08 | 0.72 ±0.06 | 17.3 ±2.9 | 17.8 ±2.9 | 20.4 ±3.2 |

AK = akinesia; Ant = anterior; Api = Apical; Bas = basal; Cx = circumflex; Diag = diagnosis; Dig Angio = digital angiogram; Dys = dyskinesia; ECG = electrocardiogram; Hypo = hypokinesis; Inf = inferior; LAD = left anterior descending; n = normal; RCA = right coronary artery.

2 mA, initially at a rate of 20 beats/min above the patient's resting heart rate. The rate was increased in increments of 10 beats/min every minute until the patient experienced chest pain or until 85% of the maximal predicted heart rate was reached. If atrioventricular Wenckebach heart block developed, 1 mg atropine was administered intravenously and the pacing study was continued. When the end-point heart rate was achieved, another 10 ml digital left ventriculogram was performed. The pacemaker was then turned off. To correct for magnification, an 8 by 8 cm grid was placed on the x-ray table after the study was performed at a height corresponding to one half the patient's anteroposterior thoracic dimension. The image intensifier and x-ray tube were adjusted to the position used in the study and the grid was fluoroscopically imaged and recorded on videotape for subsequent analysis of ventriculograms.

Left ventricular pressure was recorded through the fluid-filled 7-French pigtail catheter using a Statham P23ID transducer. Left ventricular end-diastolic pressure was measured from the pressure tracing as the point after the "a" wave where the rapid upstroke of the left ventricular pressure curve began. Pressure was recorded before the digital angiography studies, after the initial resting 10-ml digital study, and then after the 10-ml digital study obtained during atrial pacing. In the latter 2 situations, left ventricular pressure was recorded within 3 minutes after the contrast material was injected. The mean end-diastolic pressure at rest and after the baseline 10-ml digital study was compared using Student's $t$ test.

Electrocardiographic (ECG) monitoring was performed at rest and during atrial pacing using leads II and $V_6$. Acute ischemic changes were interpreted as 1 mm horizontal S-T depression persisting 0.08 second after the J point.

**Analysis:** The rest and pacing images recorded on videotape were reviewed and the heart beats in which the greatest concentration of dye was seen in the left ventricle were chosen for analysis. Images from these cardiac cycles were redigitized by the computer system so that the boundary of the left ventricle could be electronically traced directly on the video image. An end-diastolic frame was chosen by identifying the image with the largest iodinated area and the end-systolic frame was identified as the image with the smallest contrast-filled area. End-diastolic and end-systolic volumes at rest and during atrial pacing were calculated by the computer using the area-length method corrected for magnification by the grid.[13,14] Ejection fractions were computed from the volume calculations. Statistical analysis was performed with Student's $t$ test for paired data comparing end-diastolic volumes, end-systolic volumes, and ejection fractions at rest with those obtained during atrial pacing.

Coronary arteriograms were reviewed for the presence and significance of atherosclerotic lesions. Lesions were defined as anatomically significant when the diameter at the stenosis was measured by calipers to be >50% narrowed compared with the arterial segment proximal to the lesion. A panel of 3 cardiologists reviewed all the coronary angiograms. Wall motion abnormalities at rest or induced by atrial pacing were qualitatively assessed. Digital ventriculograms were interpreted by 1 member of the panel and reviewed by the other 2 members. The panel was not specifically blinded to the results of the coronary angiograms. However, in over 75% of the cases, wall motion analysis was made without knowledge of the coronary angiogram interpretation. Regions of normal and abnormal wall motion seen on digital ventriculograms were related to the presence or absence of anatomically significant coronary artery narrowing in the artery supplying those myocardial regions. Arterial lesions were defined as functionally significant if rest- or pacing-induced wall motion abnormalities were appreciated.

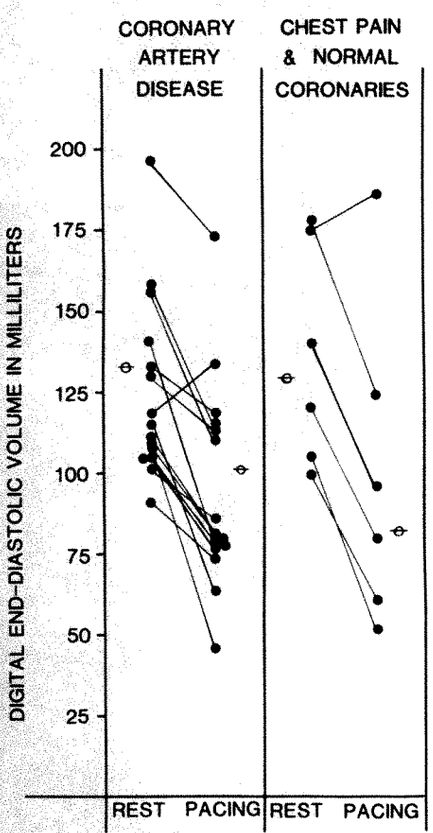



**FIGURE 2.** Comparison of left ventricular end-diastolic volume obtained with 10 ml digital subtraction angiography before and after atrial pacing. The patients were divided after coronary angiography into those with significant coronary artery disease (≥50% diameter narrowing) and those with normal coronary arteries.

## Results

**Patient characteristics:** Table I summarizes our patient data and includes the heart rate and ejection fraction data at rest and during atrial pacing in 21 patients. Twelve of the 15 patients with CAD had New York Heart Association class III or IV symptoms of angina. However, all patients were free of pain ≥24 hours before catheterization. The mean heart rate at rest was 66 ± 11 beats/min in patients with CAD and 71 ± 12 in those with normal coronary arteries (p = NS (not significant)). The mean heart rate achieved during atrial pacing was 124 ± 15 beats/min (range 108 to 150) in the group with CAD. Patients with normal coronary arteries were paced to a mean rate of 132 ± 15 beats/min (range 120 to 150) (p >0.2 compared with the paced heart rate achieved in patients with CAD). In 1 patient with CAD a complication developed during electrical stress testing. This patient had transient (6 seconds) complete heart block but suffered no sequelae.

**Hemodynamic effects:** The mean resting left ventricular end-diastolic pressure was 18 ± 8 mm Hg in patients with CAD and the left ventricular end-diastolic pressure was 17 ± 3 mm Hg in those with normal coro-

nary arteries (p = NS). After the baseline 10-ml digital left ventriculogram, no significant change was noted in left ventricular end-diastolic pressure which was 18 ± 8 mm Hg in patients with CAD and 18 ± 3 mm Hg in those with normal coronary arteries.

**Angiographic results:** Figure 2 demonstrates end-diastolic volumes before and during pacing in 15 patients with CAD and in 6 patients with chest pain but normal coronary arteries. Left ventricular end-diastolic volume decreased during atrial pacing in 14 of 15 patients with CAD. Mean end-diastolic volume was 125 ± 28 ml at rest and decreased to a mean volume of 95 ± 35 ml ($p < 0.001$) during pacing. In the 6 patients with normal coronary arteries, end-diastolic volume decreased from a mean of 137 ± 34 ml at rest to a mean of 99 ± 49 ml ($p < 0.02$) during atrial pacing. There was no significant difference between mean end-diastolic volumes at rest or during pacing between the 2 groups. Also, there was no significant difference in the percent change in mean end-diastolic volume from rest to pacing between the 2 groups.

Left ventricular end-systolic volume decreased during atrial pacing in all 6 subjects with normal coronary arteries (Fig. 3), whereas end-systolic volume decreased in only 8 of 15 patients with CAD. In patients with CAD, mean end-systolic volume was 50 ± 31 ml at rest and 47 ± 24 ml during atrial pacing ($p > 0.2$ compared with that at rest). In patients with normal coronary arteriograms, the mean resting end-systolic volume was 46 ± 16 ml, and decreased during atrial pacing to a mean end-systolic volume of 26 ± 9 ml ($p < 0.01$ compared with that at rest). Although end-systolic volumes at rest were similar in the 2 patient groups, the decrease in end-systolic volume was significantly greater in patients with normal coronary arteries compared with those with CAD ($p < 0.05$).

Ejection fraction data in the 2 groups of patients are shown in Figure 4. In the 15 patients with CAD, mean ejection fraction at rest was 62 ± 14 and decreased an average of 11 percentage points to 51 ± 15 during atrial pacing ($p < 0.001$). Ejection fraction decreased or was unchanged in 14 of the 15 patients. In the 6 patients with chest pain but normal coronary arteries, resting ejection fraction was 66 ± 9% (no significant difference compared with that of the group with CAD) and increased during pacing to 72 ± 6 ($p < 0.01$ compared with that in patients with CAD). During atrial pacing, the ejection fraction increased by at least 5 percentage points in 5 (83%) subjects and decreased in 1 subject.

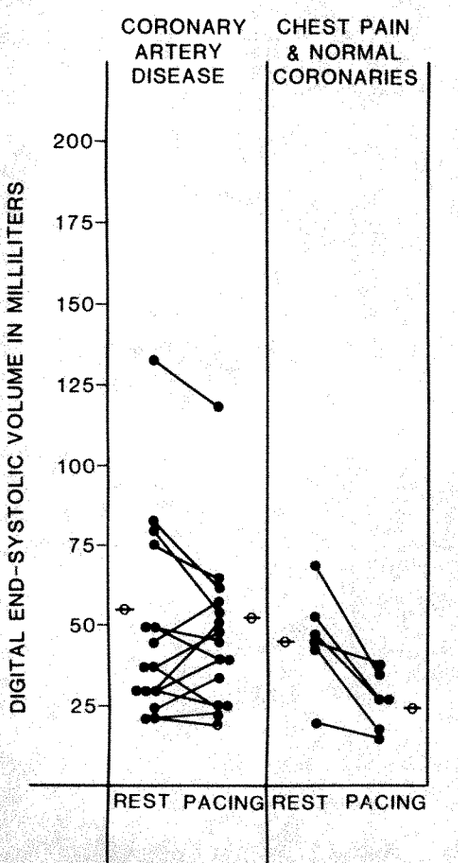



**FIGURE 3.** Comparison of left ventricular end-systolic volumes obtained with 10 ml digital subtraction angiography before and after atrial pacing.

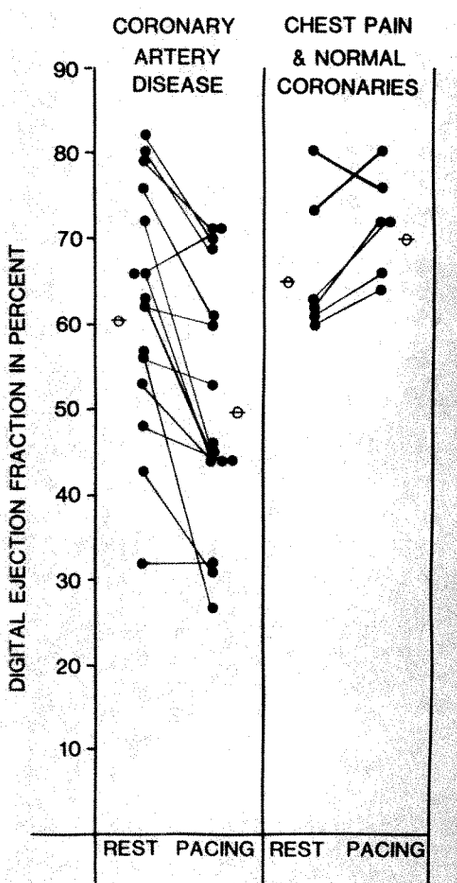



**FIGURE 4.** Comparison of left ventricular ejection fractions obtained with 10 ml digital subtraction angiography before and after atrial pacing. Fourteen of 15 patients with coronary artery disease had a decrease or no change in ejection fraction, compared with 5 of 6 patients with normal coronary arteries who had an increase in ejection fraction.

**Wall motion abnormalities:** The resting digital angiograms demonstrated wall motion abnormalities in all 5 patients who had dysfunctional contraction patterns visualized on standard cineangiogram. The areas of abnormal wall motion at rest and after pacing are listed in Table I.

Four patients had inferior wall dysfunction at rest and each of these patients had severe right coronary artery obstruction. During atrial pacing, more extensive impairment of inferior wall motion developed in these 4 patients and dyskinesia of the inferior wall developed in 2. One patient had extensive anteroapical akinesia at rest with an ejection fraction of 32%. He developed chest pain at a paced heart rate of 110 beats/min but did not develop new areas of wall motion dysfunction despite the presence of significant disease in 4 vessels. In the 10 patients with CAD who had normal wall motion at rest, 8 patients developed new areas of abnormal contraction in muscle segments that were supplied by coronary arteries with significant anatomic obstruction. In 4 of these 8 patients, the new area of wall motion abnormality was located in the anterior wall and was associated with significant obstruction in the proximal left anterior descending coronary artery. In 2 of the 8 patients, the new area of wall motion abnormality was located in the inferior wall and was associated with significant obstruction in the right coronary artery. In 2 patients abnormal wall motion developed in both the anterior and inferior walls corresponding to significant disease in both the left anterior descending and right coronary arteries.

One patient (Patient 6 in Table I) with normal wall motion at rest had a decrease in ejection fraction of 12 percentage points, but no segmental wall motion abnormality was visualized in the right anterior oblique projection. The only significant anatomic obstruction in the patient was in the circumflex artery. One patient with significant 3-vessel disease (Patient 4 in Table I) had an increase in ejection fraction of 5 percentage points during atrial pacing with normal wall motion during both studies. In this patient chest pain developed at a paced rate of 110 beats/min and the digital ventriculogram was taken within 30 seconds of the onset of chest pain.

## Discussion

It is well described that coronary angiography may underestimate the extent of coronary artery narrowing or even completely miss significant lesions due to overlapping or foreshortening of vessels.[15–17] Special angulated views help to reduce this problem.[18–20] However, it is not unusual for angiographers to disagree as to the severity of a coronary lesion on the basis of visual inspection of the angiograms.[21] A functional assessment of the hemodynamic effects of a specific lesion would be useful in that it might aid in evaluating the severity of that lesion.

One way to assess clinically the presence of myocardial ischemia is to measure ejection fraction during stress intervention such as exercise.[22] Borer et al[23] found that a decrease in ejection fraction measured by radionuclide angiography during supine bicycle exercise was more sensitive and specific than ischemic electrocardiographic changes detected during standard treadmill stress testing. Moreover, they demonstrated that wall motion abnormalities could be detected on radionuclide angiograms when myocardial ischemia developed. However, it is sometimes difficult to relate wall motion abnormalities visualized by radionuclide angiography to specific coronary artery lesions because they frequently are obtained from different views with markedly different image resolution and at different times. Previous reports have shown that atrial pacing can be used to induce angina or ischemic electrocardiographic changes when the same pressure-rate product is achieved compared with exercise stress tests.[24–26]

In the present study, we used digital angiography and atrial pacing to assess ventricular volume, global ejection fraction, and segmental wall motion in the catheterization laboratory at the same time and in the same view that 1 of our coronary arteriograms was taken. A dose of 10 ml of contrast material and high fluoroscopic exposure levels were used which made it possible to obtain multiple ventriculograms without deleterious hemodynamic effects from excessive amounts of contrast material.[27] We did not attempt to evaluate ventricular function in patients with intermediate (25 to 50%) diameter narrowing of the cornary arteries because we wanted a comparison in lesions in which the anatomic severity is accepted as being hemodynamically significant. Therefore, only patients with moderate or severe coronary artery stenosis, (that is, >50% diameter narrowing) were included in the CAD group.

In response to atrial pacing, ejection fraction decreased or did not change in 14 of 15 (93%) patients with anatomically significant coronary artery lesions, whereas 5 of 6 (83%) patients with normal coronary arteries had an increase in ejection fraction of at least 5 percentage points. Moreover, digital angiograms revealed the development of new or the exacerbation of existing wall motion abnormalities during atrial pacing in all but 2 patients with significant CAD who had either no change or a decrease in ejection fraction. The wall motion abnormalities corresponded to ventricular muscle segments that were perfused by significantly narrowed coronary arteries. Of the 2 patients who had no change or a decrease in the ejection fraction without developing a new segmental wall motion abnormality in the right anterior oblique projection, 1 had significant stenosis of the circumflex artery. Because we did not obtain ventriculograms in the left anterior oblique projection during atrial pacing, we could not assess lesions affecting primarily the lateral wall of the left ventricle. The patient with CAD who had no change in ejection fraction during pacing (Patient 3) had a low ejection fraction at rest with diffuse anteroapical akinesis. In this patient chest pain developed at a heart rate of 110 beats/min. There also was 1 other patient who had significant 3-vessel disease in whom an increase in ejection fraction and no wall motion abnormality developed during atrial pacing. Chest pain developed in this patient at a relatively low pacing rate of 110 beats/min and the digital ventriculogram was taken within 30 seconds of the onset of chest pain. Occasionally during atrial pacing it is difficult to determine if the patient is subjectively experiencing angina or just dis-

comfort from the unusual sensation of induced tachycardia. In the previous 2 patients, a positive response might well have been achieved if atrial pacing had been continued for a longer period after the onset of chest pain.

Although these results suggest that patients with significant CAD can be identified by atrial pacing studies, we must be cautious in this analysis because inadequate visualization of ventricular walls and submaximal stress may produce a negative result. In addition, other conditions besides CAD can produce wall motion abnormalities and a decrease in ejection fraction during stress, such as cardiomyopathy and valvular heart disease.[28] Also, this study has a bias in its patient selection in that patients were excluded if they had left main artery disease, unstable angina, valvular heart disease, or cardiomyopathy with normal coronary arteries. However, the patients that were entered into the study represent the typical distribution for our hospital population of patients with symptoms of ischemic heart disease.

There was so significant difference at rest in regard to end-diastolic or end-systolic volume between patients with CAD and those with chest pain but normal coronary angiograms. During atrial pacing, 19 of the 21 patients had a decrease in end-diastolic volume. This finding is consistent with other studies which show that atrial pacing decreases the end-diastolic volume.[29] However, the effect of atrial pacing on end-systolic volume was distinctly different between our 2 groups. In the 6 patients with normal coronary arteries, the end-systolic volume decreased a mean of 20 ml (43%) from the resting value ($p < 0.01$), whereas in the 15 patients with CAD the mean end-systolic volume did not change significantly during atrial pacing. Therefore, the decrease in ejection fraction seen in patients with CAD was primarily due to the fact that the left ventricle could not contract down to a smaller end-systolic volume when ischemia developed during atrial pacing. Thus, the inability of the myocardium to contract during ischemia is apparently reflected in alterations of end-systolic volume during the stress of increased heart rate, whereas the end-diastolic volume continues to reflect changes in heart rate and ventricular filling despite the presence of ischemia. The implication is that ventricular function can be assessed not only by the response of global ejection fraction to stress but also by the change in end-systolic volume during pacing. These relations are summarized in Figure 5 in which the percent changes in left ventricular volumes and ejection fraction between rest and pacing are plotted for the 2 groups of patients with or without CAD. As can be seen, ejection fraction and, to a lesser degree, end-systolic volume changes during tachycardia induced by atrial pacing

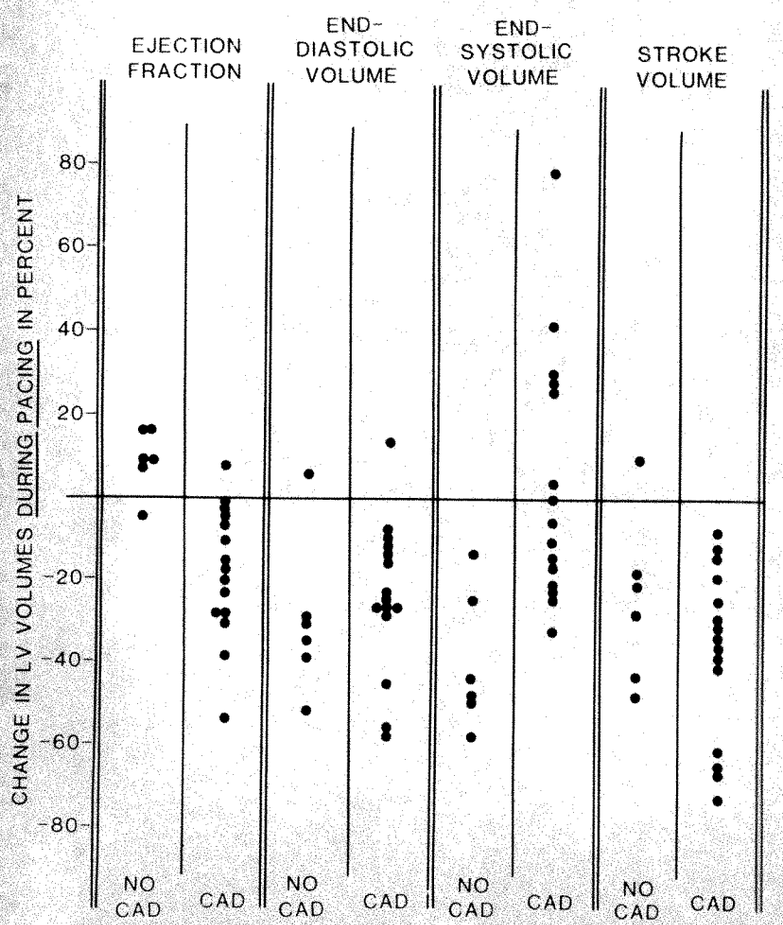



**FIGURE 5.** The percent change in left ventricular volume and ejection fraction during atrial pacing compared with rest is plotted for the patients with coronary artery disease (CAD) versus those with normal coronary arteries (NO CAD). Both the ejection fraction response and the percent change in end-systolic volume tended to discriminate between patients with normal coronary arteries and those with CAD.

were good discriminators of normal patients versus those with CAD.

Atrial pacing precipitated chest pain in 10 patients including 2 with normal coronary arteriograms. In none of the 6 patients with normal coronary arteries did ischemic ECG changes develop during pacing, whereas in only 3 of the 15 (20%) patients with CAD did ischemic ECG abnormalities develop (Table I). One explanation for the low sensitivity of the ECG response in our patients may be that only 2 ECG leads were used. Moreover, our patients achieved a relatively low level of maximal heart rate during atrial pacing. The low maximal heart rate was a result of our decision to stop increasing the atrial pacing rate and immediately perform digital angiography if the patient had chest pain. The fact that the ejection fraction decreased in 14 of the 15 (93%) patients with CAD whereas only 3 of the 15 (20%) had ischemic ECG changes and 8 of the 15 (53%) developed chest pain suggests that ischemia induced by atrial pacing is initially manifested as an abnormality of muscle contraction before either ECG alterations or the subjective sensation of chest pain. Upton et al[30] found similar results concerning the higher sensitivity of wall motion analysis as compared with the development of angina or S-T segment depression in patients undergoing bicycle exercise during radionuclide imaging. Their results for end-diastolic and end-systolic volume differ from ours probably because they used upright exercise whereas we used supine atrial pacing.

*In summary*, digital subtraction angiography permits multiple left ventriculograms to be taken during cardiac catheterization without increasing the amount of contrast or x-ray exposure to the patient and with less alteration in hemodynamics than with the traditional cineangiographic mode. Thus, functional evaluation of coronary artery stenosis is facilitated by permitting assessment of ventricular volumes, ejection fraction, and wall motion at rest and after an intervention such as atrial pacing. Similarly, it should be possible to study pharmacologic interventions or exercise stress with digital angiography in order to assess the functional significance of coronary lesions. This information could be useful in evaluating a patient with suspected or known CAD and in assessing functional improvement after coronary bypass graft surgery.

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## References


1. **Nalcioglu O, Roeck WW, Pearce JG, Gillan GD, Milne ENC.** Quantitative fluoroscopy. IEEE Trans Nucl Sci 1981;1:219–223.
2. **Mistretta CA, Crummy AB.** Diagnosis of cardiovascular disease by digital subtraction angiography. Science 1981;214:761–765.
3. **Christenson PC, Ovitt TW, Fisher HD, Frost MM, Nudelman S, Roehrig H.** Intravenous angiography using digital video subtraction: intravenous cervicocerebrovascular angiography. AJR 1980;135:1145–1152.
4. **Crummy AB, Strother CM, Sackett JF, Ergun DL, Shaw CG, Kruger RA, Mistretta CA, Turnipseed WD, Lieberman RP, Myerowitz PD, Ruzicka FF.** Computerized fluoroscopy: digital subtraction for intravenous angiocardiography and arteriography. AJR 1980;135:1131–1140.
5. **Nalcioglu O, Seibert JA, Roeck WW, Friedenberg RM, Rosenberg H, Pearce JG, Gehrich JL.** Evaluation of renal function by digital subtraction imaging. SPIE Proc 1981;273:120–124.
6. **Sasayama S, Nonogi H, Kawai C, Fujita M, Eiho S, Kuwahara M.** Automated method for left ventricular volume measurement by cineventriculography with minimal doses of contrast medium. Am J Cardiol 1981;48: 746–752.
7. **Vas R, Diamond GA, Forrester JS, Whiting JS, Swan HJC.** Computer enhancement of direct and venous-injected left ventricular contrast angiography. Am Heart J 1981;102:719–728.
8. **Meaney TF, Weinstein MA, Buonocore E, Pavlicek W, Borkowski GP, Gallagher JH, Sufka B, MacIntyre WJ.** Digital subtraction angiography of the human cardiovascular system. AJR 1980;135:1153–1160.
9. **Kruger RA, Mistretta CA, Houk TL, Kubal W, Riederer SJ, Ergun DL, Shaw CG, Lancaster JC, Rowe GG.** Computerized fluoroscopy techniques for intravenous study of cardiac chamber dynamics. Invest Radiol 1979;14: 279–287.
10. **Tobis J, Nalcioglu O, Johnston WD, Seibert A, Iseri LT, Roeck WW, Elkayam U, Henry WL.** Left ventricular imaging with digital subtraction angiography using intravenous injection and fluoroscopic exposure levels. Am Heart J 1982; 104:20–27.
11. **Ergun DL, Mistretta CA, Kruger RA, Riederer SJ, Shaw CG, Carbone DP.** A hybrid computerized fluoroscopy technique for noninvasive cardiovascular imaging. Radiology 1979;132:739–742.
12. **Shaw CG, Ergun DL, Kruger RA, Mistretta CA, Crummy AB, Myerowitz D, Strother CM, Sackett J, Van Lysel M, Zarnstorff W, Turnipseed W.** Intravenous angiography using computerized fluoroscopy. IEEE Trans Nucl Sci 1980;3:1042–1046.
13. **Sandler H, Dodge HT.** The use of single plane angiocardiograms for the calculation of left ventricular volume in man. Am Heart J 1968;73:325–335.
14. **Kennedy JW, Trenholme SE, Kasser IS.** Left ventricular volume and mass from single-plane cineangiocardiograms. A comparison of anteroposterior and right anterior oblique methods. Am Heart J 1970;80:343–352.
15. **Vlodaver Z, French R, Van Tassel RA, Edwards JE.** Correlation of the antemortem coronary arteriogram and the postmortem specimen. Circulation 1973;47:162–168.
16. **Brown BG, Bolson E, Frimer M, Dodge HT.** Quantitative coronary arteriography: estimation of dimensions, hemodynamic resistance and atheroma mass of coronary artery lesions using the arteriogram and digital computation. Circulation 1977;55:329–337.
17. **Conti CR.** Coronary arteriography. Circulation 1977;55:227–237.
18. **Sos TA, Baltaxe HA.** Cranial and caudal angulation for coronary angiography revisited. Circulation 1977;56:119–123.
19. **Aldridge HE, McLoughlin MJ, Taylor KW.** Improved diagnosis in coronary cinearteriography with routine use of 110 degree oblique views and cranial and caudal angulations. Am J Cardiol 1975;36:468–473.
20. **Lesperance J, Saltiel J, Petitclerc R, Bourassa MG.** Angulated views in the sagittal plane for improved accuracy of cinecoronary angiography. AJR 1974;121:565–574.
21. **Gensini G.** Coronary arteriography. In: Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia: WB Saunders, 1980: 353–360.
22. **Dehmer GJ, Lewis SE, Hillis LD, Corbett J, Parkey RW, Willerson JT.** Exercise-induced alterations in left ventricular volumes and the pressure-volume relationship: a sensitive indicator of left ventricular dysfunction in patients with coronary artery disease. Circulation 1981;63:1008–1018.
23. **Borer JS, Kent KM, Bacharach SL, Green MV, Rosing DR, Seides SF, Epstein SE, Johnston GS.** Sensitivity, specificity and predictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease: comparison with exercise electrocardiography. Circulation 1979;60:572–580.
24. **Balcon R, Hoy J, Malloy W, Sowton E.** Haemodynamic comparisons of atrial pacing and exercise in patients with angina pectoris. Br Heart J 1969;31: 168–171.
25. **Thadani U, Lewis JR, Mathew TM, West RO, Parker JO.** Reproducibility of clinical and hemodynamic parameters during pacing stress testing in patients with angina pectoris. Circulation 1979;60:1036–1044.
26. **O'Brien KP, Higgs LM, Glancy DL, Epstein SE.** Hemodynamic accompaniments of angina: a comparison during angina induced by exercise and by atrial pacing. Circulation 1969;39:735–743.
27. **Tobis JM, Nalcioglu O, Johnston WD, Seibert A, Roeck W, Iseri LT, Elkayam U, Henry WL.** Correlation of 10 milliliter digital subtraction ventriculograms compared with standard cine angiograms. Am Heart J, in press.
28. **Gibbons RJ, Lee KL, Cobb F, Jones RH.** Ejection fraction response to exercise in patients with chest pain and normal coronary arteriograms. Circulation 1981;64:952–957.
29. **Hung J, Kelly DT, Hutton BF, Uther JB, Baird DK.** Influence of heart rate and atrial transport on left ventricular volume and function: relation to hemodynamic changes produced by supraventricular arrhythmia. Am J Cardiol 1981;48:632–638.
30. **Upton MT, Rerych SK, Newman GE, Port S, Cobb FR, Jones RH.** Detecting abnormalities in left ventricular function during exercise before angina and ST-segment depression. Circulation 1980;62:341–349.

# Angiographic Changes Produced by Percutaneous Transluminal Coronary Angioplasty

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**Percutaneous transluminal coronary angioplasty (PTCA) is being used with increasing frequency in the treatment of patients with symptomatic coronary artery disease. Balloon inflation results in diverse angiographic findings, reflecting the great variety of anatomic and pathologic changes produced. The long-term effects of inflation on the underlying atherosclerotic lesion and the clinical outcome are unknown but may depend in part on the anatomic changes caused by the dilatation itself. To facilitate communication and evaluation of the results of PTCA, a classification of the angiographic findings and their potential mechanisms is presented. Recognition and analysis of these angiographic findings may be helpful in evaluating the long-term outcome of patients undergoing PTCA.**

Percutaneous transluminal coronary angioplasty (PTCA) has proved a frequently effective means of reducing coronary artery stenosis.[1–3] With this technique, a balloon catheter placed across the stenotic site is inflated to reduce the obstruction. The controlled injury caused by this technique results in a range of anatomic changes manifested as diverse appearances on the angiogram. The immediate and delayed consequences related to the various angiographic appearances are poorly understood. Changes may occur not only in the arterial segment in which dilatation is attempted (angioplasty segment) but also in other parts of the coronary circulation (nonangioplasty segments). Some of these effects are the planned result of the balloon inflation and controlled injury; others may be considered complications of the procedure.

During this initial period of the clinical use of PTCA, we are still trying to understand the early and late consequences of the various vascular effects. To facilitate this understanding, construction of a practical classification of the angiographic results may be helpful. We provide a broad description of the angiographic appearances produced, based on a review of the literature and experience with the first 100 cases of PTCA at the Mayo Clinic seen between October 1979 and November 1981. As PTCA is a relatively new procedure, many of the interpretations offered are speculative. By developing a classification of the many angiographic changes that may be produced by PTCA, we hope to encourage a more orderly evaluation of the clinical results and to identify areas requiring additional investigative efforts.

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**TABLE I Angiographic Findings in 100 Consecutive Patients Undergoing Percutaneous Transluminal Coronary Angioplasty**

| Finding | Patients (n)* |
|---|---|
| Changes in angioplasty segment | |
| Immediate | |
| Intraluminal haziness | 17 |
| Smooth-walled dilatation | 41 |
| Intimal flap or intramural split and dissection | 22 |
| No significant change in lesion | 20† |
| Complete occlusion | 7 |
| Intraluminal thrombosis | 0 |
| Coronary artery spasm | 2 |
| Aneurysmal dilatation | 0 |
| Coronary arterial rupture | 0 |
| Delayed—restenosis | 0 |
| Changes remote from angioplasty segment | |
| Immediate | |
| Branch occlusion | 2 |
| Distal embolization or embolic occlusion | 0 |
| Coronary spasm | 6 |
| Aneurysmal dilatation | 1 |
| Intimal flap | 1 |
| Delayed—new stenosis | 1 |

* Some patients had >1 change.
† In 18 of the 20 patients, the balloon catheter could not be passed across the stenosis.

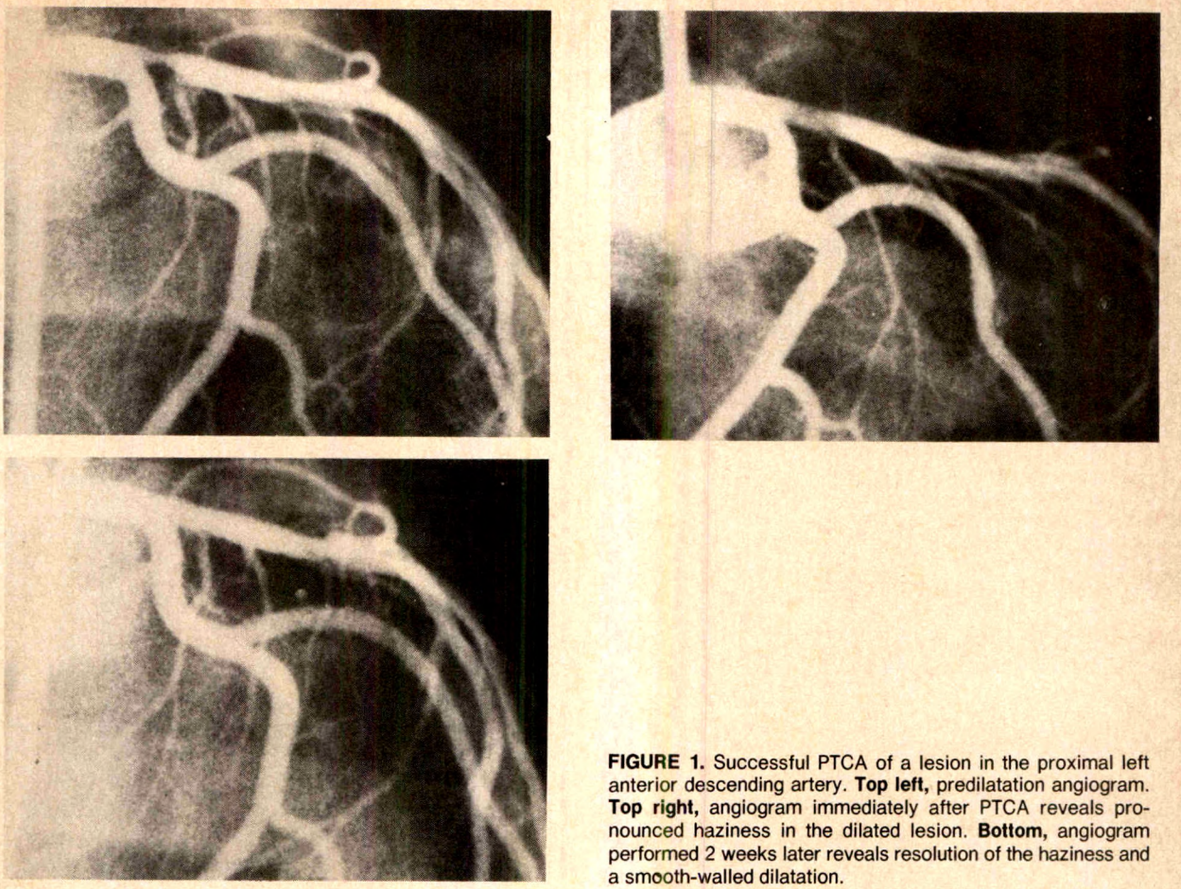


**FIGURE 1.** Successful PTCA of a lesion in the proximal left anterior descending artery. **Top left,** predilatation angiogram. **Top right,** angiogram immediately after PTCA reveals pronounced haziness in the dilated lesion. **Bottom,** angiogram performed 2 weeks later reveals resolution of the haziness and a smooth-walled dilatation.

## Changes in the Angioplasty Segment (Table I)

These may be observed at the time of PTCA (immediate) or at a later restudy (delayed).

**Immediate:** *Intraluminal haziness:* Intraluminal haziness is a frequent angiographic finding in the dilated segment.[4] Quantification and recognition of this haziness may be difficult, owing to the inherent insensitivity of angiography. Pathologically, haziness has been attributed to dispersion of contrast medium down multiple linear channels or fissures in the dilated segment.[5,6] In addition, the presence of platelet thrombi or ragged denuded intima (or both) may have a role in producing this angiographic finding. Usually, this haziness disappears within a few weeks after dilatation. In Figure 1, typical intraluminal haziness can be seen in the proximal left anterior descending artery after successful dilatation.

*Smooth-walled dilatation:* In some patients, a smooth-walled arterial segment is seen after dilatation. This finding was noted in most of our cases (Table I, Fig. 2). The significance of a smooth-walled dilatation with respect to the underlying changes in the vessel wall is unknown. It could reflect endothelial desquamation, compression of a soft atheroma, or stretching of a fibrous plaque instead of intimal fissuring and splitting of an atheromatous plaque. Alternatively, the finding of a smooth dilatation may relate to the inherent insensitivity of angiography in detecting small fissures. Depending on the underlying vessel wall changes, this smooth-walled response to dilatation may have significant implications for the eventual long-term outcome of coronary angioplasty, such as the likelihood of restenosis or remodeling.

*Intimal flap or intramural split and dissection:* The production of an intimal flap or intramural split with balloon dilatation results from splitting and fragmentation of the atheromatous plaque.[6–10] In addition, dissecting hematomas of the outer media have been seen.[4] In our series, 22 patients had evidence of intimal dissection (Fig. 3). A graded angiographic classification from intimal flap to true dissection with persistence of contrast medium in the false channel has been developed and is presently used by the National Heart, Lung, and Blood Institute (NHLBI) Registry. Some authors have concluded that intimal dissection with a small intimal flap should be expected and perhaps is a necessary part of successful PTCA.[11] In these patients, subsequent retraction and remodeling along the fissure lines and intimal dissection may lead to stabilization or actual improvement of the dilated stenosis.[12] Other authors, however, have suggested that any actual dissection may predispose to a higher rate of restenosis.[13]

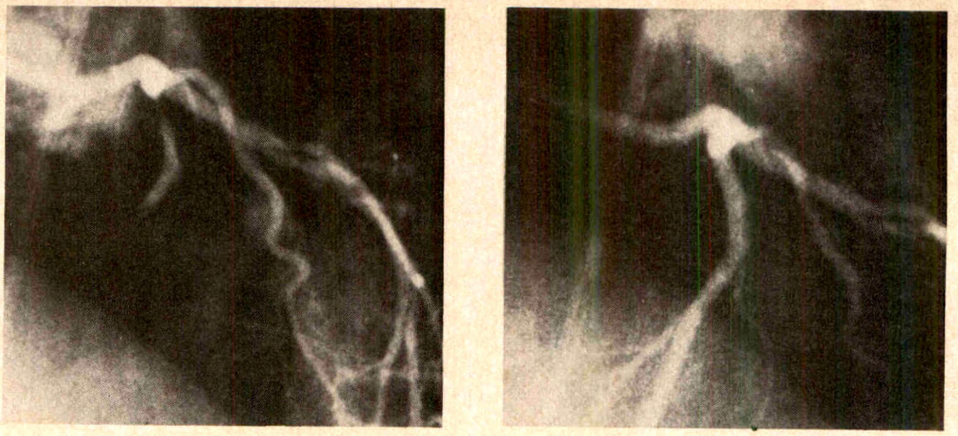


**FIGURE 2.** Successful PTCA in an occluded proximal left anterior descending artery. **Left,** preoperative angiogram. **Right,** immediate post-PTCA angiogram reveals no evidence of haziness or intimal flap.

*No significant change:* The NHLBI Registry has defined unsuccessful PTCA as no change or an improvement of <20% in the stenosis. In these patients, a firm fibrotic or calcified lesion in which the intima cannot be split may account for the lack of success. Once a stenosis has been crossed with the balloon catheter, failure of inflation to significantly decrease the stenosis is uncommon. Such failure has occurred in only 2 of our cases. This type of failure in patients undergoing balloon dilatation may become even less common in the future, with technical advances in catheter construction and less deforming balloons.[14] A more common reason for failure is the inability to intubate the coronary artery or to cross the stenosis with the balloon catheter.

It is important to avoid technical errors that may result in a less than optimal dilatation. It is essential to ensure that the balloon catheter has crossed and straddled the lesion. A number of factors can be overlooked in this regard. During inflation, the balloon may recoil out of the stenosis or be propelled distally. Sometimes, it may also be difficult to determine whether the balloon catheter inflation is being performed in the correct vessel. Problems with this usually can be avoided by constant monitoring of pressure, meticulous observation of transstenotic gradient, multiple roentgenographic views to confirm position, injection of contrast medium through the balloon catheter tip, and high-quality fluoroscopic monitoring of the balloon position during inflation.

Clinical improvement may sometimes occur when the lesion has been crossed, but PTCA has been apparently unsuccessful. Engel et al[15] reported a case in which the stenotic site in the left anterior descending artery improved spontaneously after unsuccessful initial attempts at dilatation. This fascinating observation remains unexplained but is presumably related to the complex, poorly understood remodeling process.

*Complete occlusion:* Complete occlusion is often associated with ischemic pain and electrocardiographic changes. It has been reported to be the most frequent indication for emergency coronary bypass surgery after attempted PTCA.[16] The Mayo Clinic series includes 7 patients with complete occlusion during PTCA.

Potential mechanisms include acute thrombosis, spasm, and dissection with luminal compression. Treatment varies, depending on the clinical setting. When occlusion occurs on initial passage of the dilating catheter into the coronary artery, dissection may be the most common finding. In these patients, prompt surgical intervention may be the best treatment course. Occasionally, occlusion occurs immediately after placement of the catheter across the stenotic site or after initial successful dilatation (Fig. 4). When this occurs, we attempt to reverse the occlusion by the use of intracoronary nitroglycerin and supplemental calcium antagonists. Acute occlusions have been redilated successfully. Therefore, when acute occlusion occurs as a complication of PTCA, additional consideration should be given to probing the occlusion with either a soft guide wire or the dilating catheter itself in an attempt to re-

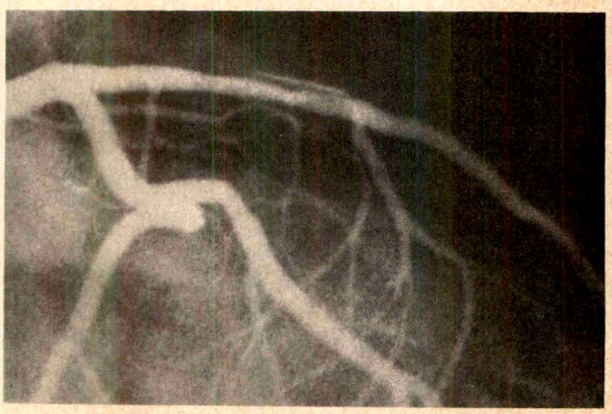


**FIGURE 3.** Angiogram performed immediately after successful PTCA in the middle left anterior descending artery with a long intimal flap.

store flow and successfully complete the dilatation. Care must be taken, however, to avoid delaying prompt surgical intervention and reperfusion.

*Intraluminal thrombosis:* At the site of dilatation, intraluminal thrombosis may occur, resulting in partial or complete occlusion. Potential mechanisms include (1) trauma to the endothelium and exposure of the intima, with subsequent platelet aggregation; (2) stasis from engaging the coronary ostia with a large guiding catheter or impacting the dilating catheter in a tight stenosis; and (3) stasis within the guiding catheter itself, with subsequent thrombus formation and embolization. In addition to anticoagulant treatment, other means of preventing platelet aggregation include the use of aspirin and dipyridamole, low-molecular-weight dextran, and calcium-channel blockers.[17,18] Despite the frequent use of these agents in PTCA, no controlled information exists. When intraluminal thrombus is recognized during dilatation, thrombolytic therapy can be helpful.

Experimental investigators have long recognized the thrombogenic effect of intimal injury. After balloon inflation in canine coronary arteries and rabbit iliac arteries, there is immediate platelet aggregation and adhesion and fibrin deposition at the site of endothelial damage.[6,7,9,19,20] It is not, therefore, surprising that thrombotic occlusion occasionally may complicate PTCA.

*Coronary artery spasm:* Mechanical stimulation of the coronary artery either at the site of the stenosis or distal to the stenosis may precipitate coronary artery spasm during balloon dilatation. The mechanical effect of distention and catheter manipulation appears to be a potent stimulus for spasm which may persist beyond the actual angioplasty. Cowley et al[13] reported that 21% of their patients had evidence of coronary artery spasm during the initial 48 hours after dilatation. Such spasm may occur despite the use of nitrates and calcium antagonists and may necessitate surgical myocardial revascularization. In our experience, 2 patients had spasm during balloon dilatation at the site of the stenosis. Each was treated with supplemental nitrates or calcium antagonists (or both), with resolution of the coronary spasm. However, suspected spasm with subsequent infarction, dysrhythmia, and even death has been reported from the NHLBI PTCA Registry.[3] Spasm also may be 1 factor that influences the occurrence of restenosis. Scholl et al[21] have noted that "variant angina"

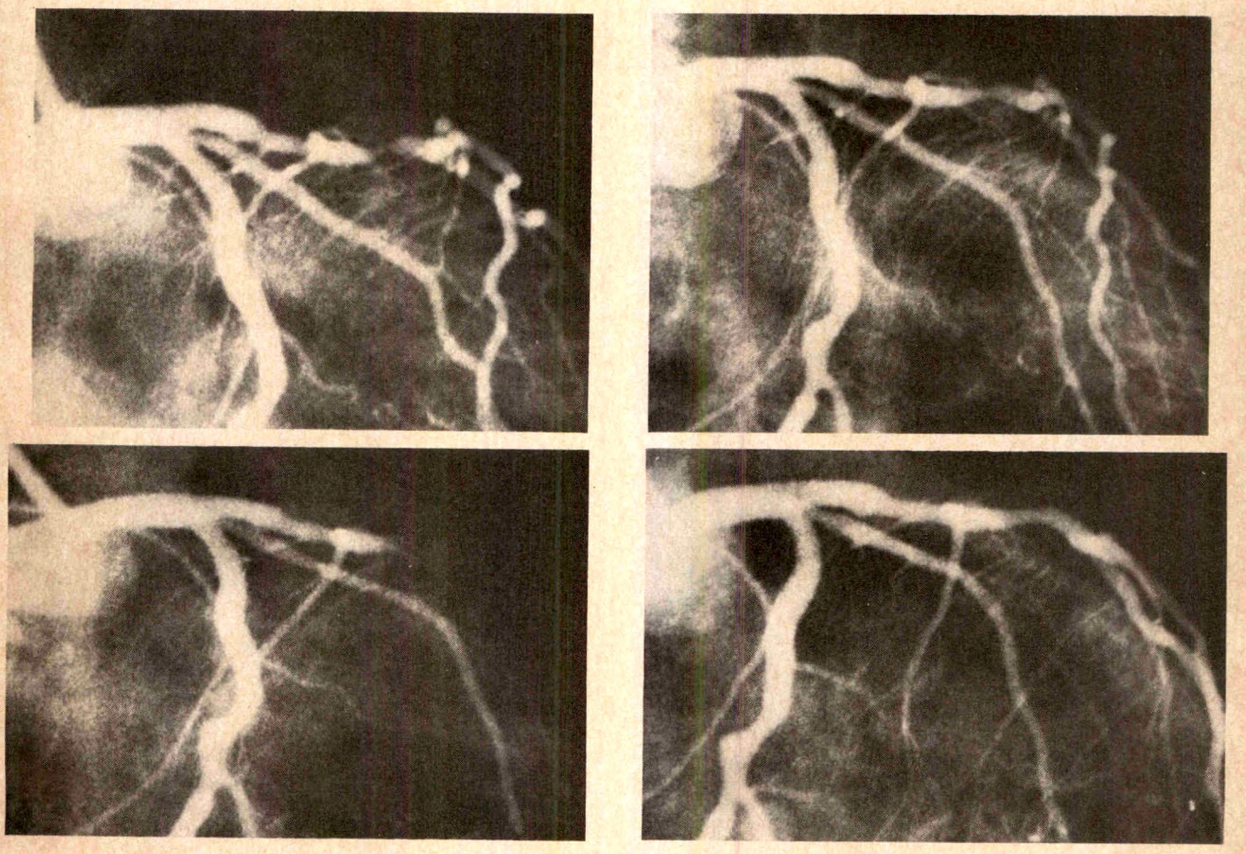


**FIGURE 4. Top left,** high-grade stenosis in the middle left anterior descending artery. **Top right,** initial improvement after PTCA. **Bottom left,** 15 minutes later, the patient had chest pain and angiography documented occlusion of the left anterior descending artery. **Bottom right,** after that, the dilating catheter was passed across the occlusion and successful PTCA resulted.

is associated with an increased incidence of restenosis. To prevent spasm, many angiographers continue treatment with calcium antagonists after angioplasty for from several days to 6 months.

*Aneurysmal dilatation:* A mismatch in size between a balloon catheter and the arterial segment dilated may result in excessive, even aneurysmal, dilatation. This occurred in 1 patient from the inadvertent dilatation of a small but normal diagonal coronary artery. As dilatation in more distal lesions of smaller arterial segments is attempted, aneurysmal changes may be seen more frequently.

Experimentally, an important relation between the size of the stenotic segment and the expanded balloon has been defined.[6] If the balloon is significantly larger than the coronary artery to be dilated, more extensive focal intimal splitting is found microscopically.

*Coronary artery rupture:* The ultimate extension of aneurysmal changes produced by excessive dilatation of a stenosis is frank rupture of the coronary artery. In a postmortem study, Lee et al[8] documented coronary artery rupture from excessive balloon inflation. Dissecting hematomas have been documented after attempted PTCA.[4] While such hematomas have the potential for rupture, to date this has not been noted clinically.

**Delayed:** *Restenosis:* Restenosis occurs in 20 to 30% of successfully dilated segments, usually within 3 to 6 months.[21,22] In the NHLBI PTCA Registry,[23] restenosis was seen in approximately 30% of patients undergoing follow-up angiography. There were no clinical characteristics before dilatation which were associated with an increase in the frequency of restenosis. Scholl et al[21] found, in a group of 11 patients with restenosis, that variant angina and eccentric or calcified lesions had an increased incidence of restenosis. Restenosis is usually heralded by the recurrence of angina pectoris, although some patients continue to be asymptomatic.[21] Whether this is a new lesion or an elastic-like recoil of the old one is not resolved. Fortunately, complete occlusion from restenosis seems rare. We have not yet observed an acute myocardial infarction in a patient who has had restenosis. In patients with restenosis, redilatation usually can be performed successfully.

## Changes in a Coronary Artery Segment Remote From the Angioplasty Site

Changes may be observed at the time of PTCA (immediate) or at later restudy (delayed).

**Immediate:** At dilatation, angiographic changes may be seen in other segments of the arterial tree, either in a different branch or in a different segment in the same vessel undergoing angioplasty. These changes may result from (1) inadvertent entry into a vessel other than the one in which dilatation is attempted, (2) close proximity of the branch vessel to the site of stenosis, and (3) downstream effects. These changes are more aptly considered complications of the procedure rather than planned consequences of the controlled injury by balloon inflation.

*Branch occlusion:* Branch occlusion most commonly results when a branch vessel arises near the stenotic site being dilated. This is particularly likely when the branch vessel has a significant ostial stenosis. In this circumstance, dilatation may further compromise the branch vessel and may result in occlusion, with subsequent infarction (Fig. 5). PTCA might best be avoided in such patients. However, where the branch vessel is small (for example, a small diseased diagonal arising in an area of stenosis in the left anterior descending artery), the benefits of successful dilatation of the large parent vessel may outweigh the risk of an occlusion of the small branch.

*Distal embolization or embolic occlusion:* An early concern with balloon dilatation was the potential for dislodging ragged atheromatous material, causing distal embolization. Although this has been reported, it is infrequent.[13,16] Recently, subsequent to our experience

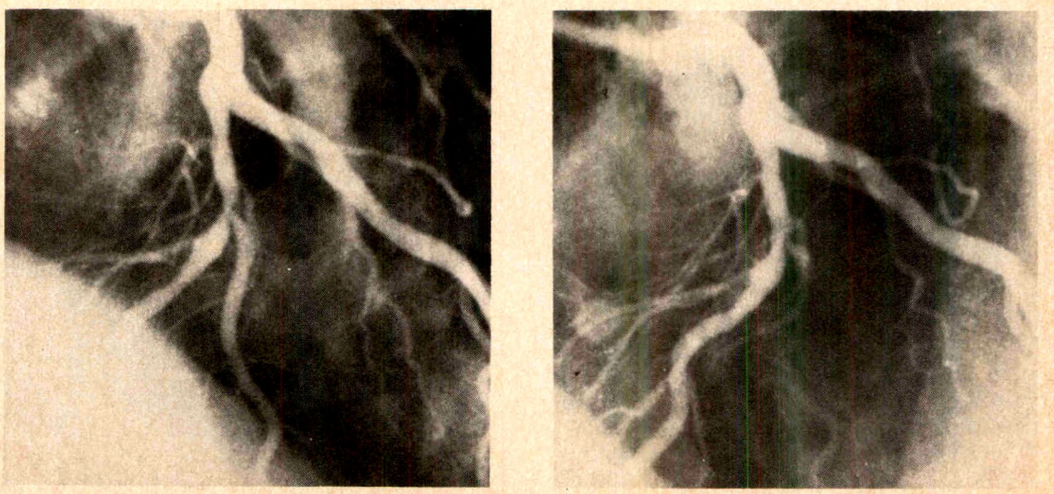


**FIGURE 5. Left,** predilatation angiogram documented a significant lesion in the mid-left anterior descending artery with involvement of a diagonal branch. **Right,** after successful PTCA, there is 100% occlusion of the diagonal branch, with retrograde filling.

with the first 100 patients, we had 1 patient in whom new, small filling defects were seen in the distal segment of the right coronary artery after successful dilatation of a mid-right coronary artery stenosis. Whether these represented embolization of thrombus adherent to an atherosclerotic lesion, atheromatous material itself, or thromboembolism from the guiding catheter is unknown. This patient subsequently had enzymatic and electrocardiographic documentation of a subendocardial infarction.

*Coronary spasm:* As previously discussed, mechanical distention, overinflation, or catheter manipulation may result in coronary spasm at the site of stenosis. Similarly, spasm results if the dilating catheter is inadvertently placed in a branch vessel or distal to the lesion. Distal spasm has been seen in 6 patients. Careful attention to catheter placement and inflation pressure, plus pretreatment with nitrates and calcium antagonists, is currently the most effective method for avoiding spasm.

*Aneurysmal dilatation:* Aneurysmal changes may occur in other segments of the arterial tree where dilatation is inadvertently performed. Dilatation in a small diagonal vessel can result in aneurysmal changes in that vessel (Fig. 6). The long-term results of inadvertent dilatation in a nondiseased or minimally diseased coronary artery are as yet unknown but are potentially adverse. Balloon dilatation has been used experimentally to produce focal atherosclerosis.[24] Fallon[25] pointed out the irony that balloon dilatation is used to treat the atherosclerotic lesions that were originally produced experimentally by balloon inflation itself.

*Intimal flap:* The intimal changes induced in segments of the coronary artery not planned for dilatation have been variable and have ranged from intimal flaps to frank dissection of the coronary artery. These usually are consequences of unsuccessful attempts to intubate the appropriate arterial segment. Figure 7 shows dissection in the circumflex coronary artery in a patient with a significant stenosis of the left anterior descending artery. Entry into the left anterior descending artery was difficult, and during attempts to do so, the circumflex artery was repeatedly entered, with subsequent intimal damage. Improvements in technology, improved patient selection, and increased operator experience with the technique will likely reduce the incidence of these complications.

**Delayed:** *New stenosis:* A new site of coronary artery stenosis remote from the angioplasty segment has been observed in 1 patient during follow-up angiography. We believe this reflects the natural history of the coronary artery disease; however, long-term evaluation must consider the possibility that new remote lesions may be related to previous dilatation.

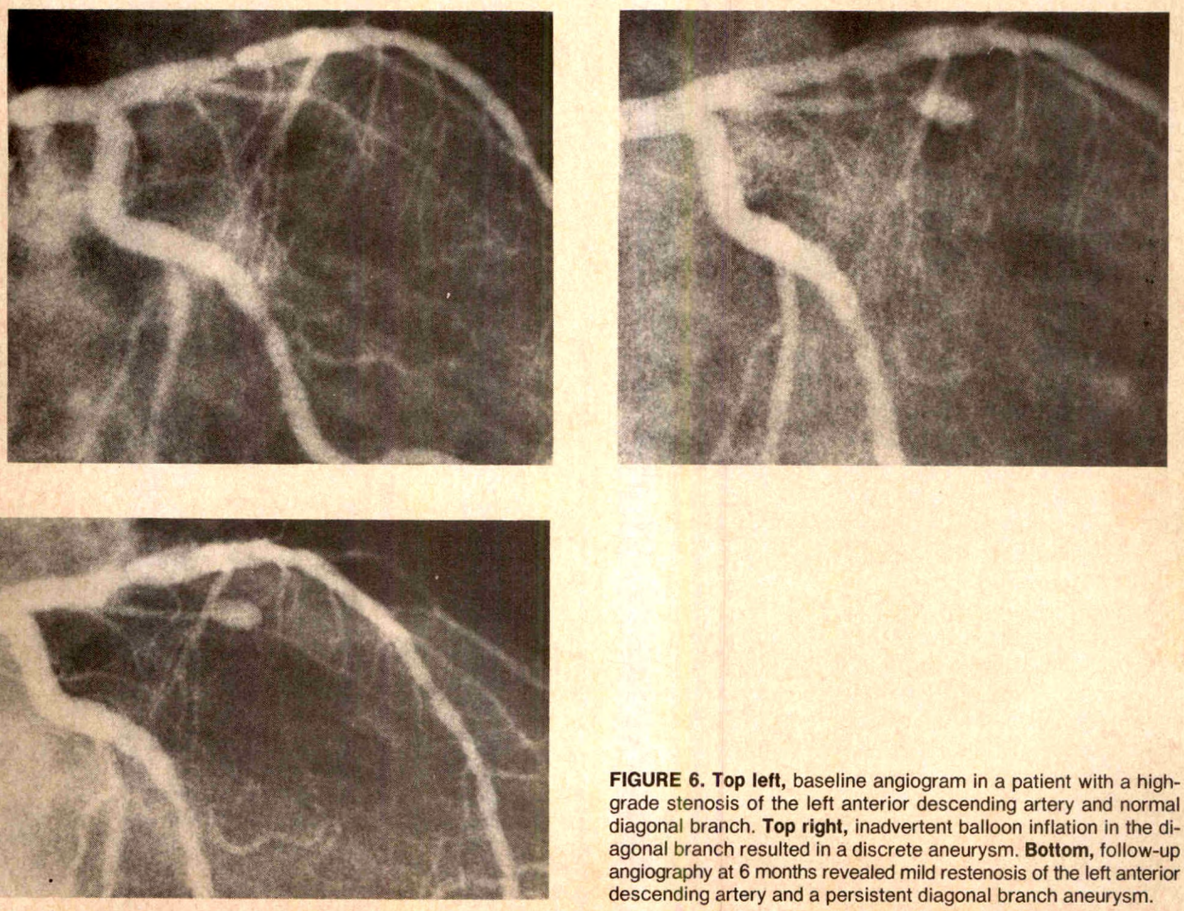


**FIGURE 6. Top left,** baseline angiogram in a patient with a high-grade stenosis of the left anterior descending artery and normal diagonal branch. **Top right,** inadvertent balloon inflation in the diagonal branch resulted in a discrete aneurysm. **Bottom,** follow-up angiography at 6 months revealed mild restenosis of the left anterior descending artery and a persistent diagonal branch aneurysm.

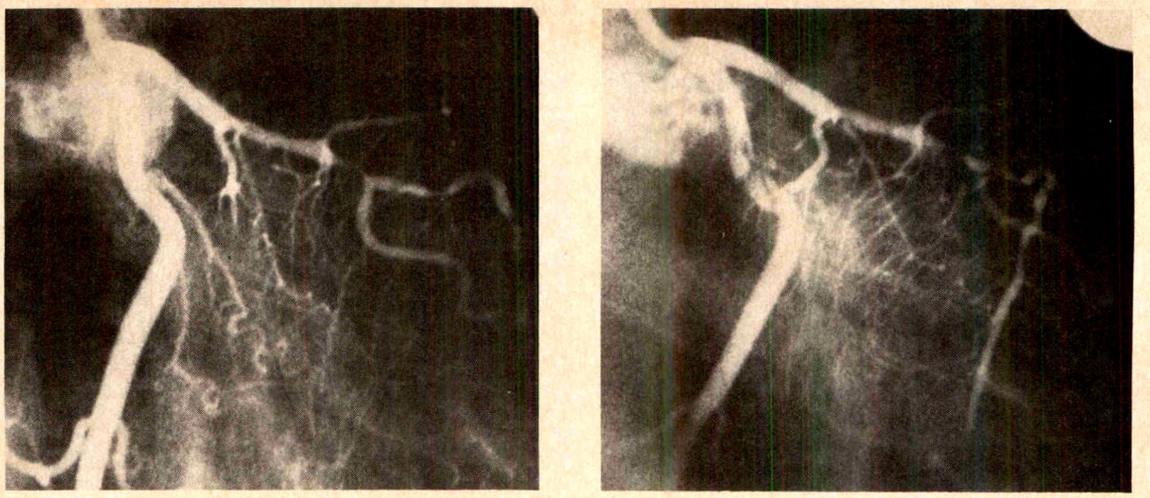


**FIGURE 7. Left,** baseline angiography in patient with a normal circumflex artery and severe stenosis of left anterior descending coronary artery. **Right,** during attempts to intubate the left anterior descending coronary artery, dissection of the circumflex artery occurred.

## Discussion

PTCA has altered the way in which angiographers view the coronary arteries. More attention is now directed to the course of diseased and nondiseased segments, as this may affect the procedure. PTCA also has modified the approach of many cardiologists in patients with symptomatic coronary artery disease. Recognition that the "controlled injury" produced by balloon inflation may result in clinical improvement requires a radical departure from our previous understanding and has led to a reappraisal of our management strategies.

The wide range of angiographic findings that result from coronary angioplasty correlates with the histopathologic findings.[9] These variable angiographic changes may be the result of catheter manipulation or balloon inflation itself. They may be seen both in the nondilated segment of the arterial tree and in the segment undergoing dilatation, and as such they may be considered complications of the technique or simply a manifestation of the controlled injury.

Proper recognition of the wide range of angiographic results is clinically important. This recognition depends on a high-quality x-ray imaging and recording system, as well as on obtaining properly angulated multiple views of all related arterial segments. After initial recognition and classification, long-term follow-up of the different angiographic groups may yield more specific prognostic information as to the outcome of patients undergoing PTCA. An example of this is the significant problem of restenosis, which may occur in as many as 30% of patients undergoing dilatation. At present, little information is available about the determinants of restenosis. Careful classification and follow-up of the diverse angiographic patterns may yield information in this regard, as these patterns reflect in part the underlying anatomic changes in the vessel wall.[9]

The angiographic classification proposed herein does not represent the complete or final statement on the issue. In fact, the terminology currently used—for example, dissection or intramural split—may undergo significant change. The classification is intended to portray some of the angiographic findings observed. Recognition and classification of these findings will become increasingly important in the evaluation of the long-term effects of PTCA and in developing new approaches for avoiding adverse effects. In addition, intensive evaluation of the clinical experiment that PTCA represents eventually may advance our understanding of coronary atherosclerosis.

## References


1. **Grüntzig AR, Senning Å, Siegenthaler WE.** Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979;301:61–68.
2. **Vlietstra RE, Holmes DR Jr, Smith HC, Hartzler GO, Orszulak TA.** Percutaneous transluminal coronary angioplasty: initial Mayo Clinic experience. Mayo Clin Proc 1981;56:287–293.
3. **Kent KM, Bentivoglio LG, Block PC, Cowley MJ, Dorros G, Gosselin AJ, Grüntzig A, Myler RK, Simpson J, Stertzer SH, Williams DO, Fisher L, Gillespie MJ, Mullin SM, Mock MB.** Percutaneous transluminal coronary angioplasty: report from the Registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1982;49:2011–2020.
4. **Block PC, Myler RK, Stertzer S, Fallon JT.** Morphology after transluminal angioplasty in human beings. N Engl J Med 1981;305:382–385.
5. **Castaneda-Zuniga WR, Formanek A, Tadavarthy M, Edwards JE, Zollikofer C, Amplatz K.** The mechanism of balloon angioplasty. Radiology 1980;135:565–571.
6. **Block PC, Fallon JT, Elmer D.** Experimental angioplasty: lessons from the laboratory. AJR 1980;135:907–912.
7. **Block PC, Baughman KL, Pasternak RC, Fallon JT.** Transluminal angioplasty: correlation of morphologic and angiographic findings in an experimental model. Circulation 1980;61:778–785.
8. **Lee G, Ikeda RM, Joye JA, Bogren HG, DeMaria AN, Mason DT.** Evaluation of transluminal angioplasty of chronic coronary artery stenosis: value and limitations assessed in fresh human cadaver hearts. Circulation 1980; 61:77–83.
9. **Weber VJ, Faxon DP, Haudenschild C, Gottsman SB, McGovern WA, Ryan TJ.** Acute and chronic effects of transluminal angioplasty in experimental atherosclerosis (abstr). Am J Cardiol 1981;47:395.
10. **Freudenberg H, Wefing H, Lichtlen PR.** Risks of transluminal coronary angioplasty: a postmortal study (abstr). Circulation 1978;58:Suppl II:II-80.
11. **Dorros G, Spring DA.** Healing of coronary artery intimal dissection after percutaneous transluminal angioplasty (abstr). Am J Cardiol 1980;45: 423.

12. **Block PC.** Percutaneous transluminal coronary angioplasty. AJR 1980; 135:955–959.
13. **Cowley MJ, Vetrovec GW, Wolfgang TC.** Efficacy of percutaneous transluminal coronary angioplasty: technique, patient selection, salutary results, limitations and complications. Am Heart J 1981;101:272–280.
14. **Abele JE.** Balloon catheters and transluminal dilatation: technical considerations. AJR 1980;135:901–906.
15. **Engel H-J, Kaltenbach M, Kober G, Scherer D, Lichtlen PR.** Spontaneous regression of coronary obstructions after transluminal dilatation (abstr). Circulation 1980;62:Suppl III:III-159.
16. **Cowley M, Bentivoglio L, Block P, Bourassa M, Detre K, Dorros G, Gosselin A, Grüntzig A, Kent K, Myler R, Simpson J, Stertzer S, Williams D, Mullin S, Mock M, Participating Centers.** Emergency coronary artery bypass surgery for complications of coronary angioplasty: NHLBI PTCA Registry experience (abstr). Circulation 1981;64:Suppl IV:IV-193.
17. **Fuster V, Chesebro JH.** 10. Antithrombotic therapy: role of platelet-inhibitor drugs. II. Pharmacologic effects of platelet-inhibitor drugs (second of three parts). Mayo Clin Proc 1981;56:185–195.
18. **Pumphrey CW, Fuster V, Dewanjee M, Kaye M, Chesebro J, Vlietstra R.** Verapamil is an effective in vivo inhibitor of platelet activation in peripheral vascular grafts in dogs (abstr). Circulation 1981;64:Suppl IV:IV-56.
19. **Pasternak RC, Baughman KL, Fallon JT, Block PC.** Scanning electron microscopy following coronary transluminal angioplasty with balloon dilatation catheter (abstr). Circulation 1978;58:Suppl II:II-242.
20. **Pasternak RC, Baughman KL, Fallon JT, Block PC.** Scanning electron microscopy after coronary transluminal angioplasty of normal canine coronary arteries. Am J Cardiol 1980;45:591–598.
21. **Scholl JM, David PR, Chaitman BR, Lespérance J, Crépeau J, Dyrda I, Bourassa MG.** Recurrence of stenosis following percutaneous transluminal coronary angioplasty (abstr). Circulation 1981;64:Suppl IV:IV-193.
22. **Gruentzig A, Schlumpf M, Siegenthaler W.** Late functional results after success or failure of coronary angioplasty (PTCA) (abstr). Circulation 1981;64:Suppl IV:IV-193.
23. **Holmes DR Jr, Vlietstra RE, Smith HC, Vetrovec GW, Cowley MJ, Kent KM, Detre KM, Myler R.** Restenosis following percutaneous transluminal coronary angioplasty (PTCA): a report from the NHLBI PTCA Registry (abstr). Am J Cardiol 1982;49:905.
24. **Lee WM, Lee KT.** Advanced coronary atherosclerosis in swine produced by combination of balloon-catheter injury and cholesterol feeding. Exp Mol Pathol 1975;23:491–499.
25. **Fallon JT.** Pathology of arterial lesions amenable to percutaneous transluminal angioplasty. AJR 1980;135:913–916.

# Ergonovine Provocation to Assess Efficacy of Long-Term Therapy With Calcium Antagonists in Prinzmetal's Variant Angina

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**In the patient with Prinzmetal's variant angina, the response to therapy with calcium antagonists may be assessed symptomatically, electrocardiographically (that is, by ambulatory electrocardiographic monitoring), or by response to ergonovine provocation. Although some studies have suggested a good relation between anginal frequency and ergonovine responsiveness in these patients, none has compared ambulatory electrocardiographic activity with the results of ergonovine provocation during the long-term administration of calcium antagonists. Therefore, the present study was performed to compare ergonovine responsiveness with both clinical and ambulatory electrocardiographic activity in patients with Prinzmetal's variant angina during long-term therapy with placebo, verapamil, and nifedipine. Accordingly, 27 patients with variant angina (19 men and 8 women, mean age 52 years) received placebo and verapamil for 2 months each, after which 23 of the 27 also received nifedipine for 2 months. All patients kept a diary of chest pains, and all had weekly 24-hour 2-channel ambulatory electrocardiographic (Holter) monitoring, from which episodes of transient S-T segment deviation were quantitated. During the final week of therapy with each agent, ergonovine was administered, beginning at 0.025 mg and incrementally increasing to 0.20 mg. It was discontinued when the patient had chest pain with S-T segment elevation $\geq$0.1 mV or received a total dose of 0.50 mg. Of the 74 tests, 59 were negative; 6 of the negative tests occurred during a treatment period in which the patient had $>$10 chest pains/week and $>$25 episodes of S-T segment deviation/week. Of the 15 positive tests, 8 became positive during administration of $<$0.20 mg ergonovine; 5 of the positive tests occurred during a treatment period in which the patient had no chest pain or S-T segment deviation. Thus, in patients with variant angina, disease activity cannot be monitored reliably by ergonovine provocation because some patients have negative ergonovine tests at a time of marked clinical and electrocardiographic activity, whereas others have positive tests at a time of little (or no) disease activity.**

Ergonovine maleate has been shown to induce coronary arterial spasm in patients with Prinzmetal's variant angina,[1–3] and calcium antagonists have been shown to block such ergonovine-induced spasm.[4,5] Previous reports have demonstrated a good relation between ergonovine responsiveness and anginal frequency during both short-term[6,7] and long-term[8,9] treatment with calcium antagonists. These same studies[8] used ergonovine provocation as a means of detecting spontaneous remissions in disease activity in patients with this syndrome.

Several studies have shown that patients with variant angina have electrocardiographic evidence of ischemia more frequently than they have angina.[10–12] Thus, the patient with this disease may demonstrate numerous episodes of transient S-T segment deviation, most (or all) of which are not accompanied by chest pain. In these persons, ambulatory electrocardiographic (Holter) monitoring is required to ascertain that the disease is not totally quiescent. The present study was performed to compare ergonovine responsiveness with clinical and ambulatory electrocardiographic activity in a group of patients with variant angina during the long-term ad-

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ministration of placebo, verapamil, and nifedipine. In so doing, we attempted to address the following questions: (1) Is the response to ergonovine provocation closely linked to other reflectors of disease activity, such as anginal frequency and ambulatory electrocardiographic evidence of ischemia, or, alternatively, (2) is ergonovine responsiveness independent of the symptomatic and electrocardiographic markers of disease activity?

## Methods

**Patient group:** The study group consisted of 27 consecutive patients (19 men and 8 women, average age 52 years, range 33 to 62) with Prinzmetal's variant angina. All had angina at rest in association with transient S-T segment elevation (≥0.2 mV) on a standard 12-lead electrocardiogram. In addition, ergonovine maleate was administered at the time of initial evaluation in 21 of the 27 patients (such provocation was not performed in the remaining 6 because of concern over the presence of severe obstructive coronary artery disease). Of these 21 patients, ergonovine caused typical angina and S-T segment elevation ≥0.2 mV in 20. Simultaneous coronary angiography was performed in 16, demonstrating focal coronary arterial spasm in all. Cardiac catheterization with selective coronary arteriography was performed in 26: 10 had obstructive coronary artery disease (defined as ≥70% luminal diameter narrowing), whereas the remaining 16 had minimal or no coronary artery disease. The criteria for exclusion from the study have been described previously.[11]

**Study design:** After a diagnosis of variant angina was made, informed consent was obtained, and each patient was given open-label verapamil for 1 month, during which the maximal dose of verapamil that did not cause intolerable adverse effects was determined. Subsequently, each patient was randomly assigned to 1 of 2 groups for the next 8 months of the study: four 2-month blocks, with each patient receiving either placebo-verapamil-placebo-verapamil or verapamil-placebo-verapamil-placebo. During this part of the study, neither the physicians nor the patients knew which agent was being administered.

After the 8 months of blinded therapy, 23 patients agreed to receive nifedipine (as an "open-label" medication) for 2 more months. Both verapamil and nifedipine were administered in doses that afforded maximal relief of angina without adverse effects.

**Variables analyzed:** *Clinical and electricardiographic response to therapy:* During the entire study period, each patient maintained a written diary of anginal episodes. In addition, each patient had weekly calibrated 2-channel ambulatory electrocardiographic monitoring for 24 hours, as previously described.[11,12] Transient S-T segment deviations from baseline were said to be present if S-T segment depression or elevation ≥1 mm (0.1 mV) was present for ≥1 minute.[13] Both S-T segment depression and elevation were utilized as electrocardiographic evidence of coronary arterial spasm because patients with variant angina often demonstrate both during therapy with calcium antagonists.[10,11] A period of at least 10 minutes of baseline S-T segment morphology was required between episodes in order for these episodes to be considered separate. For each 24-hour tape, the number of transient episodes of S-T segment deviation was quantitated.

*Ergonovine provocation:* During the final week of blinded treatment periods 3 and 4, 25 of the 27 patients enrolled in the placebo-verapamil comparison had provocative testing with ergonovine maleate. One patient was tested during period 3 but died during period 4 before testing, and another patient refused. Subsequently, all 23 patients who received nifedipine had ergonovine testing during the final week of that treatment period. Thus, during therapy with placebo, verapamil, and nifedipine, 74 ergonovine tests were performed. All tests were done between 10 A.M. and 12 P.M.; they were begun 1.5 hours after a regularly scheduled dose of study medication and at least 12 hours after the last dose of long-acting nitrates. During the 24 hours before ergonovine testing, no sedatives or other cardioactive medications (that is, atropine, adrenergic or antiadrenergic agents, or antihistamines) were administered.

After a baseline 12-lead electrocardiogram and blood pressure were recorded, each patient received intravenous ergonovine maleate every 3 minutes according to the following schedule: 0.025 mg ×4 (cumulative dose, 0.10 mg); 0.05 mg ×2 (cumulative dose, 0.20 mg); 0.10 mg ×1 (cumulative dose, 0.30 mg); and 0.20 mg ×1 (cumulative dose, 0.50 mg). Before each intravenous injection, the patient was questioned about chest pain or other symptoms, and a 12-lead electrocardiogram was recorded. Ergonovine administration was discontinued when one of the following occurred: (1) chest pain in association with electrocardiographic evidence of ischemia (≥0.1 mV of S-T segment elevation), or (2) administration of a cumulative dose of 0.50 mg. All patients with a positive test had chest pain coincident with S-T segment elevation.

**Data analysis:** First, each variable (anginal episodes and S-T segment deviations) was quantitated during the latter 4 months of blinded therapy (2 months placebo, 2 months verapamil) and the 2 months of nifedipine therapy, and the average value for each variable during each 2-month period was compared with the results of ergonovine provocation during the final week of that period. Second, each variable was quantitated during the 7 days in closest temporal proximity to ergonovine provocation, and this value was compared with the ergonovine test results. Finally, these same relations (that is, clinical and electrocardiographic activity compared with ergonovine test results) were examined only in the 16 persons who did not have significant obstructive coronary artery disease and in whom, therefore, angina and S-T segment deviations must have resulted from coronary arterial spasm. For both anginal episodes and S-T segment deviations, the percentage of patients with substantial disease activity (defined as >10 episodes of angina/week and >25 episodes of S-T segment deviation/week) during a treatment period associated with a negative ergonovine test was compared with the percentage of patients with marked disease activity during a period associated with a positive ergonovine test using a chi-square analysis.[14,15]

In comparing the frequency of angina and S-T segment deviations in the 3 treatment periods, a repeated measures analysis of variance was performed. All values are reported as mean ±1 standard deviation. A p value ≤0.05 was considered significant.

## Results

The 27 patients enrolled in the long-term comparison of placebo and verapamil received 450 ± 83 mg/day of verapamil, and the 23 patients who subsequently received nifedipine averaged 71 ± 24 mg/day, both administered in 3 to 4 divided doses.

**Clinical and electrocardiographic response to therapy:** Compared with placebo, both verapamil and nifedipine reduced the frequency of angina and transient S-T segment deviations (Table I).

**Ergonovine provocation:** For the entire group of 27 patients, there were 6 positive tests during placebo therapy, 5 positive tests during verapamil (difference

**TABLE I Clinical and Electrocardiographic Response to Therapy**

| | Anginal Episodes/Week | S-T Segment Deviations/Week |
|---|---|---|
| Placebo | 9.3 ± 23.4 | 21.7 ± 32.7 |
| Verapamil | 2.7 ± 3.6* | 4.6 ± 8.3* |
| Nifedipine | 1.9 ± 2.9* | 5.4 ± 10.1* |

* $p < 0.05$ in comparison with placebo.
All values are mean ± standard deviation.

not significant [NS] compared with placebo), and 4 positive tests during nifedipine (NS compared with placebo and verapamil).

*Disease activity during the entire 2-month treatment period versus ergonovine responsiveness:* Figure 1 shows the relation between anginal episodes and S-T segment deviations for each 2-month treatment period and the results of ergonovine provocation during the final week of each treatment period. Of the 59 negative ergonovine tests, 6 (10%) were performed during periods in which the patient was having >10 episodes of chest pain/week and >25 episodes of S-T segment deviation/week. Of the 15 positive tests, 2 (13%) were done during periods in which the patient noted >10 episodes of chest pain/week (NS) and 4 (27%) during periods in which the patient was having >25 episodes of S-T segment deviation/week (NS).

*Disease activity versus ergonovine responsiveness in close temporal proximity to one another:* Figure 2 shows the relation between anginal episodes and S-T segment deviations during the 7 days in closest proximity to ergonovine provocation and the results of each ergonovine test. Of the 59 negative ergonovine tests, 6 (10%) were performed during a week when the patient had >10 episodes of chest pain, and 5 (8%) were done during a week when the patient had >25 episodes of S-T segment deviation. Of the 15 positive tests, 3 (20%) were done during a week in which the patient had >10 episodes of chest pain (NS) and 4 (27%) during a week in which the patient had >25 episodes of S-T segment deviation (NS).

*Disease activity versus ergonovine responsiveness in the 6 patients with positive ergonovine tests during placebo therapy:* For the 6 patients who had a positive ergonovine test during placebo therapy, the relation between ergonovine responsiveness and disease activity (assessed during both the entire 2-month treatment period as well as the 7 days in closest temporal proximity to ergonovine provocation) was similar to that described for all 27 patients. In this subset of patients, ergonovine provocation was sometimes negative during a period of marked symptomatic or electrocardiographic activity, and, conversely, ergonovine testing was often markedly positive during a period of little or no disease activity.

*Disease activity versus ergonovine responsiveness in patients without significant obstructive coronary artery disease:* Of the 27 patients in the present study, 16 did not have significant obstructive coronary artery disease. In these patients, chest pain and S-T segment deviations are almost always caused by coronary arterial spasm. For these 16, 36 ergonovine tests were negative, and 12 were positive. Of the 36 negative tests, 3 (8%) were performed during a week when the patient had >10 episodes of chest pain and 2 (6%) were performed during a week in which the patient had >25 episodes of S-T segment deviation. Of the 12 positive tests, 2 (17%) were done during a week in which the patient had >10 episodes of angina (NS) and 3 (25%) were done during a week in which the patient had >25 episodes of S-T segment deviation (NS).

## Discussion

Ergonovine maleate has been shown to induce coronary arterial spasm in certain patients with Prinzmetal's variant angina,[1-3] and calcium antagonists have been shown to block ergonovine-induced spasm.[4,5] Over the past few years, several studies utilized ergonovine provocation to assess the adequacy of as well as the need for continued medical therapy in patients with this disease. First, Theroux,[6] Waters,[7] and their co-workers demonstrated an excellent relation between the results of ergonovine provocation and the short-term (2 day) clinical response to therapy with calcium antagonists, and similar findings were reported using methergine (an ergot alkaloid similar to ergonovine maleate)[9] and hyperventilation.[16] Second, Waters et al[7] showed that ergonovine testing within several days of the initiation of calcium antagonist therapy can be used reliably to predict the long-term (1 to 15 month) response to such therapy. Third, these same investigators[8] suggested that some patients with variant angina who are pain-free during long periods of treatment may not require indefinite therapy; ergonovine provocation appears to be a good method of evaluating the status of the disease process in these patients.

In contrast to these reports, the present study demonstrates no relation between the results of ergonovine provocation and disease activity, as assessed during both the entire 2-month treatment period preceding such ergonovine testing (Fig. 1) as well as the 7 days in closest temporal proximity to testing (Fig. 2). Both clinical and electrocardiographic evidence of marked disease activity occurred with similar frequency during periods with a positive ergonovine test and those with a negative test, and there was a wide variation in disease activity during both positive and negative test periods (Fig. 1 and 2). This was true for all 27 patients as well as for the 16 patients without significant obstructive coronary artery disease, a group in which chest pain and S-T segment deviations are almost always caused by coronary arterial spasm. Thus, the results of ergonovine provocation during long-term therapy with verapamil and nifedipine bear no relation to the clinical and electrocardiographic response to therapy.

The present study demonstrates an obvious disparity between ergonovine responsiveness and both clinical and electrocardiographic evidence of disease activity in a group of patients with Prinzmetal's variant angina, but the reasons for this disparity are not clear. The total dose of ergonovine used in the present study—0.50

mg—is lower than that employed by Waters,[6] Theroux,[8] and their associates, but this difference cannot explain the discrepancy in results between the present study and these previous reports. On the one extreme, several patients had positive ergonovine tests at small dosages during periods of little or no clinical or electrocardiographic activity (Fig. 1 and 2); this poor relation cannot be explained by differences in ergonovine dosages. On the other extreme, several other patients had negative ergonovine tests during periods of marked clinical or electrocardiographic activity. Because the cumulative dose of ergonovine given in the present study (0.50 mg) exceeds that in most available reports,[1–3,5,17–20] it is unlikely that the negativity of these tests can be attributed to an insufficient dose of ergonovine. Although it is possible that some of them would have become positive if more ergonovine had been given, the data of Waters,[6] Theroux,[7] and co-workers demonstrate that virtually all clinically active patients have a positive response before receiving a total of 0.50 mg of ergonovine. Thus, the poor relation between clinical activity and the results of ergonovine provocation cannot be explained entirely by differences in ergonovine doses. Similarly, before enrollment in the study, these patients had sufficient coronary arterial spasm to justify a diagnosis of variant angina: all 27 had chest pain at rest in association with reversible S-T segment elevation, and 20 of the 21 given ergonovine had a positive response. It appears unlikely that our patient group was in any way atypical or different from those described by other investigators. For reasons that are unclear at present, therefore, ergonovine responsiveness appears completely independent of the symptomatic and electrocardiographic markers of dis-

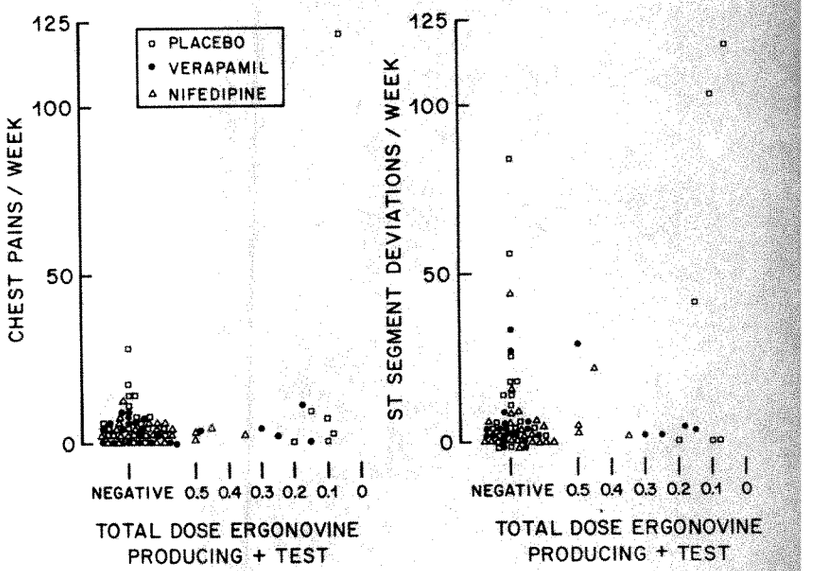



**FIGURE 1. Left panel,** relation between clinical evidence of disease activity, displayed as chest pains/week (during entire 2-month treatment period with each pharmacologic agent), and the results of ergonovine provocation (during the final week of the treatment period). **Right panel,** relation between electrocardiographic evidence of disease activity, shown as S-T segment deviations/week (during the entire 2-month treatment period with each agent) and the results of ergonovine testing (performed during the final week of the treatment period). Note that several patients with negative ergonovine tests had frequent chest pains and S-T segment deviations; conversely, most of the ergonovine tests that were positive at small cumulative doses (≤0.20 mg) were not associated with frequent angina or S-T segment deviations.

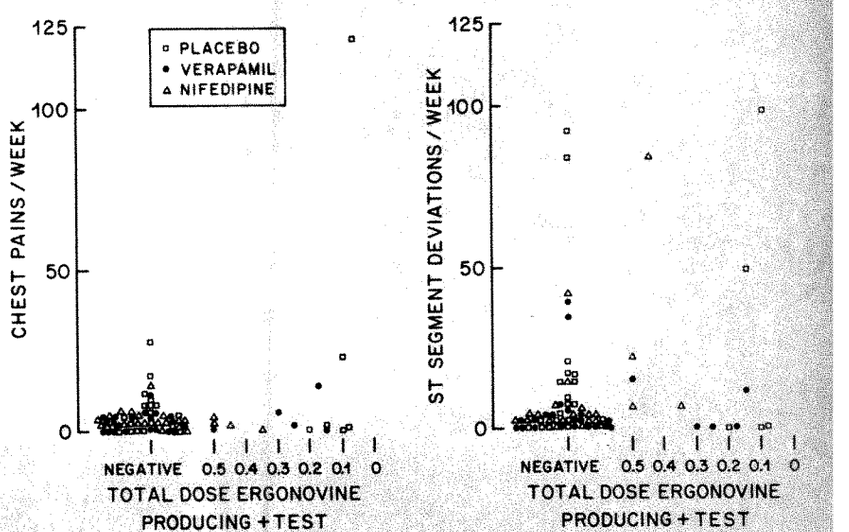



**FIGURE 2. Left panel,** relation between clinical evidence of disease activity, displayed as chest pains/week (during the week in closest proximity to ergonovine provocation), and the results of ergonovine testing. **Right panel,** relation between electrocardiographic evidence of disease activity, shown as S-T segment deviations/week (during the week in closest proximity to ergonovine administration), and the results of ergonovine provocation. Note that several patients with negative ergonovine tests had frequent chest pains and S-T segment deviations, whereas most of the ergonovine tests that were positive were not associated with frequent chest pain or S-T segment deviations.

ease activity in this group of patients with Prinzmetal's variant angina.

All the ergonovine tests in the present study were done under close clinical and electrocardiographic scrutiny, but selective coronary arteriography was not performed during ergonovine administration. Although the relation between ergonovine responsiveness and both clinical and electrocardiographic activity is poor, that between ergonovine responsiveness and the results of coronary arteriography might conceivably be better. Because coronary arteriography was not performed during each ergonovine provocation, we cannot comment on this relation.

In the present study, 74 ergonovine tests were performed without complications during clinical and electrocardiographic monitoring in patients both with and without obstructive coronary artery disease. Although previous reports[20] emphasized the potentially serious side effects of ergonovine administration, such reactions can be minimized if the initial doses of ergonovine are sufficiently small and separated temporally from one another. Specifically, the ergonovine provocation described in the present study is initiated with 4 doses of 0.025 mg each, administered 3 minutes apart. Subsequently, the ergonovine dose is gradually increased, so that a final dose of 0.20 mg is given only after the patient has not responded to smaller amounts.

*Conclusion:* This study demonstrates no relation between ergonovine responsiveness and clinical or electrocardiographic evidence of disease activity in patients with Prinzmetal's variant angina during long-term therapy with calcium antagonists. These data suggest that disease activity cannot be monitored reliably by ergonovine provocation because some patients have negative ergonovine tests at a time of marked clinical and electrocardiographic activity, whereas others have positive tests at a time of little (or no) disease activity. In patients with variant angina, anginal frequency and ambulatory electrocardiographic monitoring are preferable to ergonovine provocation in allowing an accurate assessment of disease activity.

**Acknowledgment:** We are indebted to B. J. Erck, S. B. Brown, J. R. Cary, and K. Lancaster for their technical assistance and J. Alexander for secretarial help.

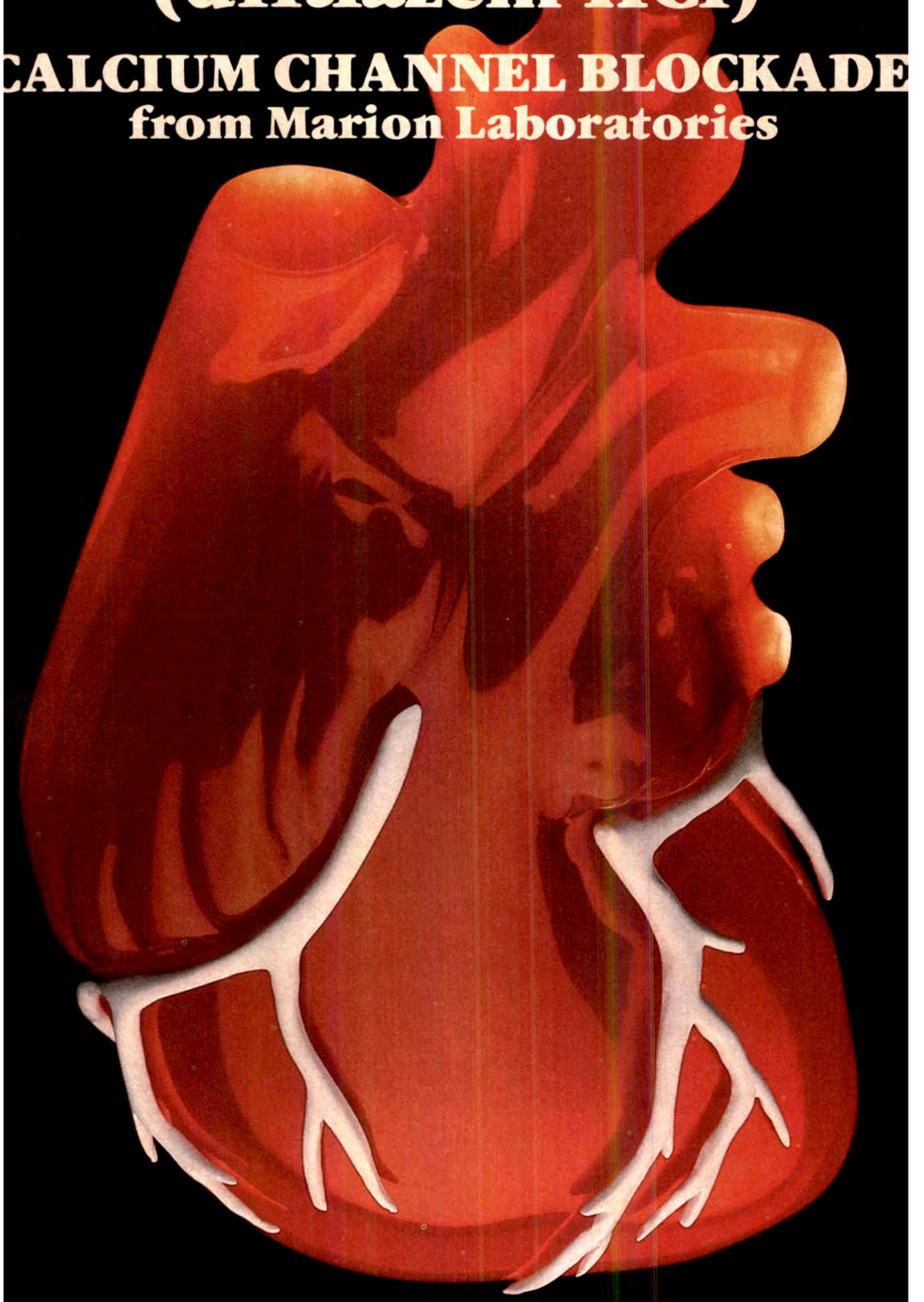
## References


1. **Nelson C, Nowak B, Childs H, Weinrauch L, Forwand S.** Provocative testing for coronary arterial spasm: rationale, risk and clinical illustrations. Am J Cardiol 1977;40:624–629.
2. **Schroeder JS, Bolen JL, Quint RA, Clark DA, Hayden WG, Higgins CB, Wexler L.** Provocation of coronary spasm with ergonovine maleate: new test with results in 57 patients undergoing coronary arteriography. Am J Cardiol 1977;40:487–491.
3. **Heupler FA Jr, Proudfit WL, Razavi M, Shirey EK, Greenstreet R, Sheldon WC.** Ergonovine maleate provocation test for coronary artery spasm. Am J Cardiol 1978;41:631–640.
4. **Goldberg S, Reichek N, Wilson J, Hirshfeld JW Jr, Muller J, Kastor JA.** Nifedipine in the treatment of Prinzmetal's (variant) angina. Am J Cardiol 1979;44:804–810.
5. **Tiefenbrunn AJ, Sobel BE, Gowda S, McKnight RC, Ludbrook PA.** Nifedipine blockade of ergonovine-induced coronary arterial spasm: angiographic documentation. Am J Cardiol 1981;48:184–187.
6. **Theroux P, Waters DD, Affaki GS, Crittin J, Bonan R, Mizgala HF.** Provocative testing with ergonovine to evaluate the efficacy of treatment with calcium antagonists in variant angina. Circulation 1979;60:504–510.
7. **Waters DD, Theroux P, Szlachcic J, Dauwe F.** Provocative testing with ergonovine to assess the efficacy of treatment with nifedipine, diltiazem and verapamil in variant angina. Am J Cardiol 1981;48:123–130.
8. **Waters DD, Szlachcic J, Theroux P, Dauwe F, Mizgala HF.** Ergonovine testing to detect spontaneous remissions of variant angina during long-term treatment with calcium antagonist drugs. Am J Cardiol 1981;47:179–184.
9. **Bertrand ME, Lablanche JM, Tilmant PY.** Treatment of Prinzmetal's variant angina: role of medical treatment with nifedipine and surgical coronary revascularization combined with plexectomy. Am J Cardiol 1981;47:174–178.
10. **Maseri A, Severi S, DeNes M, L'Abbate A, Chierchia S, Marzilli M, Ballestra AM, Parodi O, Biagini A, Distante A.** "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia. Am J Cardiol 1978;42:1019–1035.
11. **Johnson SM, Mauritson DR, Willerson JT, Hillis LD.** A controlled trial of verapamil for Prinzmetal's variant angina. N Engl J Med 1981;304:862–866.
12. **Johnson SM, Mauritson DR, Willerson JT, Hillis LD.** Comparison of verapamil and nifedipine in the treatment of variant angina pectoris: preliminary observations in 10 patients. Am J Cardiol 1981;47:1295–1300.
13. **Johnson SM, Mauritson DR, Winniford MD, Willerson JT, Firth BG, Cary JR, Hillis LD.** Continuous electrocardiographic monitoring in patients with unstable angina pectoris: identification of high risk subgroup with severe coronary disease, variant angina, and/or impaired early prognosis. Am Heart J 1982;103:4–12.
14. **Zar JH.** Biostatistical analysis. Englewood Cliffs, NJ: Prentice-Hall, 1974:173.
15. **Noether GE.** Introduction to Statistics: A Nonparametric Approach. Boston: Houghton-Mifflin, 1971:147.
16. **Girotti LA, Crosatto JR, Messuti H, Kaski JC, Dyszel E, Rivas CA, Araujo LI, Vetulli HD, Rosenbaum MB.** The hyperventilation test as a method for developing successful therapy in Prinzmetal's angina. Am J Cardiol 1982;49:834–841.
17. **Feldman RL, Curry RC Jr, Pepine CJ, Mehta J, Conti CR.** Regional coronary hemodynamic effects of ergonovine in patients with and without variant angina. Circulation 1980;62:149–159.
18. **Goldberg S, Lam W, Mudge G, Green LH, Kushner F, Hirshfeld JW, Kastor JA.** Coronary hemodynamic and myocardial metabolic alterations accompanying coronary spasm. Am J Cardiol 1979;43:481–487.
19. **Orlick AE, Ricci DR, Cipriano PR, Guthaner DF, Harrison DC.** Coronary hemodynamic effects of ergonovine maleate in human subjects. Am J Cardiol 1980;45:48–52.
20. **Buxton A, Goldberg S, Hirshfeld JW, Wilson J, Mann T, Williams DO, Overlie P, Oliva P.** Refractory ergonovine-induced coronary vasospasm: importance of intracoronary nitroglycerin. Am J Cardiol 1980;46:329–334.

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- Produces dose-dependent decreases in peripheral resistance
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**Reduces the pressure/rate product for any given work load in patients with effort-associated angina**

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(5) Increases coronary blood flow.

(6) Little or no negative inotropic effect at recommended doses while providing a powerful inhibition of coronary artery spasm.

(7) A positive effect on left ventricular function in patients with reduced left ventricular ejection fraction.[2]

(8) Increases ejection fraction at both submaximal and maximal exercise. Exercise ejection fraction is especially increased in patients with poor ventricular function.[3]

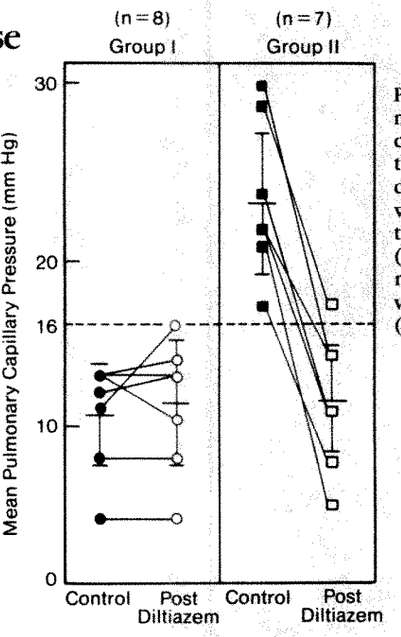
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The effect of a single 120-mg† dose of Cardizem was evaluated on symptom-limited upright exercise in 15 patients with effort angina.[4]

†It should be noted that this study employed a single 120-mg dose of diltiazem for hemodynamic measurement purposes. The approved maximum dose for Cardizem is 240 mg given in divided doses, three to four times daily.




**CHANGE IN FILLING PRESSURE AT MAXIMAL EXERCISE[4]**

Patients with control PCPs in normal range at maximal exercise showed little change in these values following diltiazem (Group I). Patients with markedly elevated control PCPs at maximal exercise (>16 mm Hg) showed dramatic reductions in these values following diltiazem (Group II).

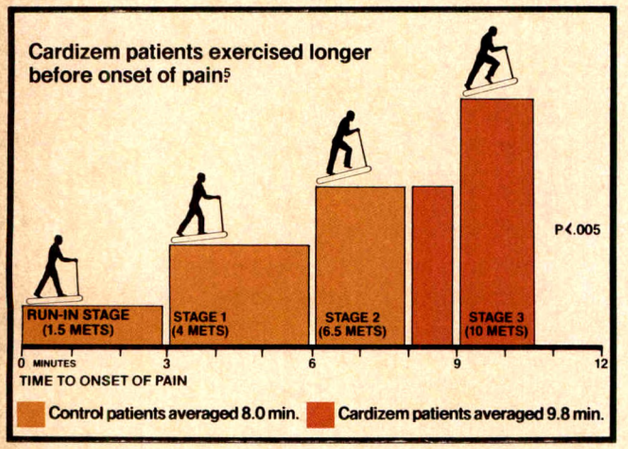

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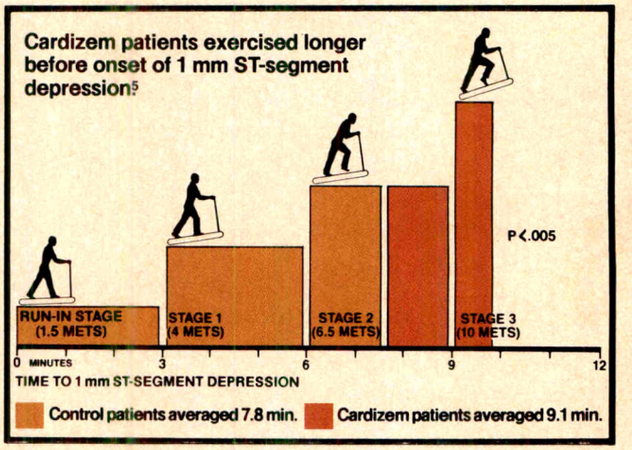
1. Rosenthal SJ, Ginsburg R, Lamb IH, et al: Efficacy of diltiazem for control of symptoms of coronary arterial spasm. *Am J Cardiol* 46:1027-1032, 1980.
2. Low RI, Takeda P, Lee G, et al: Effects of diltiazem-induced calcium blockade upon exercise capacity in effort angina due to chronic coronary artery disease. *Am Heart J* 101:713-718, 1981.
3. Wagner JM, Anderson JL, Bray BE, et al: Comparative effects of diltiazem, propranolol and placebo using exercise radionuclide ventriculography. Presented at American Heart Association meeting, Dallas, TX, Nov 1982. Abstracted, *Circulation* 66:11-22, 1982.
4. Hossack KF, Bruce RA, Ritterman JB, et al: Divergent effects of diltiazem in patients with exertional angina. *Am J Cardiol* 49:538-546, 1982.


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# EXCELLENT CLINICAL RESPONSE TO CARDIZEM™ (diltiazem HCl) IN THE MANAGEMENT OF CLASSIC EFFORT ANGINA

CARDIZEM™ (diltiazem HCl) allows angina patients to significantly prolong exercise tolerance, even in demanding Bruce protocol exercise tests[5] (n=15)*




## Protocol:

A Bruce protocol with a run-in stage was used. Each stage lasts three minutes.

Succeeding stages represent such an increase in speed and slant of the treadmill that each minute spent in a succeeding stage represents a highly significant increase in metabolic equivalents (METS). For example, METS expenditure in run-in stage of the protocol (0 to 3 min) is 1.5. METS expenditure of stage 1 (3 to 6 min) is 4.0. Stage 2 (6 to 9 min) expenditure is 6.5, and stage 3 (9 to 12 min) is 10.

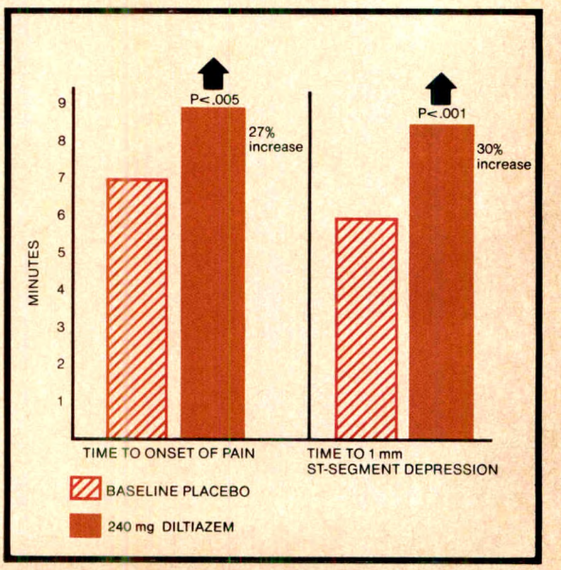
The study[5,6] was double-blind, randomized, triple cross-over comparing diltiazem with placebo, lasting 7 weeks.


5. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78(July suppl): 234-238, 1980.
6. Hossack KF, Pool PE, Steele P, et al: Efficacy of diltiazem in angina on effort: A multicenter trial. *Am J Cardiol* 49:567-572, 1982.


*This study is a report from one center in a multicenter study.

## CARDIZEM™ (diltiazem HCl) produced marked angina improvement in multicenter study[6]

- 27% increase in time to onset of pain
- 30% increase in time to ST-segment depression




**RESULTS OF 57 PATIENTS EVALUATED IN A MULTICENTER STUDY[6]**

# CARDIZEM™ (diltiazem HCl) PRODUCED SIGNIFICANT DECREASE IN EFFORT ANGINA ATTACKS COMPARED WITH PLACEBO IN 63-PATIENT DIARY STUDY[7]

Cardizem therapy resulted in a mean reduction of 5.3 attacks per week during weeks 7 and 8, compared with a mean reduction with placebo of 2.0 attacks per week.

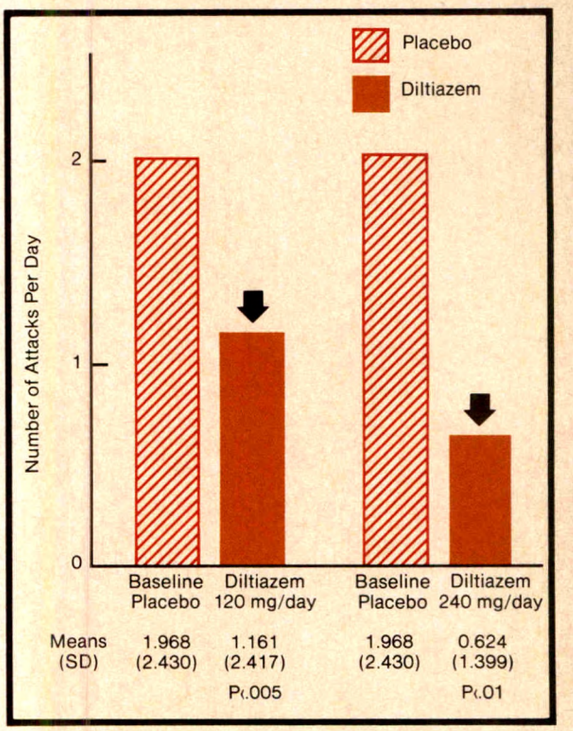
During weeks 9 and 10, Cardizem therapy resulted in a mean reduction of approximately 5.9 attacks per week compared with a mean reduction of 2.5 attacks per week with placebo.

## 41% TO 68% REDUCTION IN FREQUENCY OF PRINZMETAL'S VARIANT ANGINA ATTACKS WITH CARDIZEM™ (diltiazem HCl)[8]

Mean attack rate during 120-mg/day dosage period was reduced 41% from baseline period. In 240-mg/day phase, decrease with Cardizem was 68%. This shows a positive dose-related response.

**75% reduction in attack rate reported in 13-patient, cross-over, placebo-controlled study[1]**

**71% reduction in attack rate reported in 11-patient, cross-over, placebo-controlled study[9]**





7. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. *Am J Cardiol* 49:560-566, 1982.
8. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.
9. Pepine CJ, Feldman RL, Whittle J, et al: Effect of diltiazem in patients with variant angina: A randomized double-blind trial. *Am Heart J* 101:719-725, 1981.


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Those adverse reactions reported most frequently with CARDIZEM™ (diltiazem HCl) have been:

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- Swelling/edema . . . . . 2.4%
- Arrhythmia . . . . . 2.0%
- Headache . . . . . 2.0%
- Rash . . . . . 1.8%
- Fatigue . . . . . 1.1%

In many cases, the relationship to Cardizem has not been established.

Other reactions infrequently reported (<1.0%) during supervised trials were:

- Cardiovascular: Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart
- Central Nervous System: Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations
- Gastrointestinal: Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis
- Dermatologic: Pruritus, petechiae, urticaria
- Other: Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain

Of those adverse reactions reported, the most severe were:
A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of Cardizem.

Experience in 959 patients taking oral doses of Cardizem resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

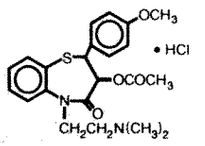
In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during Cardizem therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

# PROFESSIONAL USE INFORMATION

**cardizem™**
**(diltiazem HCl)**
30 mg and 60 mg tablets

## DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:




Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

## CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

**Mechanism of Action.** Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

**Hemodynamic and Electrophysiologic Effects.** Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

**Pharmacokinetics and Metabolism.** Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

## INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous chronic stable angina presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

## CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

## WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to drug is uncertain.

## PRECAUTIONS

**General.** CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

**Drug Interaction.** Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

**Carcinogenesis, Mutagenesis, Impairment of Fertility.** A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

**Pregnancy.** Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers.** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

**Pediatric Use.** Safety and effectiveness in children have not been established.

## ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

| | |
|---|---|
| Cardiovascular: | Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart. |
| Central Nervous System: | Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations. |
| Gastrointestinal: | Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis. |
| Dermatologic: | Pruritus, petechiae, urticaria. |
| Other: | Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain. |

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

## OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

| | |
|---|---|
| Bradycardia | Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. |
| High-Degree AV Block | Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing. |
| Cardiac Failure | Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics. |
| Hypotension | Vasopressors (eg, dopamine or levarterenol bitartrate). |

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral $LD_{50}$'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous $LD_{50}$'s in these species were 60 and 38 mg/kg, respectively. The oral $LD_{50}$ in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

## DOSAGE AND ADMINISTRATION

**Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm.** Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

**Concomitant Use With Other Antianginal Agents.**

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy** – CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

## HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

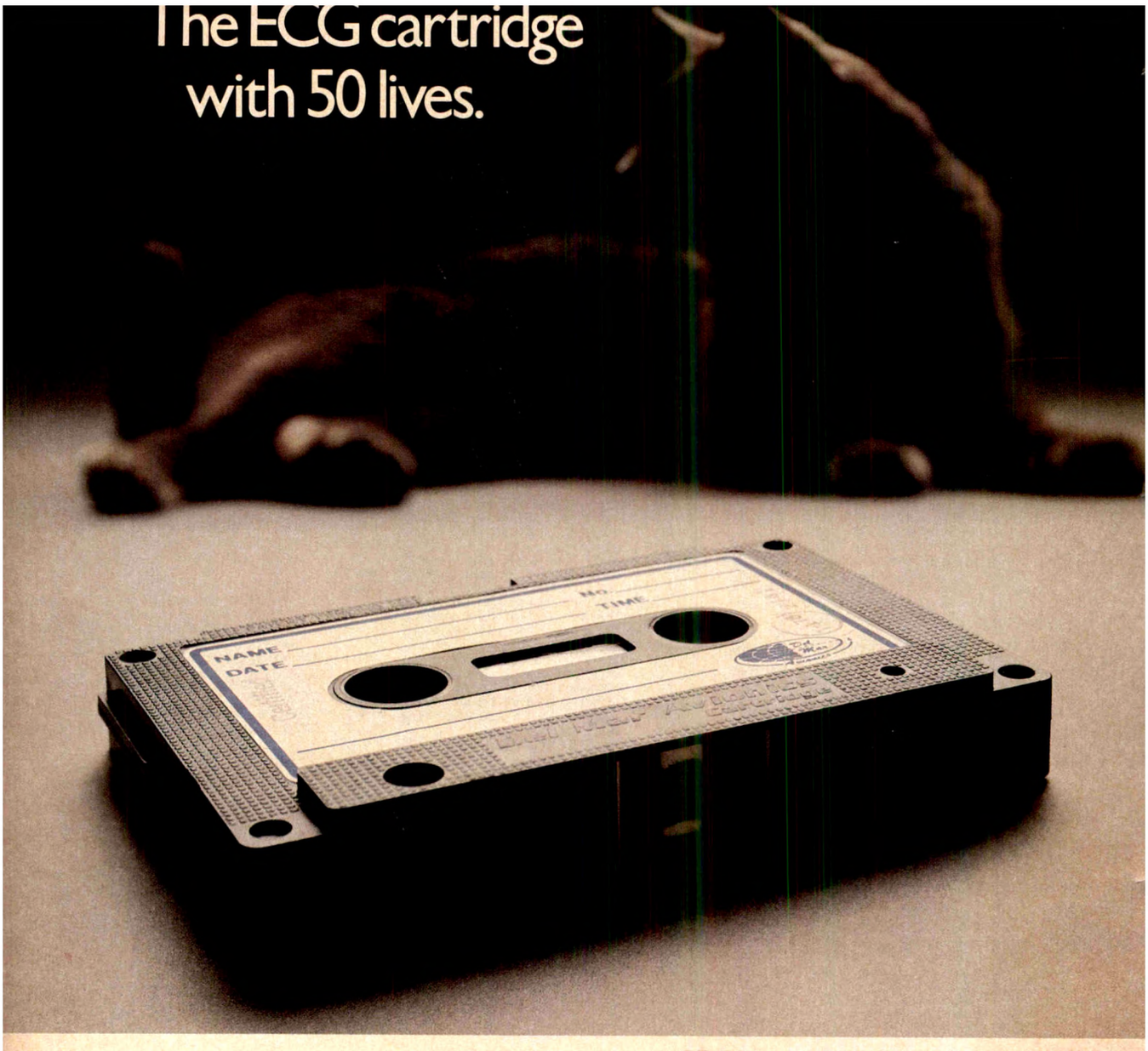
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*Test data available upon request.
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# Frequency in Nonangioplasty Patients of Morphologic Findings Reported in Coronary Arteries Treated With Transluminal Angioplasty

JEFFREY M. ISNER, MD and ROBERTA V. FORTIN, BS

**The coronary arteries from 70 consecutive patients in whom percutaneous transluminal angioplasty (PTA) had *not* been performed during life were examined at necropsy for findings that have been previously described in patients or animals treated with PTA. In 33 (49%) of the 70 patients, 1 or more findings identical to those observed in necropsy studies of PTA-treated arteries were observed: "plaque fractures" in 31 (44%), "dissection clefts" in 26 (33%), and extensive medial thinning in 40 (57%). Observations in these 70 patients indicate that findings previously described in PTA-treated patients cannot necessarily be assumed to represent the results of PTA. The fact that improved vessel patency may be seen in the absence as well as the presence of such lesions precludes firm assurance that such lesions are the sole basis for successful angioplasty.**

Despite the fact that percutaneous transluminal angioplasty (PTA) has now been used successfully to treat peripheral, renal, and coronary arterial stenoses in thousands of patients, the mechanism by which PTA improves vascular patency remains an enigma. Dotter and Judkins[1] in their original description of the procedure as well as Grüntzig,[2] 12 years later, attributed the mechanism of PTA to redistribution and compression of the atheromatous intima. Subsequent investigators carried out a variety of pathologic studies to define the mechanism by which PTA improves vascular patency.[3–10] Most studies employed either human cadaver specimens subjected to PTA postmortem[3,5,8,9] or animals in which lesions had been experimentally induced[4,10]; few were performed in humans who had undergone PTA antemortem.[6,7] Most of these studies did not include comparison of the PTA-treated vessel with control, that is, non-PTA–treated, vessels. Accordingly, this study determines the frequency with which morphologic findings ascribed to PTA are present in histologic sections of coronary arteries excised at necropsy from patients who never were treated with PTA.

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## Methods

The major extramural coronary arteries were excised intact from the hearts of 70 consecutive patients who had died and undergone necropsy examination. None had been treated with PTA. The coronary arteries were prepared for histologic examination as described elsewhere.[11] Briefly, each coronary artery was decalcified in a solution of 10% formic acid and formalin (Decalcifier I, Surgipath) if necessary, fixed overnight in 10% buffered formalin, and then cut transversely into 5 mm long segments. Representative segments were then dehydrated in graded alcohols, cleared with xylene, impregnated with and then embedded in paraffin, and finally cut into 4 $\mu$m thick sections. Sections stained with Verhoeff's elastic tissue stain as well as sections stained with hematoxylin and eosin were prepared from each 5 mm segment. Histologic sections prepared from the coronary arteries of each patient were reviewed by light microscopy for morphologic changes described previously in patients or animals treated with PTA.

## Results

**Plaque fractures:** Vertical or serpentine cracks in the atherosclerotic plaque, extending from the lumen into the plaque, have been interpreted as "fractures" resulting from PTA.[4,6,7,9,10] Plaque cracks extending from the lumen for variable lengths into the plaque and at times associated with an apparent secondary dissection cleft were observed in 31 (44%) of the 70 non-PTA–treated patients. Examples of these plaque cracks are illustrated in Figures 1 and 3a.

**Dissection clefts:** Apparent clefts within the atherosclerotic plaque or media, as well as cleft-like sepa-

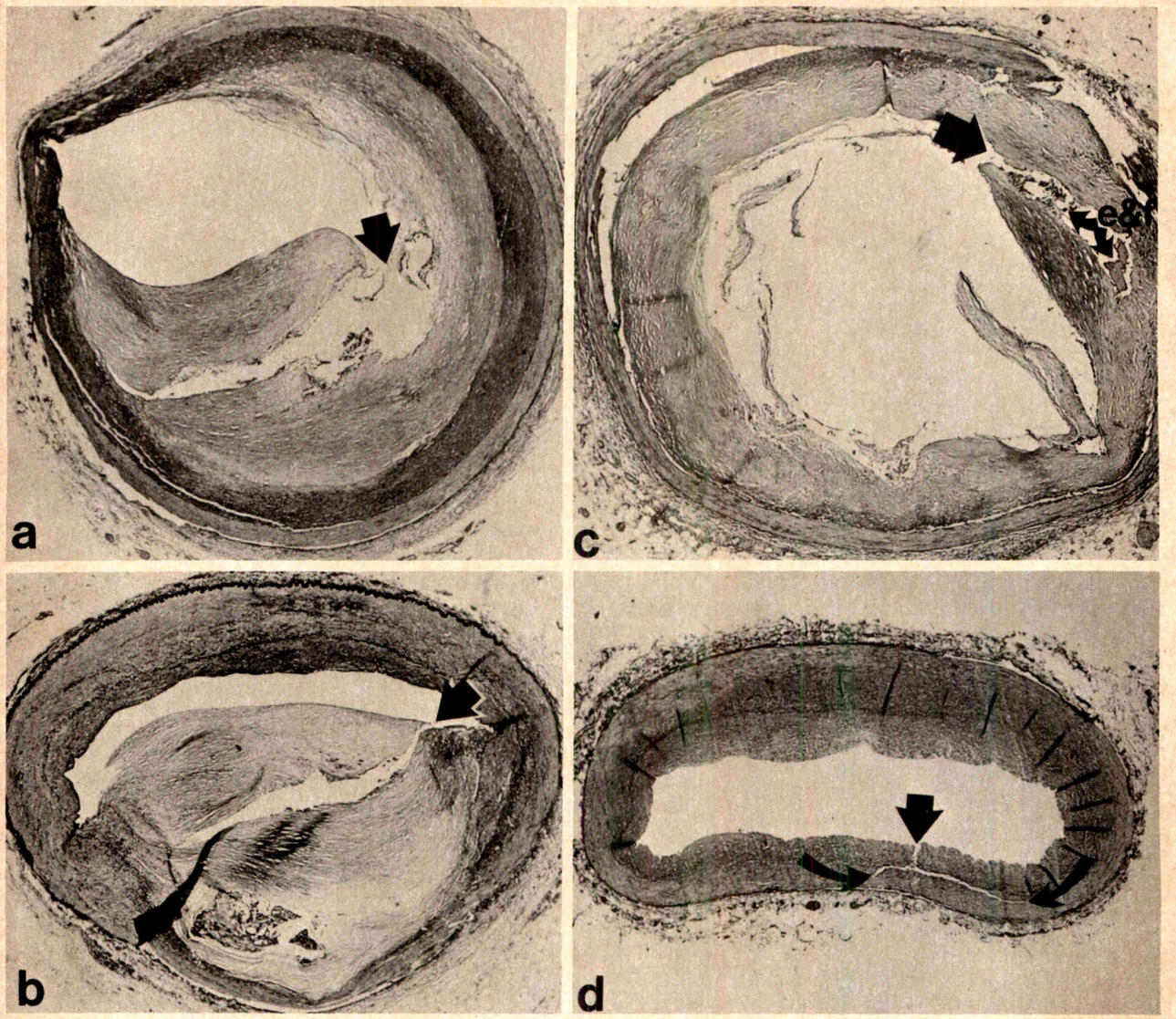



**FIGURE 1.** Photomicrographs of representative histologic sections of coronary arteries from nonangioplasty patients illustrating findings (**arrows**) similar to what have been called plaque fractures in angioplasty patients. In **d,** the vertical plaque fracture is continuous with a dissection cleft at the intima-media junction. In **c,** erythrocytes and fibrin (**e & f**) are present within the "fracture." (Elastic-tissue stain; all magnification ×5, reduced 6%).

rations at the junction of plaque and media were observed in sections from 26 (37%) of the patients in the present series. In 9 (13%) patients, these clefts were confined to the plaque itself, in 7 (10%) such clefts were limited to the media of the vessel, and in 10 (14%) the clefts involved the junction of plaque and media. Representative examples of such clefts are illustrated in Figures 1c and d, and 2.

**Stretching, thinning, or focal disruption of the media:** "Focal interruptions" or an absolute diminution in the smooth muscle content of tunica media component of the coronary arterial wall, or both, were observed in 40 (57%) of 70 control patients. In some patients near-obliteration of the media was seen in association with extensive atherosclerosis. These pathologic findings involving the media are illustrated in Figure 3.

## Discussion

That PTA is an effective means of improving vascular patency is no longer a matter for debate. Persistent amelioration of signs and symptoms of peripheral arterial insufficiency,[12] renal arterial stenosis,[13] and coronary arterial narrowing[14] have now been well documented. That PTA can be performed with low morbidity and mortality rates is attested to by the paucity of reported necropsy studies of patients treated with PTA. Partially as a result of such limited necropsy data, certainty regarding the efficacy of PTA has not been paralleled by an equal degree of certainty regarding the mechanism by which PTA reduces arterial narrowing.

Excepting 4 patients who died shortly after PTA and were studied at necropsy,[6,7] studies of the acute mor-

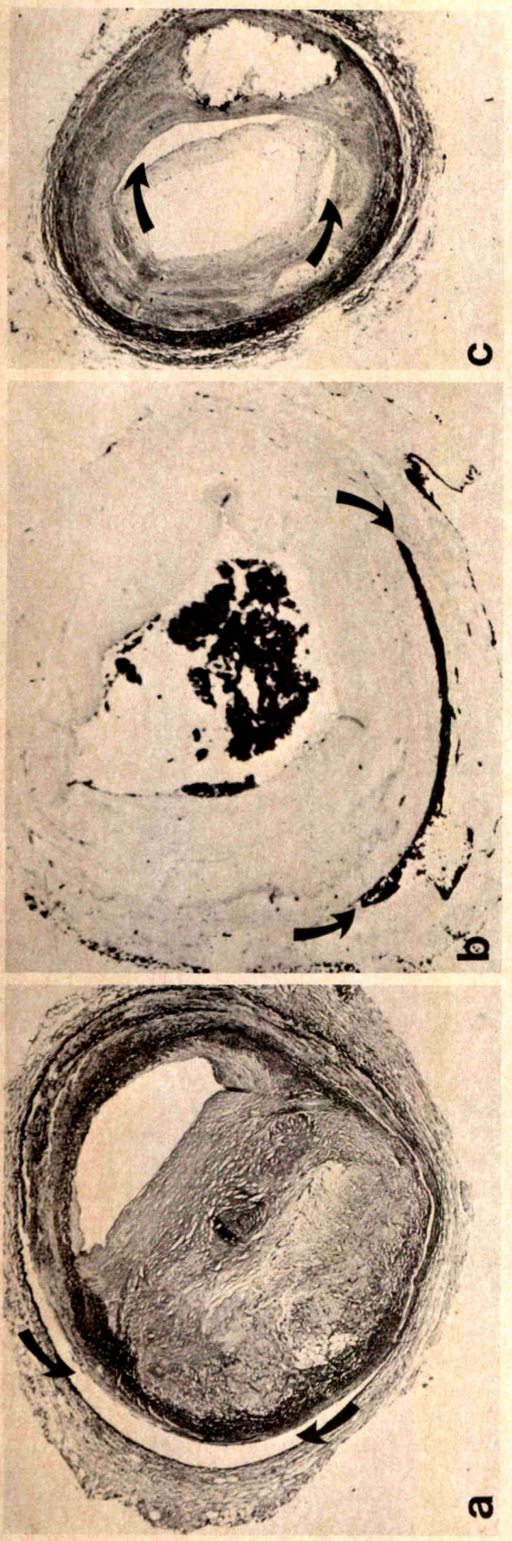



**FIGURE 2.** Photomicrographs of representative histologic sections of coronary arteries from nonangioplasty patients illustrating findings (**arrows**) similar to what have been called dissection clefts in angioplasty patients. **a,** cleft separates media from adventitia; **b,** barium sulfate injectate from a postmortem arteriogram within the cleft at the plaque-media junction; **c,** clefts are within plaque. (**a, c,** elastic-tissue stain; **b,** hematoxylin and eosin; all magnification X5, reduced 21%.)

phologic consequences of PTA have been limited to the effects of PTA on (1) the coronary arteries of cadaver hearts, and (2) artificially induced atherosclerotic lesions in the aorta and peripheral arteries of experimental animals. Major liabilities inherent in each of these methods have been acknowledged by the investigators themselves. The coronary arteries of cadaver specimens, for example, are "... more susceptible to damage than vessels in vivo ..." as a result of dehydration and the absence of normal luminal pressure distension; as a result, "... dilation catheters may ... [cause] dissection if forced through fixed stenotic segments."[4]

The use of experimental animal models has been limited by the nature of the atherosclerotic lesion in such models. The 2% cholesterol diet used to induce lesions in the aorta and peripheral arteries of the rabbit, for example, generally results in a lesion composed almost entirely of lipid-laden foam cells[4,10]; this is in marked contrast to the complicated atherosclerotic plaque seen in human coronary arteries that is composed primarily of collagen with a relatively small lipid content.[15] The morphologic changes induced by angioplasty of a foam-cell lesion cannot necessarily be extrapolated to the predominantly fibrous lesion of humans.[4]

Furthermore, there is a striking lack of unanimity among the findings reported by previous investigators. Although Castaneda-Zuniga[5] and Baughman[8] reported finding plaque fractures in segments of cadaver coronary arteries treated with PTA, Lee et al,[3] using the same model, found no plaque fractures among 21 lesions similarly treated. In a study of the rabbit diet-induced foam cell plaque treated with PTA, Block et al[4] found a dissection cleft in 1 and a plaque fracture in 2 segments of dilated iliac artery; 8 of 10 aortic stenoses that were successfully dilated, however, contained neither fractures nor clefts. Faxon et al[10] observed plaque fractures in 3 of 3 and dissection clefts in 1 of 3 successfully dilated rabbit peripheral arterial *foam cell* lesions; however, among 9 successfully dilated *complicated plaques* (analogous to human atherosclerotic lesions) induced by an indwelling catheter with or without dietary cholesterol supplementation, no plaque fractures and only 1 dissection cleft were observed. On occasion, an acute inflammatory response has been described in association with plaque fracture,[10] and in 2 reports of a dilated iliac artery, erythrocytes and fibrin were demonstrated within the plaque crack[6,9] (see Fig. 1c). Most reports,[4,5,7,8,10] however, have described a lone vertical or curvilinear split such as was found in sections from the present group of non-PTA control patients (Fig. 1a, b, and d).

In addition to the variability in findings reported from 1 laboratory to another, plaque fractures, dissection clefts, and medial thinning have not been consistently observed in all successfully dilated segments from an individual laboratory. Freudenberg[9] found plaque fractures and dissection clefts in some cadaver coronary arteries treated with PTA, but neither fractures nor clefts were observed in 6 of 17 and 12 of 17 dilated arteries, respectively. Likewise, Faxon[10] found dissection

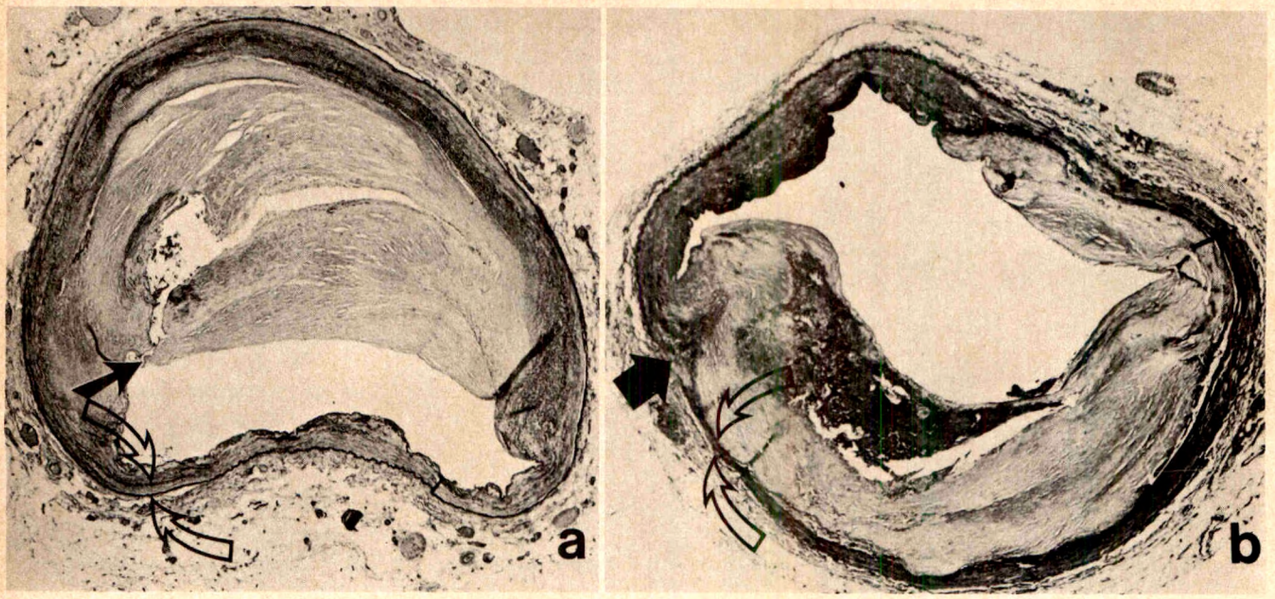



**FIGURE 3.** Photomicrographs of representative histologic sections of coronary arteries from nonangioplasty patients illustrating medial thinning (**a, b**) and interruption of the medial layer (**arrow** in **b**) of the coronary arterial wall. The media is defined as that portion of the coronary arterial wall between the internal and external elastic membranes (**white arrows**). (Elastic-tissue stain; magnification ×5, reduced 7%.)

clefts in only 2 of 12 successfully dilated rabbit arteries.

That findings similar to those described in PTA-treated patients were observed in the present group of non-PTA–treated control patients suggests that these findings cannot necessarily be invoked to explain the mechanism by which PTA improves vascular patency. Plaque fractures and dissection clefts observed in the present group of patients are most likely the result of artifact related to preparation of the coronary arteries for histologic examination. Dissection clefts may be seen in sections of coronary arteries prepared from mummies frozen 1,600 years before the advent of PTA.[16] Spurious dissection clefts also may be produced by postmortem injection of radiographic contrast media, particularly in a vessel with a high-grade proximal stenosis (Fig. 2b). On the other hand, the *lack* of a supporting medium (for example, postmortem injectate of barium sulfate) in the lumen of the coronary artery may result in artifactual fracture of the luminal surface of the atherosclerotic plaque when the artery is sectioned, particularly if the artery is sectioned before fixation. The extent of arterial calcific deposits also influences the likelihood of creating artifact in the preparation of coronary arteries for histologic examination. Although decalcification of coronary arteries is routine in most laboratories, including our own, incomplete decalcification may result in brittle arteries which tend to crack or develop circumferential dissociation of the layers of the arterial wall when the arteries are cut.[15] Interestingly, Baughman et al[8] found that the incidence of "intimal or medial disruption" in dilated cadaver coronary arteries was increased in those arteries that contained calcium compared with those that did not. Whether the morphologic changes in the calcified vessels were the result of PTA or the result of preparation, including cutting, for histologic examination remains speculative.



**FIGURE 4.** Photomicrograph of a section of the renal artery at the site of antemortem angioplasty. The histologic features of the atherosclerotic plaque and arterial wall are unremarkable. (Elastic-tissue stain; magnification ×5, reduced 13%.)

While the plaque fractures and dissection clefts seen in the present group of patients appear for the most part to represent artifactual findings, medial thinning (or medial disruption or medial interruption) is a finding *typical* of complicated atherosclerotic arterial segments.[11] The more extensive the plaque, that is, the greater the degree of cross-sectional area narrowing, the greater is the likelihood of the plaque eroding partially

or entirely through the media. Displacement of medial smooth muscle is a finding so frequently observed in non-PTA-treated coronary arteries that no special interpretation should be attached to its presence in PTA-treated segments.

As mentioned above, most previously published studies include a variable number of successfully dilated arterial segments in which no remarkable findings were observed on histologic examination. In fact, such a benign picture is common in patients who have died and been studied at necropsy late after angioplasty (Fig. 4).[17,18] The explanation for the paucity of remarkable findings in such patients has been that remodeling and healing have obliterated the unique pathologic features. This theory, however, is at odds with the observation that serial angiographic studies of patients treated with PTA tend to demonstrate *improvement* in vascular patency from the angiogram done initially postangioplasty to that performed several months later. If pathologic changes such as plaque fractures and dissection clefts are to be considered the basis for improved vascular patency after angioplasty, then it is difficult to resolve the paradox of late improvement in the angiographic appearance of the dilated vessel at a time when pathologic changes alleged to be responsible for the improvement are no longer observed.

The absence of unique pathologic findings in many PTA-treated animals and humans studied postmortem implies that successful arterial dilatation may occur by alternative mechanisms, such as transluminal dilatation of the vessel wall or the "compression" theory originally advanced by Dotter and Judkins[1] and later by Grüntzig.[2] Admittedly, the observations made in the present study do not provide direct evidence for either the dilatation or compression theories. Since neither compression nor dilatation (each of which implies a *serial* change) are phenomena that can be witnessed on a single histologic slide, other methodologies must be utilized to confirm or reject these theories. The compression and transmural dilatation theories, however, are attractive because each is compatible with the absence of unique histologic features. In this regard, each takes into account both (1) findings in the present study which suggest that pathologic findings previously described as unique consequences of PTA may be observed in the coronary arteries of patients who have not been treated with PTA, and (2) previous animal and human studies in which such unique pathologic features have not been observed despite successful dilatation.[3,10] The recent observation by Block et al[19] that the postangioplasty arterial effluent in the rabbit model contains no embolic debris might, in fact, be interpreted as evidence favoring either the transmural dilatation or compression theories. Plaque fractures, for example, would be more likely to result in release of plaque debris than would either plaque compression or transmural dilatation.

Finally, the fact that lesions resembling plaque fractures and dissection clefts have been observed to occur as the result of artifact does not exclude the possibility that such lesions may develop as a result of PTA. The fact that improved vessel patency may be seen in the absence as well as the presence of such lesions, however, precludes firm assurance that such lesions are the sole basis for a successful dilatation.

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## References

1. **Dotter CT, Judkins MP.** Transluminal treatment of atherosclerotic obstruction: description of new technic and a preliminary report of its application. Circulation 1964;30:654–670.
2. **Grüntzig AR.** Transluminal dilatation of coronary artery stenosis (letter). Lancet 1978;1:263.
3. **Lee G, Idea RM, Joye JA, Bogren HG, De Maria AN, Mason DT.** Evaluation of transluminal angioplasty of chronic coronary artery stenosis. Circulation 1980;61:77–83.
4. **Block PC, Baughman KL, Pasternak RC, Fallon JT.** Transluminal angioplasty: correlation of morphologic and angiographic findings in an experimental model. Circulation 1980;61:778–785.
5. **Castaneda-Zuniga WR, Formarek A, Todavarthy M, Vlodaver Z, Edwards J, Zolliker C, Amplatz K.** The mechanism of balloon angioplasty. Radiology 1980;135:565–571.
6. **Hoffman MA, Fallon JT, Greenfield AJ, Waltman AC, Athanasoulis CA, Block PC.** Arterial pathology after percutaneous transluminal angioplasty. Am J Radiol 1981;137:147–149.
7. **Block PC, Myler RK, Stertzer S, Fallon JT.** Morphology after transluminal angioplasty in human beings. N Engl J Med 1981;305:382–385.
8. **Baughman KL, Pasternak RC, Fallon JT, Block PC.** Transluminal coronary angioplasty of postmortem human hearts. Am J Cardiol 1981;48:1044–1047.
9. **Freudenberg H, Lichten PR, Engel HJ.** Transluminal angioplasty of the coronary arteries—an analysis of the most important complications by a post-mortal study in the human heart. Z Kardiol 1981;27:39–44.
10. **Faxon DP, Weber VJ, Haudenschild C, Gottsman SB, McGovern WA, Ryan TJ.** Acute effects of transluminal angioplasty in three experimental models of atherosclerosis. Arteriosclerosis 1982;2:125–133.
11. **Isner JM, Wu M, Virmani R, Jones AA, Roberts WC.** Comparison of degrees of coronary arterial luminal narrowing determined by visual inspection of histologic sections under magnification among three independent observers and comparison to that obtained by video planimetry. An analysis of 559 five-millimeter segments of 61 coronary arteries from eleven patients. Lab Invest 1980;42:566–570.
12. **Grüntzig AR.** Die perkutane transluminale Rekanalisation chronischer Arterien verschlusse mit einer neuen Dilatations technik. Baden-Baden: G. Witzstrock Verlag, 1977:50.
13. **Millan VG, Mast WE, Madias NE.** Nonsurgical treatment of severe hypertension due to renal-artery intimal fibroplasia by percutaneous transluminal angioplasty. N Engl J Med 1979;300:1371–1373.
14. **Kent KM, Bentivoglio LG, Block PC, Cowley MJ, Borros G, Gosselin AJ, Grüntzig AJ, Myler RK, Simpson J, Stertzer SH, Williams DO, Fisher L, Gillespie MJ, Detre K, Kelsey S, Mullin SM, Mock MB.** Percutaneous transluminal coronary angioplasty: report from the registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1981;49:2011–2020.
15. **Roberts WC.** The pathology of acute myocardial infarction. Hosp Pract 1971;6:89–104.
16. **Zimmerman MR, Smith GS.** A probable case of accidental inhumation of 1,600 years ago. Bull NY Acad Med 1975;51:828–837.
17. **Grüntzig AR, Senning A, Sigenthaler WE.** Nonoperative dilatation of coronary-artery stenosis. Percutaneous transluminal angioplasty. N Engl J Med 1979;301:61–68.
18. **Detre K.** PTCA operations memos Nos. 21, 22, 47. Cardiac Disease Branch, Division of Heart and Vascular Disease, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.
19. **Block PC, Elmer D, Fallon JT.** Release of atherosclerotic debris after transluminal angioplasty. Circulation 1982;65:950–952.

# Intravenous Nitroglycerin for the Treatment of Angina at Rest Unresponsive to Standard Nitrate Therapy

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**Thirty-five patients who had angina at rest that was unresponsive to standard therapy comprised of oral or topical nitrates and beta-blocking drugs were treated with a continuous infusion of intravenous nitroglycerin (IVNTG). The infusion was started at 10 μg/min and increased by 10 μg/min increments every 5 minutes until an infusion rate of 50 μg/min was reached. After each episode of rest angina, the infusion was increased by 50 μg/min in the same stepwise manner. Data from a 24-hour baseline control period were compared with those from a 24-hour IVNTG endpoint period at which time the highest IVNTG infusion rate was administered. The average IVNTG infusion rate was 140 ± 15 μg/min. With IVNTG therapy, the number of episodes of angina at rest decreased from 3.5 ± 0.4 to 0.3 ± 0.1, sublingual nitroglycerin use decreased from 1.9 ± 0.3 to 0.4 ± 0.1 mg/day, and morphine sulfate administration decreased from 5.5 ± 1.3 to 0.4 ± 0.2 mg/day (all $p < 0.001$). When each patient's response on the endpoint day was analyzed, 25 were defined as complete (no rest angina), 8 as partial (>50% decrease in the number of episodes/day from control values), and 2 as nonresponders. No significant drug-induced adverse effects occurred.**

**IVNTG appears to be effective therapy for angina at rest refractory to standard oral and topical medications.**

Intravenous nitroglycerin (IVNTG) was recently approved by the Food and Drug Administration for treatment of angina pectoris; however, insufficient information is available concerning effective infusion rates, response rates, and complications. This study was designed to answer 2 questions about IVNTG therapy: Is it effective in controlling angina at rest in patients who have failed to respond to standard medical therapy? If it is, what is the range of effective infusion rates?

Angina at rest requires urgent therapy whether it is the first sign of ischemic heart disease, follows stable exertional angina, or occurs after an acute myocardial infarction.[1–4] Standard medical therapy with bed rest, oxygen, sedation, beta-adrenergic blocking agents, and oral or topical nitrates is effective in controlling angina at rest in most patients.[5] The role of beta-adrenergic blocking agents in the therapy of this condition is widely accepted,[5] but certain aspects remain controversial.[6] When angina at rest recurs despite standard medical therapy, calcium antagonists, intraaortic balloon counterpulsation, and emergency coronary artery bypass surgery have been advocated.[2,7–10]

Nitrates have been used for many years to treat myocardial ischemia because of their ability to decrease myocardial oxygen consumption and increase coronary artery blood flow.[11,12] Nitrates are available in sublingual, topical, oral, and intravenous preparations. IVNTG offers several possible advantages over other forms because of its ease of administration, rapid titration, and 100% bioavailability. Several reports suggest that IVNTG is effective in treating myocardial ischemia.[13–16]

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## Methods

**Patient selection:** Patients with angina at rest unresponsive to standard medical therapy were entered into the protocol for IVNTG administration. Angina at rest was defined by the presence of typical chest pain associated with either reversible electrocardiographic changes (S-T elevation or depression ≥1 mm or symmetrical T-wave inversion in any

2 leads), or transient defects in a thallium myocardial scan obtained during pain. Standard medical therapy included bed rest in a coronary care unit with continuous cardiac rhythm monitoring, oxygen therapy, sedation, and at least 1 of the following nitrate regimens which are the usual doses recommended in the *Physicians' Desk Reference*[17]: (1) nitroglycerin ointment, 2 inches every 4 hours; (2) isosorbide dinitrate, 30 mg orally every 6 hours; (3) isosorbide dinitrate, 10 mg sublingually every 2 hours. The use of beta-adrenergic blocking agents was left to the discretion of the patient's attending physicians. In each instance, IVNTG was started only after angina at rest continued to occur despite progressively increasing topical and oral nitrate doses that exceeded maximal recommended doses. Twenty-four of the 35 patients had ≥3 episodes of angina at rest during the 24-hour period before initiation of IVNTG.

**Study design:** IVNTG supplied by American Critical Care Corporation was diluted with 5% dextrose in water to a concentration of 300 μg/ml. It was infused through polyvinyl chloride intravenous tubing; the infusion rate was controlled by an IMED volumetric infusion pump. The infusion was started at a rate of 10 μg/min; if no adverse effects occurred, it was increased every 5 minutes at 10 μg/min increments until an infusion rate of 50 μg/min was reached. This dose level was maintained until another episode of angina at rest occurred, at which time the infusion rate was increased in the same stepwise manner until a dose of 100 μg/min was achieved. Thus, after each anginal attack, the dose was increased by 50 μg/min. By titrating to therapeutic effect, each patient's highest infusion rate either represented the minimal effective therapeutic dose or the highest infusion rate received before IVNTG was considered a therapeutic failure. A therapeutic failure was identified by the need for the initiation of alternative antianginal therapy such as calcium-channel blocking agents, intraaortic balloon counterpulsation, and/or emergency coronary artery bypass surgery. During the study, no changes were made in the antianginal therapy other than modifications of the IVNTG infusion rates. Specifically, no changes were allowed in the dose of beta-blocking agents or oral or topical nitrates. Episodes of angina at rest were treated with sublingual nitroglycerin and, if unresponsive, with intravenous morphine sulfate. No fixed protocol was followed for discontinuing IVNTG. During the study the following information was collected daily: (1) number of episodes of angina at rest, (2) amount of morphine sulfate and sublingual nitroglycerin administered, (3) adverse effects of IVNTG, and (4) lowest blood pressure and highest and lowest pulse rates recorded at times other than during an ischemic episode.

**Data analysis:** Analysis was performed by comparing the 24-hour period immediately preceding the initiation of IVNTG—the baseline control period—with each subsequent 24-hour period during IVNTG administration. A 24-hour endpoint period was defined as the period during which the highest IVNTG infusion rate was given. This rate was either the minimal effective dose or the highest dose of IVNTG given before it was considered a therapeutic failure. The average number of episodes of rest angina, amount of sublingual nitroglycerin, and amount of intravenous morphine sulfate were compared for the baseline control period, each subsequent 24-hour period, and the endpoint period using a Student's *t* test of the difference. The incidence of rest angina was also compared for each day using analysis of variance. All numbers are reported as an average ± standard error of the mean.

In addition to analyzing the average response of the group, the response of each patient was considered in comparison with the control period. A complete response was defined as no episodes of rest angina occurring on the day under analysis; a partial response as >50% decrease in the number of episodes compared with the control period, and a nonresponse ≤50% decrease in anginal attacks compared with the control period.

## Results

**Patient population:** Fifty-three patients over an 18-month period met the inclusion criteria and began receiving IVNTG. Eighteen of these patients had changes in their antianginal therapy dictated by factors other than failure to control myocardial ischemia: In 8 patients propranolol dose was decreased because of bradycardia or congestive heart failure, whereas in 10 the nitrate or propranolol doses, or both, were changed simultaneously with the initiation of IVNTG. These 18 patients did not differ from the remaining 35 with regard to inclusion data, adverse effects, or outcome (myocardial infarction, death, intraaortic balloon counterpulsation, and/or coronary artery bypass grafting). However, because it was impossible to assess the relative contribution of the addition of IVNTG and the changes in other antianginal therapy on the improvement of rest angina, these patients were excluded from further analysis.

The remaining 35 patients included 22 men and 13 women with an average age of 63 years (range 36 to 81). Twenty of the 35 had recurrent angina at rest 1 to 7 days after an acute myocardial infarction. Comparison of the results for the 20 patients with postinfarction angina and the remaining 15 patients with unstable angina showed no significant difference in the groups. Therefore, all further data combine the results from these 2 subsets.

Twenty-two patients had had a previous myocardial infarction at least 2 weeks before beginning IVNTG therapy. Twenty-one of the 35 patients subsequently underwent cardiac catheterization; all had coronary artery disease. Four had single-vessel disease; 6 had 2-vessel and 11 had 3-vessel disease. Of the 35 patients, 34 had either a previous myocardial infarction or angiography-proven coronary artery disease.

The nitrate doses given to the study patients before starting the IVNTG were much higher than the minimum required by the protocol. Thirty-four patients were receiving nitroglycerin ointment in an average amount of 18 ± 0.8 inches/day, 27 patients were receiving oral isosorbide dinitrate at an average dose of 229 ± 31 mg/day, and 26 patients were receiving both forms of nitrates. Seventeen patients were receiving propranolol in an average dose of 202 ± 28 mg/day.

**IVNTG administration:** The average endpoint dose of IVNTG was 140 ± 15 μg/min (range 50 to 350), with an average length of infusion of 5.6 ± 0.8 days (range 2 to 25). The lowest mean arterial pressure and highest pulse rate did not change significantly from the baseline control day to the endpoint day. The average mean arterial pressure changed from 79 ± 9 to 77 ± 10 mm Hg ($p = 0.19$) and the heart rate from 84 ± 3 to 86 ± 3 beats/min ($p = 0.42$). In order to exclude the effect of beta blockade, the data on the 18 patients not receiving propranolol were analyzed separately and demonstrated no significant changes in heart rate or blood pressure.

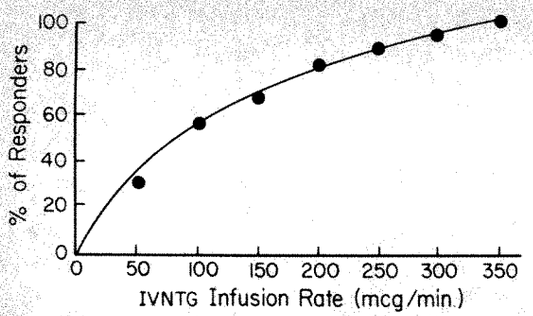



**FIGURE 1.** Percentage of complete or partial responders for each infusion rate of IVNTG, showing the IVNTG dose on the endpoint day for the 33 patients who had a >50% decrease in anginal episodes on the endpoint day compared with the control day.

**TABLE I Clinical Response to IVNTG: Control Day Versus Endpoint Day***

| | Control Day | Endpoint Day |
|---|---|---|
| Episodes of rest angina | 3.5 ± 0.4 | 0.3 ± 0.1† |
| Sublingual nitroglycerin (mg/day) | 1.9 ± 0.3 | 0.4 ± 0.1† |
| Morphine sulfate (mg/day) | 5.5 ± 1.3 | 0.4 ± 0.2† |

* Mean ± standard error of the mean.
† $p < 0.001$ for comparison of control and endpoint days.

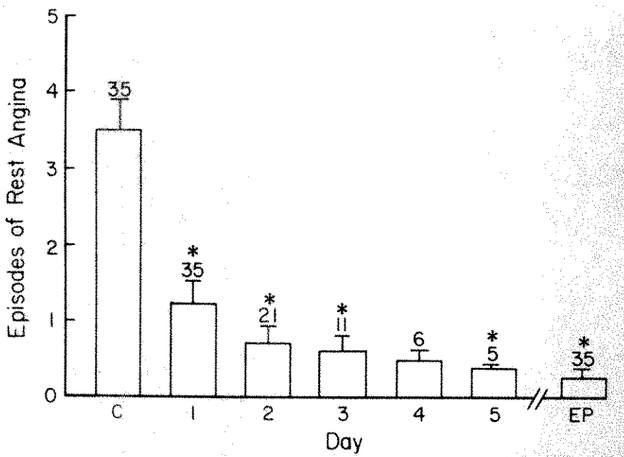



**FIGURE 2.** Number of episodes of rest angina for baseline control day (C) and each day with IVNTG up to the endpoint day (EP). The average number of episodes of rest angina for the control day and each day of IVNTG is shown. Patients were removed from this analysis after reaching their endpoint day because at that time they either had no further rest angina or were considered a therapeutic failure and started receiving an alternate form of therapy. The **numbers above the bars** represent the number of patients left for analysis on each day. **Asterisks** indicate $p < 0.05$ compared with control day.

No association was demonstrated between the maximal dose of IVNTG and age, sex, weight, extent of coronary artery disease, history of previous myocardial infarction, previous administration of beta-blocking agents, or number of episodes of rest angina on the control day. Figure 1 shows the percentage of complete or partial responders with each infusion rate of IVNTG. Of the patients who responded to IVNTG, over half were controlled at an infusion rate of ≤100 μg/min and over two thirds at ≤200 μg/min.

**Clinical response:** The number of episodes of rest angina, amount of sublingual nitroglycerin, and amount of morphine sulfate were significantly decreased when the control and endpoint periods were compared (Table I). Episodes of rest angina decreased from 3.5 ± 0.4 to 0.3 ± 0.1/day ($p < 0.001$), sublingual nitroglycerin use decreased from 1.9 ± 0.3 to 0.4 ± 0.1 mg/day ($p < 0.001$), and morphine sulfate administration decreased from 5.5 ± 1.3 to 0.4 ± 0.2 mg/day ($p < 0.001$).

To show that this benefit is not an artifact that results from arbitrarily selecting a particular day and labeling it the therapeutic endpoint, a day-by-day analysis was done of the average number of episodes of rest angina. Patients were removed from this analysis after reaching their endpoint day because at this time they either had no further rest angina or were considered a therapeutic failure and an alternate form of therapy was begun (Fig. 2). The number of episodes of rest angina clearly decreased for each time period in comparison with the control day. When each patient's response on the endpoint day was analyzed, 25 were complete responders, 8 were partial responders, and 2 were nonresponders.

The average number of days from the start of IVNTG to attaining the maximal dose was 2.7 ± 0.6. Fourteen patients received their maximal IVNTG dose on the first day, 10 on the second, and 5 on the third day of nitroglycerin administration.

No correlation was found between therapeutic response (assessed by degree of reduction in pain from the control day to the endpoint day) and age, sex, extent of coronary artery disease, initial mean arterial pressure or change in mean arterial pressure during therapy. In addition there was no significant difference in the therapeutic response of patients with and without recent or remote myocardial infarction, or those who were or were not receiving propranolol.

**Adverse effects:** An adverse effect was defined as an event that prompted a decrease in the rate or discontinuation of the IVNTG infusion. Fifteen patients had a headache which either required no treatment or responded to standard analgesics. In 1 patient, severe headache necessitated a decrease in the IVNTG dose. In no instance was an adjustment of the infusion rate dictated by the development of hypotension, bradycardia, or tachycardia.

**Outcome:** Of the 35 patients, 23 were eventually weaned from IVNTG: 14 without a change in their standard medical therapy compared with the control period, 5 with an increase in nitrates, 2 with an increase in propranolol, and 2 with an increase in both nitrates and propranolol.

Two patients receiving IVNTG because of recurrent rest angina after a recent myocardial infarction had extension of their infarct, developed cardiogenic shock, and died. Ten patients continued receiving IVNTG until coronary artery bypass was performed; they received IVNTG for an average of 8 days. Three of these had a recent myocardial infarction and were operated

on an average of 13 days after their infarction. There were 2 perioperative deaths: 1 in a patient with combined coronary and carotid artery revascularization who suffered a cerebrovascular accident, and another after a combined coronary artery bypass and insertion of an aortic valve prosthesis that was complicated by cardiogenic shock.

## Discussion

Several previous reports suggest that intravenous nitrates are effective in treating refractory angina pectoris.[13–16] Dauwe[13] reported on 14 patients with unstable rest angina refractory to conventional medical therapy. All 14 patients had a decrease in the incidence of chest pain during treatment with an average of 47 μg/min of IVNTG. Distante[14] used intravenous isosorbide dinitrate in a double-blind crossover trial of 12 patients with myocardial ischemia at rest. They had a significant decrease in the number of episodes of ischemia between the placebo and treatment periods. Mikolich[15] reported retrospective results in 75 patients with chest pain treated with IVNTG. Pain relief was obtained in 40 of 45 patients with unstable angina and 22 of 30 patients with chest pain after myocardial infarction. They did not describe the concurrent medical therapy their patients were receiving or whether that therapy remained constant during the IVNTG infusion. This study also differed from ours in using a much lower mean maximal infusion rate (54 μg/min) of a nonindustrially prepared solution of IVNTG. In a review article on IVNTG, Hill[16] states that he administered IVNTG to 20 patients with unstable angina refractory to maximal therapy and that all patients responded; however, no details are provided.

Nitrates may be effective in treating myocardial ischemia because they decrease myocardial oxygen consumption and increase myocardial blood flow.[11] Their primary pharmacologic action is the relaxation of vascular smooth muscle, having greater effect on venous than arterial vessels. By dilating peripheral veins and increasing venous capacitance, venous return to the heart is decreased. This reduction in preload results in decreased left ventricular wall tension and myocardial oxygen consumption.[18–20] Nitrates act as vasodilators on native and collateral coronary arteries[21–23]; however, it is uncertain whether the blood flow to ischemic myocardial tissue is actually increased.[24–26] Because angina at rest has been shown to be secondary to transient decreases in myocardial blood flow,[27–29] it is possible that IVNTG acts in this situation to combat coronary artery spasm.[20]

We have shown that the use of IVNTG is associated with the suppression of angina at rest in patients who have failed to respond to standard medical therapy; however, it is well-known that unstable angina has a tendency to spontaneous remission. The only way to address this problem would have been to use a double-blind, placebo-controlled crossover format, but we felt that the clinical status of our patients was too tenuous to include a placebo phase. Nevertheless, we believe that the results demonstrate a therapeutic effect for 2 reasons. First, patients were not aware of the infusion rate they were receiving, yet there was a correlation between the IVNTG dose and the clinical response. Second, there were 3 instances of recurrence of rest angina during temporary accidental interruption of the IVNTG infusion that the patients were not aware of. After the infusion was reinstituted, angina did not recur.

Another limitation of the study is that IVNTG was infused through polyvinyl chloride tubing. It is known that nitroglycerin is adsorbed by this type of tubing and, therefore, the exact amount reaching the patient is unknown. When using polyvinyl chloride tubing, the concentration of IVNTG reaching the patient also depends on variables such as length of intravenous tubing, infusion flow rate, duration of infusion, and initial concentration of the solution.[30] When IVNTG is infused through polyethylene tubing—which is now commercially available—insignificant amounts are lost. The doses used in this study were administered using polyvinyl chloride tubing and cannot be applied when a more efficient delivery system is used. Unfortunately, the polyethylene system was not available when this study was initiated.

The mechanism whereby the addition of IVNTG was successful in controlling rest angina that had not responded to high doses of oral and topical nitrates is not entirely clear. One would expect that the response would be dependent on total nitrate levels regardless of the method of administration, and it appears that similar levels are obtained with topical and intravenous nitroglycerin.[31] Unfortunately, we were not able to measure nitrate blood levels so we cannot correlate the nitrate concentration with therapeutic response. The superior results with IVNTG could be due to the stability of nitrate blood levels which avoids the fluctuations seen with standard therapy. Alternatively, the ability to more rapidly attain a new level could account for the improved efficacy.

Although IVNTG is a known arterial vasodilator, its use in our patients was not associated with a significant hypotensive effect. This may be due to the fact that our patients were already receiving large amounts of nitrates before IVNTG was initiated. It is also possible that by decreasing afterload, cardiac output was increased sufficiently to maintain blood pressure.

We have shown that IVNTG can be given safely without hemodynamic monitoring and that infusion rates of 50 to 350 μg/min are effective in controlling myocardial ischemia previously unresponsive to oral and topical nitrates.

## References


1. **Neill WA, Wharton TP, Fluri-Lundeen J, Cohen IS.** Acute coronary insufficiency-coronary occlusion after intermittent ischemic attacks. N Engl J Med 1980;302:1157–1162.
2. **Conti CR, Curry RC, Christie LG, Mehta J, Pepine CJ.** Initial medical and surgical management of unstable angina pectoris. Clin Cardiol 1979;2:311–316.
3. **Schuster EH, Bulkley BH.** Early post-infarction angina. Ischemia at a distance and ischemia in the infarct zone. N Engl J Med 1981;305:1101–1105.
4. **Singer DE, Mulley AG, Thibault GE, Barnett GO.** Unexpected readmissions to the coronary-care unit during recovery from acute myocardial infarction. N Engl J Med 1981;304:625–629.
5. **Cohn PF, Braunwald E.** Chronic coronary artery disease. In: Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia:

WB Saunders, 1980:1387–1436.
6. **Hillis LD, Braunwald E.** Coronary artery spasm. N Engl J Med 1978;299: 695–702.
7. **Stone PH, Antman EM, Muller JE, Braunwald E.** Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II: Hemodynamic effects and clinical applications. Ann Intern Med 1980;93:886–904.
8. **Gold HK, Leinbach RC, Buckley MJ, Mundth ED, Daggett WM, Austen WG.** Refractory angina pectoris: follow-up after intraaortic balloon pumping and surgery. Circulation 1976;54:Suppl III:III-41–III-46.
9. **Golding LAR, Loop FD, Sheldon WC, Taylor PC, Groves LK, Cosgrove DM.** Emergency revascularization for unstable angina. Circulation 1978;58: 1163–1166.
10. **Weintraub RM, Aroesty JM, Paulin S, Levine FH, Markis JE, LaRaia PJ, Cohen SI, Kurland GF.** Medically refractory unstable angina pectoris. I. Long-term follow-up of patients undergoing intraaortic balloon counterpulsation and operation. Am J Cardiol 1979;43:877–882.
11. **Brown BG, Bolson E, Petersen RB, Pierce CD, Dodge HT.** The mechanisms of nitoglycerin action: stenosis vasodilatation as a major component of the drug response. Circulation 1981;64:1089–1097.
12. **Opie LH.** Nitrates. Lancet 1980;1:750–753.
13. **Dauwe F, Affaki G, Waters DD, Theroux P, Mizgala HF.** Intravenous nitroglycerin in refractory unstable angina (abstr). Am J Cardiol 1979;43: 416.
14. **Distante A, Maseri A, Serveri S, Biagini A, Chierchia S.** Management of vasospastic angina at rest with continuous infusion of isosorbide dinitrate. A double crossover study in a coronary care unit. Am J Cardiol 1979;44: 533–539.
15. **Mikolich JR, Nicoloff NB, Robinson PH, Logue RB.** Relief of refractory angina with continuous intravenous infusion of nitroglycerin. Chest 1980; 77:375–379.
16. **Hill NS, Antman EM, Green LH, Alpert JS.** Intravenous nitroglycerin. A review of pharmacology, indications, therapeutic effects and complications. Chest 1981;79:69–76.
17. 1981 Physicians' Desk Reference. 35th ed. Oradell, NJ: Medical Economics, 1981:947,979,1107,1761,1893.
18. **Strauer BE, Scherpe A.** Ventricular function and coronary hemodynamics after intravenous nitroglycerin in coronary artery disease. Am Heart J 1978;95:210–219.
19. **Armstrong PW, Walker DC, Burton JR, Parker JO.** Vasodilatory therapy in acute myocardial infarction. A comparison of sodium nitroprusside and nitroglycerin. Circulation 1975;52:1118–1122.
20. **Loeb HS.** Intravenous nitroglycerin. Chest 1980;77:374–375.
21. **Feldman RL, Pepine CJ, Curry RC, Conti CR.** Coronary arterial responses to graded doses of nitroglycerin. Am J Cardiol 1979;43:91–96.
22. **Jugdutt BI, Becker LC, Hutchins GM, Bulkley BH, Reid PR, Kallman CH.** Effect of intravenous nitroglycerin on collateral blood flow and infarct size in the conscious dog. Circulation 1981;63:17–28.
23. **Capurro N, Kent KM, Epstein SE.** Effects of intracoronary and intravenous nitroglycerin on coronary collateral function. J Pharmacol Exp Ther 1976;199:262–268.
24. **Fukuyama T, Roberts R.** The effect of intravenous nitroglycerin on coronary blood flow and infarct size during myocardial infarction in conscious dogs. Clin Cardiol 1980;3:317–323.
25. **Forman R, Kirk ES, Downey JM, Sonnenblick EH.** Nitroglycerin and heterogeneity of myocardial blood flow. J Clin Invest 1973;52:905–911.
26. **Most AS, Williams DO, Millard RW.** Acute coronary occlusion in the pig: effect of nitroglycerin on regional myocardial blood flow. Am J Cardiol 1978;42:947–953.
27. **Maseri A, Severi S, De Nes M, L'Abbate A, Chierchia S, Marzilli M, Ballestra AM, Parodi O, Biagini A, Distante A.** "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia. Am J Cardiol 1978;42:1019–1035.
28. **Figueras J, Singh BN, Ganz W, Charuzi Y, Swan HJC.** Mechanism of rest and nocturnal angina: observations during continuous hemodynamic and electrocardiographic monitoring. Circulation 1979;59:955–968.
29. **Feldman RL, Pepine CJ, Whittle JL, Curry RC, Conti CR.** Coronary hemodynamic findings during spontaneous angina in patients with variant angina. Circulation 1981;64:76–82.
30. **Baaske DM, Amann AH, Wagenknecht DM, Mooers M, Carter JE, Hoyt HJ, Stoll RG.** Nitroglycerin compatibility with intravenous fluid filters, containers, and administration sets. Am J Hosp Pharm 1980;37:201–205.
31. **Wei JY, Reid PR.** Quantitative determination of trinitroglycerin in human plasma. Circulation 1979;59:588–592.

# Effects of Verapamil on Coronary Hemodynamic Function And Vasomobility Relative to Its Mechanism Of Antianginal Action

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**The effect of intravenous verapamil on systemic and coronary hemodynamic function was studied at cardiac catheterization in 12 patients with coronary artery disease. Verapamil was administered as a 2-minute bolus (0.145 mg/kg) followed by an infusion (0.005 mg/kg/min). Cardiac output and coronary sinus blood flow were measured by thermodilution techniques. Caliber of the large coronary arteries and of diseased segments was determined from the coronary angiogram using a computer-assisted method. Verapamil reduced mean arterial pressure 14% ($p < 0.001$), systemic vascular resistance 21% ($p < 0.01$), and stroke work index 16% ($p < 0.001$). Coronary vascular resistance decreased 24% ($p < 0.01$) with a small increase in coronary sinus blood flow (+13%, difference not significant [NS]). Myocardial oxygen consumption determined in 5 patients showed no significant change with verapamil. Luminal area in 39 coronary lesions was measured in the "normal" portion of the diseased segment and at its maximal constriction, and an estimate of flow resistance in the stenosis was computed. Overall, 50% of "normal" and of diseased coronary segments dilated significantly with verapamil. Stenosis dilation resulted in an average 14% reduction ($p < 0.01$) in estimated flow resistance. In 8 patients, the luminal changes ($n = 27$) induced by sublingual nitroglycerin were compared with those induced by verapamil. Nitroglycerin induced a significantly greater increase in coronary caliber in both normal and diseased segments; estimated stenosis flow resistance decreased 28% with nitroglycerin compared with 14% with verapamil ($p < 0.01$).**

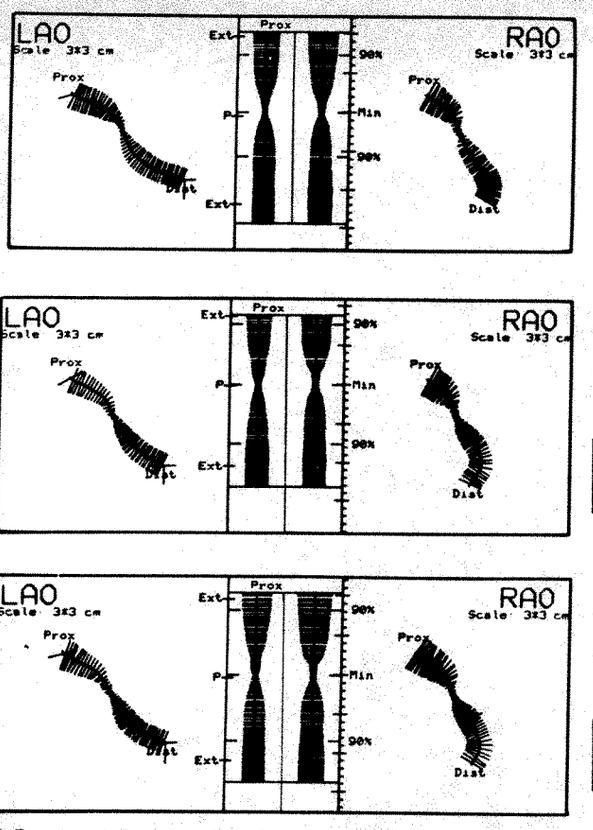
**Thus, verapamil moderately dilates the systemic and coronary small vessel resistance bed without apparently increasing myocardial metabolic demand. Furthermore, verapamil mildly dilates large coronary conductance vessels in both "normal" and diseased segments, although significantly less than does nitroglycerin.**

Slow-channel inhibitors are being used increasingly in the management of various myocardial ischemic syndromes.[1–3] In contrast to beta-adrenergic antagonists, these compounds have been shown experimentally to dilate coronary arteries,[4,5] and thus their antianginal effects are of potential value in exertional as well as in vasospastic ischemic syndromes. However, relatively little data are available on coronary hemodynamic function and vasomobility in patients with coronary artery disease. From gross angiographic appearances, Mignault[6] concluded that intravenously administered verapamil did not alter the caliber of normal and atherosclerotic coronary vessels, whereas Luebs et al,[7] using myocardial clearance of rubidium as an index of coronary blood flow, found that intravenous verapamil increased coronary blood flow in patients without coronary artery disease whereas no such effect was observed in patients with coronary artery disease. More recently, however, Simonsen[8] found that intravenous verapamil produced a small but significant reduction in coronary vascular resistance in patients with coronary heart disease.

The purpose of our study, therefore, was to determine the effects of intravenously administered verapamil, a prototype of the slow-channel inhibitors, on systemic

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| | NORMAL AREA ($mm^2$) | MINIMUM DIAMETER (mm) | MINIMUM AREA ($mm^2$) | FLOW RESISTANCE (mmHg/$cm^2$/sec) |
|---|---|---|---|---|
| **CONTROL** | | | | |
| ABSOLUTE | 8.7 | 0.69 | 0.42 | 25.8 |
| % STENOSIS | | 76% | 93% | |
| **VERAPAMIL** | | | | |
| ABSOLUTE | 8.9 | 0.77 | 0.47 | 19.9 |
| % STENOSIS | | 74% | 93% | |
| CHANGE WITH VERAPAMIL | 0.2 (2%) | 0.08 (12%) | 0.05 (12%) | -5.9 (23%) |
| **NTG** | | | | |
| ABSOLUTE | 10.3 | 0.80 | 0.51 | 17.5 |
| % STENOSIS | | 74% | 93% | |
| CHANGE WITH NTG | 1.6 (18%) | 0.11 (16%) | 0.09 (21%) | -8.3 (32%) |

**FIGURE 1.** Representative computer printout of segmental stenosis images and dimensional data from a 76% stenosing lesion of the left anterior descending artery before and after verapamil and after nitroglycerin (NTG). Note that in the doses used, nitroglycerin is a much more potent dilator of normal and narrowed segments of the coronary artery.

and coronary hemodynamic functions and on coronary artery caliber with particular reference to changes in large vessel cross-sectional area and stenosis flow resistance as measured by quantitative coronary angiography.

## Methods

Twelve male patients undergoing diagnostic cardiac catheterization for the evaluation of coronary artery disease were studied. The mean age of the group was 53 years (range 48 to 69). Two had 1-vessel coronary disease, 7 had 2-vessel disease, and 3 had 3-vessel disease. Their ventricular ejection fractions ranged from 22 to 70 (mean 50.5). All patients and the design of the protocol were reviewed and approved by the Human Subjects Committee of the Wadsworth Veterans Administration Hospital. All patients had sinus rhythm with no evidence of atrioventricular heart block. Patients who were receiving a chronic beta-adrenoreceptor blocking drug were studied 48 hours after its discontinuation. All chronic nitrate therapy was discontinued 10 to 12 hours before angiography.

**Hemodynamic measurements:** Systemic hemodynamic measurements were obtained through percutaneous cannulation of both femoral artery and vein. Right heart pressures and cardiac output were obtained with a triple lumen thermodilution catheter connected to an output computer (Santa Barbara model 1700). In 9 patients, a 7Fr catheter (Wilton Webster Laboratories, Altadena, California) was placed in the mid-coronary sinus through the left basilic vein, and coronary sinus blood flow (CSBF) was measured by the method of Ganz et al.[9] Repeated contrast injection was used to document the positional stability of the coronary sinus catheter. Heart rate was monitored in lead II of the electrocardiogram.

Systemic vascular resistance (SVR) (dynes s $cm^{-5}$) was calculated as SVR = MAP/Co, where MAP = mean arterial pressure. Stroke work index (SWI in g-m/$m^2$) was calculated as SWI = (MAP − PCWP) × SVI × 1.36 × $10^{-3}$, where PCWP = pulmonary capillary wedge pressure in mm Hg and SVI = stroke volume index in ml/$m^2$. Coronary vascular resistance (CVR) was calculated as the ratio of MAP to CSBF (CVR = MAP/CSBF). Myocardial oxygen consumption ($MVO_2$) was determined in 5 patients as the product of CSBF and arterial-coronary venous oxygen difference: $MVO_2$ = CSBF × (AO − Cs) $O_2$.

**Quantitative coronary angiographic analysis:** Computer-assisted analysis of coronary arterial segments was performed by a technique recently described[10,11] and validated in several laboratories.[12–14] The method is briefly described here.

High-quality coronary cineangiograms were obtained in the conventional fashion using the Judkins technique in multiple projections. For each left anterior oblique (LAO) projection, a corresponding perpendicular right anterior oblique (RAO) projection was obtained. For quantitative analysis, cineangiographic frames were selected from the perpendicular pair of projections that showed the lesion most clearly. Three frames were selected, usually in diastole, from each of the 2 views. The frames were projected at about 5-fold magnification onto a large surface marked off in X,Y coordinates. The outline of the magnified, projected lesion image was traced from the "normal" proximal to the "normal" distal portion

of the diseased arterial segment. The scaling factor was calculated from a traced section of the catheter tip of known dimensions. The traced images were digitized and transmitted to a PDP 11/45 computer which was programmed to reduce the lesion image to true scale by compensating for pincushion distortion, x-ray beam divergence, and magnification. An example of a computer printout of a typical processed lesion is shown in Figure 1. The true scale images from the 2 perpendicular views are then matched along their center lines and the combination of data from the perpendicular projections provides a 3-dimensional characterization of the diseased coronary arterial segment. From these data the computer calculates the vessel diameter and cross-sectional area in the "normal" proximal and distal portion and at the point of the greatest narrowing of the diseased segment. Percent diameter and area stenosis were calculated according to the formula described by Brown et al[10] and estimates of stenosis flow resistance at a hypothetical flow of 1.0 ml/s are calculated using published formulas.[11] This method is accurate to within 0.08 mm for measurements of known dimensions and has a variability of 0.1 mm (standard deviation) on repeated estimates for minimal luminal diameter and ±3% for percent stenosis estimates.[11–13] The angiographic sequence was carefully concealed from those making the lesion measurements using a blinding protocol described elsewhere.[15]

**Protocol:** The sequence of data acquisition was as follows: 10 minutes were allowed to elapse after diagnostic left ventriculography and coronary angiography. Control hemodynamic and coronary sinus blood flow measurements were then obtained over a 3-minute period. Verapamil hydrochloride (0.145 mg/kg) was given intravenously as a loading dose over 2 minutes and a constant infusion (0.005 mg/kg/min) begun at the end of the loading period and continued for approximately 20 minutes. Hemodynamic variables were recorded continuously for the first 5 minutes, after which steady state conditions were achieved. A further measurement of these variables was made at the 10th minute after which a second coronary angiographic study with identical projections as the control study was performed. At least 15 minutes after discontinuation of the verapamil infusion, with return of the hemodynamic variables to within 10% of the initial control values, 0.4 mg of sublingual nitroglycerin was administered in 8 patients while aortic pressure and heart rate were monitored. Coronary angiograms were repeated in the selected views approximately 30 seconds after the aortic systolic pressure nadir (within 4 to 5 minutes after nitroglycerin administration).

**Statistical analysis:** Observations made before and after verapamil and nitroglycerin administration were compared for significance or differences using 2-tailed Student's *t* test for paired data. Differences were considered not significant if the probability of the null hypothesis was >0.05. The data are presented as mean values ±1 standard deviation.

## Results

**Verapamil dose:** For the entire series of patients studied, the mean total dose of verapamil was 19 ± 4 mg and the duration of infusion averaged 20 ± 5 minutes. We previously showed that the regimen of verapamil administration used in this study produced steady-state plasma drug levels with stable hemodynamic variables by the fifth minute of drug administration which was maintained during drug infusion.[16]

**Systemic and coronary hemodynamics:** Mean hemodynamic data for all patients are presented in Table I. Verapamil decreased mean arterial pressure 14% ($p < 0.001$), systemic vascular resistance 21% ($p < 0.01$), and coronary vascular resistance 24% ($p < 0.01$). There was a significant increase of 5 mm Hg (31%; $p < 0.001$) in the value of mean pulmonary capillary wedge pressure and mean pulmonary arterial pressure of 4 mm Hg (+17%; $p < 0.01$), but the changes in heart rate, cardiac index, stroke volume index, or pulmonary vascular resistance were not significant. Verapamil *increased* coronary sinus blood flow from 96 ± 32 to 108 ± 35 ml/min, but this change did not reach statistical significance. In 5 patients, $MVO_2$ remained unchanged by verapamil despite significant reduction in the heart rate × systolic blood pressure product. In these 5 patients, mean values for coronary vascular resistance and coronary sinus flow did not differ significantly from those of the other patients in whom $MVO_2$ could not be determined for technical reasons.

**Effects of verapamil on coronary caliber:** A total of 39 coronary arterial segments with various degrees of luminal obstruction of the left anterior descending or circumflex coronary arteries were analyzed by quantitative coronary angiography. This method allows for accurate quantitation of very small changes in coronary caliber which are not usually appreciated by subjective visual interpretation.

The effects of verapamil on coronary caliber and predicted stenosis flow resistance are summarized in Figures 2 and 3. Each point on the plot in each figure represents the value from a single lesion. In "normal"

**TABLE I Effects of Intravenous Verapamil on Systemic and Coronary Hemodynamics (Mean Values ± 1 Standard Deviation)**

| | n | Before Verapamil | After Verapamil | p Value |
|---|---|---|---|---|
| Heart rate (beats/min) | 12 | 74 ± 11 | 76 ± 12 | NS |
| Systolic arterial pressure (mm Hg) | 12 | 128 ± 11 | 107 ± 14 | 0.001 (−16%) |
| Diastolic arterial pressure (mm Hg) | 12 | 75 ± 7 | 65 ± 10 | 0.001 (−13%) |
| Mean arterial pressure (mm Hg) | 12 | 96 ± 10 | 83 ± 9 | 0.001 (−14%) |
| Mean pulmonary arterial pressure (mm Hg) | 12 | 24 ± 7 | 28 ± 8 | 0.01 (+17%) |
| Mean pulmonary capillary wedge pressure (mm Hg) | 12 | 16 ± 7 | 21 ± 8 | 0.001 (+31%) |
| Systemic vascular resistance (dynes s $cm^{-5}$) | 12 | 1,176 ± 180 | 928 ± 108 | 0.01 (−21%) |
| Pulmonary vascular resistance (dynes s $cm^{-5}$) | 12 | 127 ± 43 | 116 ± 42 | NS |
| Stroke work index (g-m/$m^2$) | 12 | 44 ± 13 | 37 ± 14 | 0.001 (−16%) |
| Coronary vascular resistance (mm Hg/ml/min) | 9 | 1.1 ± 0.31 | 0.84 ± 0.29 | 0.01 (−24%) |
| Myocardial oxygen consumption (ml/min) | 5 | 8.4 ± 1.4 | 8.4 ± 0.29 | NS |
| Cardiac index (liters/min/$m^2$) | 12 | 3.0 ± 0.47 | 3.2 ± 0.47 | NS |
| Stroke volume index (ml/$m^2$) | 12 | 39 ± 7 | 41 ± 11 | NS |
| Coronary sinus flow (ml/min) | 9 | 96 ± 32 | 108 ± 35 | NS (n = 9) |

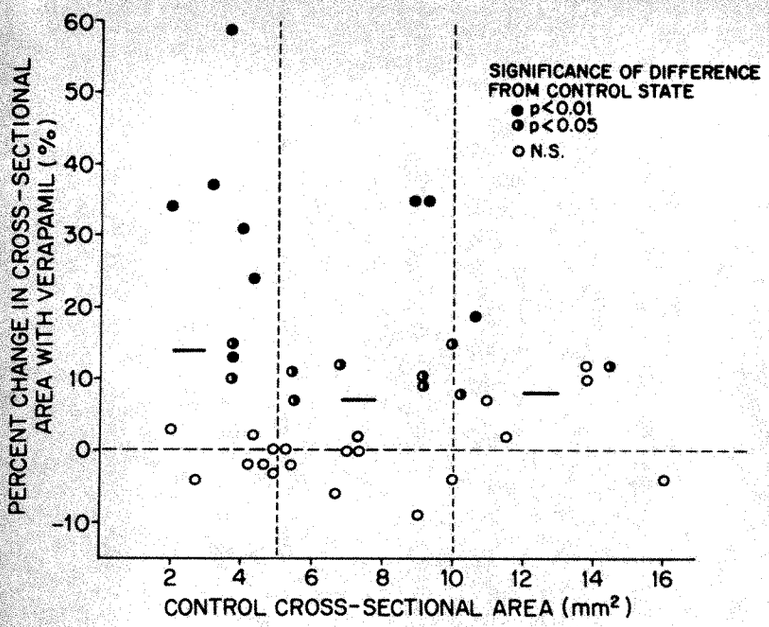



**FIGURE 2.** Individual changes in cross-sectional area in "normal" coronary segments after intravenous verapamil. Each point represents data from a single lesion and is averaged from 6 estimates of coronary calibers. Partly or totally "closed" circles show a statistically significant change by the paired *t* test of the 6 estimates in each of the pre- and postverapamil angiographic images. The overall data indicate the vasodilatory propensity of verapamil at the site of coronary stenosis.

areas, verapamil increased cross-sectional area in 19 of 39 lesions (49%) analyzed (Fig. 2). Smaller vessels (<5 $mm^2$ cross-sectional area) tended to be more vasoreactive with a mean increase of 14% compared with medium-sized vessels (5 to 10 $mm^2$) and larger vessels (> 10 $mm^2$) which dilated by a mean of 7 and 8%, respectively. However, this difference between small and medium to large arteries did not attain statistical significance. In stenosed segments, verapamil induced a comparable increase in cross-sectional area in both "mild" and significant (>50% diameter stenosis) lesions with a resultant decrease in estimated stenosis flow resistance (Fig. 3). However, not all stenosed lesions dilated with verapamil. Nineteen of 38 lesions (50%) showed no significant change in caliber in the diseased segment.

**Comparative effects of verapamil and nitroglycerin on coronary vasomobility:** In 27 diseased segments (average 38% stenosis, range 8 to 82%) in 8 patients, changes in coronary caliber after verapamil and after sublingual nitroglycerin were compared directly. The mean data are summarized in Figures 4 and 5. In "normal" segments, verapamil and nitroglycerin increased cross-sectional area by 7 and 22%, respectively ($p < 0.01$), whereas in the stenosed areas the changes were 13 and 28% ($p < 0.01$), respectively. Nitroglycerin decreased stenosis flow resistance 28%, twice that induced by verapamil (14%, $p < 0.01$).

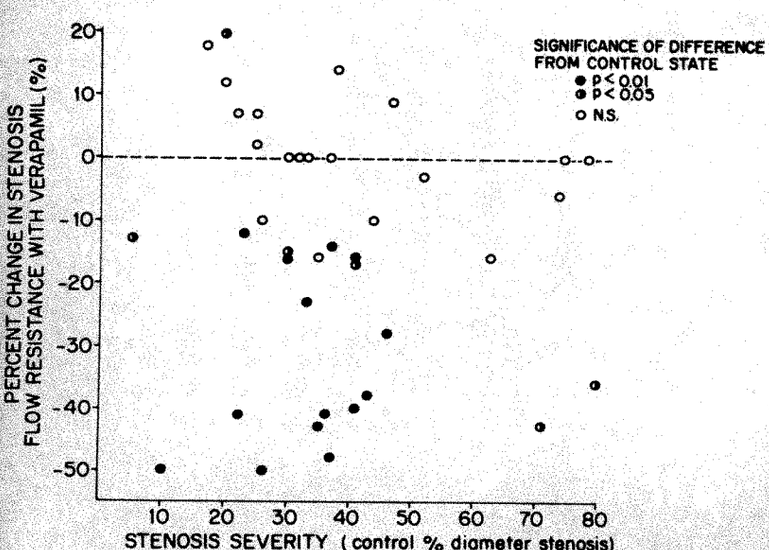



**FIGURE 3.** Individual changes in estimated stenosis flow resistance after verapamil. Each point represents a single lesion. Points falling below the zero line indicate stenosis dilation. Points that are partly or totally darkened show statistically significant change by paired *t* test of the 6 estimates in each of the pre- and postverapamil angiographic images. Verapamil reduced stenosis flow resistance significantly.

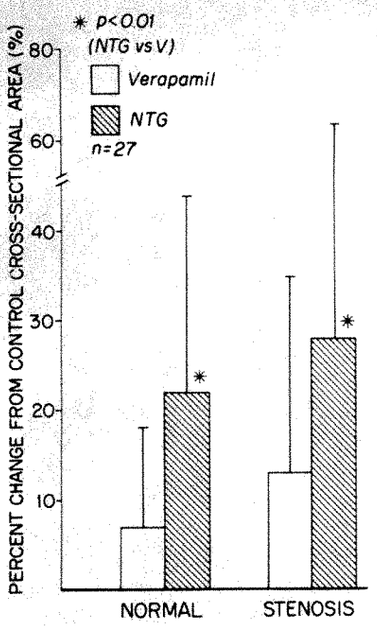



**FIGURE 4.** Comparative effects on luminal cross-sectional areas after verapamil (V) and nitroglycerin (NTG) with both "normal" and stenosed segments of coronary arteries. The data are means and standard deviations. Both drugs increase cross-sectional areas in normal as well as in narrowed segments of the coronary arteries; nitroglycerin is more potent.

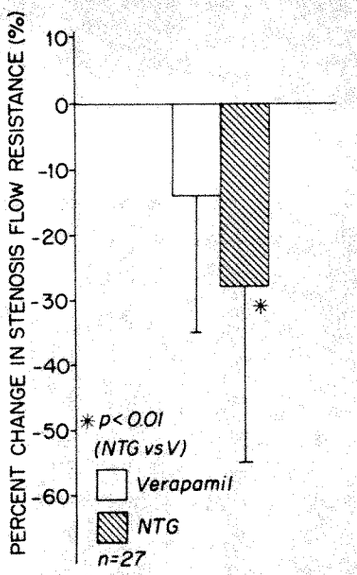



**FIGURE 5.** Comparative changes in estimated stenosis flow resistance after verapamil (V) and nitroglycerin (NTG). The effects were tested in the same lesions sequentially and data were acquired at doses of the drugs that were equipotent with respect to reduction in systolic arterial pressure. The data are means ± standard deviations; nitroglycerin had a more significant effect in reducing stenosis flow resistance.

## Discussion

The present findings demonstrate that verapamil is frequently but inconsistently a mild dilator of epicardial coronary arteries, producing dilation not only of their "normal" but also of their narrowed segments, with a resulting reduction in estimated stenosis flow resistance. These results contradict the generally held belief that atherosclerotic lesions in man do not have the propensity to dilate under the action of pharmacologic intervention. Total coronary vascular resistance also decreased after verapamil with a tendency for coronary sinus blood flow to increase. Because the coronary sinus flow did not decrease, as occurs with dipyridamole,[22] our observations suggest that verapamil dilates both conductance as well as resistance components of the coronary arteries. The findings agree with recent experimental work[17] using in vitro strips of canine coronary arteries in which verapamil was found to block calcium-dependent action potentials in both the large and the small coronary vessels.

Our data on coronary hemodynamics, however, differ somewhat from those recently reported by Ferlinz and Turbow.[18] These investigators found that in patients with coronary artery disease, verapamil (0.1 mg/kg bolus followed by infusion of 0.005 mg/kg per minute) *decreased* CSBF 12% with no significant effect on coronary vascular resistance, whereas myocardial oxygen consumption was reduced 18%. In our study, coronary vascular resistance invariably *decreased* after verapamil, and this decrease was maintained during the entire period of drug infusion. Absolute coronary sinus blood flow increased, although it reached statistical significance only at the third minute of drug administration when plasma verapamil concentration was at its peak.[16] In an earlier study, Simonsen[8] found that in patients with coronary disease, intravenous verapamil decreased coronary arteriolar resistance 13% compared with 24% in our study. However, in this study by Simonsen, verapamil was given as a single bolus injection (0.15 mg/kg) without a subsequent continuous infusion and the test measurements were made 15 minutes later. We previously showed[16] that many characteristic hemodynamic responses to single-bolus injection of verapamil are largely dissipated in 10 minutes after intravenous drug administration. Therefore, it is likely that in Simonsen's study, hemodynamic variables were measured at a time when changes were minimal. This possibility is further supported by the fact that the changes in systemic hemodynamics were much smaller than those observed in our study. The alteration in systemic hemodynamic variables noted in the present study were comparable to those previously reported by us[16,20] and found by others.[19]

Fifty percent of the lesions analyzed showed no significant change in coronary cross-sectional area with verapamil. Failure of these segments to dilate may be a reflection of the decrease in distending pressure with verapamil, possibly mediated by reflex vasoconstriction.[21] However, we were unable to find any correlation between the directional changes in coronary caliber with the degree of reduction in aortic pressure or systemic vascular resistance. A second explanation for variation in vasomobility response may reflect the greater degrees of ongoing adrenergic or calcium-mediated vasomotor tone in some patients at the time of cardiac catheter-

ization. We recently showed that verapamil is able to block adrenergically mediated coronary constriction.[22] A third explanation for variability in the vasodilatory response to verapamil may relate to the histologic aspects of the coronary stenosis. In an eccentric lesion in which the remaining lumen is circumscribed by a relatively normal segment of arterial wall, the potential for vasomobility would be greater than that in a concentric lesion, the lumen of which is surrounded entirely by more rigid components of the atherosclerotic plaque.[23]

Our data show that the degree of large vessel coronary dilatation induced by verapamil is relatively mild and perhaps only appreciated in our study by a computer-assisted method for analysis of changes in coronary caliber. This finding may explain the previous findings of Mignault,[6] who, using gross angiographic appearances, reported that intravenous verapamil altered the caliber of neither normal nor atherosclerotic coronary vessels.

The observed coronary caliber changes induced by verapamil appeared to be relatively minor compared with those after nitroglycerin, although a dose-response relation was not examined. However, these changes with verapamil are of greater magnitude than those induced by dipyridamole, which produces only a slight nonsignificant dilation of normal and diseased coronary segments.[24] Using a similar technique of computer-assisted analysis of 85 coronary lesions from 57 patients with ischemic heart disease, Brown et al,[15] in our laboratory, recently showed that nitroglycerin dilated normal segments of coronary arteries by an average of 18% in cross-sectional area, whereas estimated stenosis flow resistance decreased 25% in moderately severe lesions and 38% in severe lesions. However, these changes, albeit from a larger data base, are of comparable magnitude to those found in our study. Thus, in the resting state, nitroglycerin is 2 to 3 times more potent a vasodilator of epicardial conductance vessels than verapamil. Relatively mild coronary vasodilator effects using a similar, but not identical, computer-assisted technique were recently described for nifepidine.[25] However, the observations with verapamil pertain only to the coronary vessel in the basal state and do not negate the obvious clinical efficacy of verapamil and other calcium antagonists in vasospastic angina[26–29] where the degree of vasodilation could be greater. Furthermore, evidence is accumulating that a major role for calcium antagonists lies in the *prevention* of coronary artery spasm associated with Prinzmetal's angina.[30,31] Nifepidine was recently shown to exert a selective antivasoconstrictor effect in the coronary vasculature by preventing abnormal hemodynamic coronary changes due to the cold pressor test.[32] In human studies using quantitative coronary angiography, intravenous verapamil inhibited both sympathetic and ergonovine-induced coronary vasoconstriction in diseased human coronary arteries.[22]

**Clinical implications:** Although data from intravenous studies cannot always be extrapolated directly to the clinical contexts in which calcium antagonists are being used to alleviate myocardial ischemia, our data permit some inferences. Verapamil reduces coronary vascular resistance while producing an increase, albeit small, in lumen cross-sectional area of both diseased and "normal" coronary vessels. These findings, in addition to the recent observation that verapamil reverses both sympathetically mediated as well as ergonovine-induced coronary vasoconstriction,[22] provide the physiologic basis for the drug's salutary effects in Prinzmetal's and other vasospastic ischemic syndromes. In chronic stable angina, the mechanism of the beneficial action is less clear and unlike that of beta-blocking agents, not explainable solely on the basis of changes in the gross indexes of myocardial oxygen consumption.[33] Our data suggest that stenosis dilatation as a contributing mechanism cannot be discounted.

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## References


1. **Elirodt G, Chew CYC, Singh BN.** Therapeutic implications of slow-channel blockade in cardiocirculatory disorders. Circulation 1980;62:669–679.
2. **Stone P, Antman E, Muller J, Braunwald E.** Calcium channel blocking agents in the treatment of cardiovascular disorders. Ann Intern Med 1980;93:875–890.
3. **Singh BN, Elirodt G, Peter CT.** Verapamil: a review of its pharmacological properties and therapeutic use. Drugs 1978;15:169–203.
4. **Melville KI, Benfey BC.** Coronary vasodilatory and cardiac adrenergic blocking effects of iproveratnil. Can J Physiol Pharmacol 1965;43:339–362.
5. **Melville KI, Shister HE, Huq S.** Iproveratnil: experimental data on coronary dilatation and antiarrhythmic action. Can Med Assoc J 1964;90:761–770.
6. **Mignault SH.** Coronary cineangiographic study of intravenously administered isoptin. Can Med Assoc J 1966;95:1252–1253.
7. **Luebs ED, Cohen A, Zaleski EJ, Bing RJ.** Report on therapy: effect of nitroglycerin, intensain, isoptin and papaverine on coronary bood flow in man. Am J Cardiol 1966;17:535–541.
8. **Simonsen S.** Effect of verapamil on coronary hemodynamics in patients with coronary artery disease. Eur J Cardiol 1978;8:9–18.
9. **Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC.** Measurement of coronary sinus blood flow by continuous thermodilution. Circulation 1971;44:181–195.
10. **Brown BG, Bolson E, Frimer M, Dodge HT.** Quantitative coronary angiography: estimation of dimensions, hemodynamic resistance and atheroma mass of coronary artery lesions using the arteriogram and digital computation. Circulation 1977;55:329–337.
11. **McMahon MM, Brown BG, Cukingnan R, Rollett EL, Bolson E, Frimer M, Dodge HT.** Quantitative coronary angiography: measurement of the "critical" stenosis in patients with unstable angina and single vessel disease without collaterals. Circulation 1979;60:106–113.
12. **Koh D, Mitten S, Stewart D, Bolson E, Dodge HT.** Comparison between computerized quantitative coronary angiography and clinical interpretation (abstr). Circulation 1979;60:Suppl II:II-160.
13. **Kelley K, Gould L.** Validation of computerized quantitative coronary angiography (abstr). Circulation 1981;64:Suppl IV:IV-392.
14. **Harrison DG, White CW, Hiratzka LF, Wright CB, Doty DB, Miller MR, Eastham CL, Marcus ML.** Can the significance of a coronary stenosis be predicted by quantitative coronary angiography (abstr)? Circulation 1981;64:Suppl IV:IV-601.
15. **Brown BG, Bolson E, Petersen RB, Pierce CD, Dodge HT.** The mechanisms of nitroglycerin action: stenosis vasodilatation as a major component of the drug response. Circulation 1981;64:1089–1097.
16. **Chew CYC, Hecht HS, Collett JT, McAllister RG, Singh BN.** Influence of severity of ventricular dysfunction on hemodynamic responses to intravenously administered verapamil in ischemic heart disease. Am J Cardiol 1981;47:917–922.
17. **Brown BG, Pierce CD, Petersen RB, Singh BN, Bolson EL, Dodge HT.** Verapamil: a mild epicardial coronary dilator inhibits sympathetic and ergonovine-induced coronary constriction in humans (abstr). Circulation 1981;64:Suppli IV:IV-150.
18. **Harder DR, Belardinelli L, Sperelakis N, Rubio R, Berne RM.** Differential effects of adenosine and nitroglycerin on the action potentials of large and small coronary arteries. Circ Res 1979;44:176–182.
19. **Ferlinz J, Turbow ME.** Antianginal and myocardial metabolic properties of verapamil in coronary artery disease. Am J Cardiol 1980;46:1019–1026.
20. **Singh BN, Roche AHG.** Effects of intravenous verapamil on hemodynamics in patients with heart disease. Am Heart J 1977;94:593–599.
21. **Ferlinz J, Easthope JL, Aronow WS.** Effects of verapamil on myocardial performance in coronary disease. Circulation 1979;59:313–319.
22. **Vatner SF, Pagani M, Manders WT, Pasipoularides AD.** Alpha adrenergic vasoconstriction and nitroglycerin vasodilation of large coronary arteries in the conscious dog. J Clin Invest 1980;65:5–14.
23. **Brown BG.** Coronary vasospasm: observations linking the clinical spectrum

of ischemic heart disease to the dynamic pathology of coronary atherosclerosis. Arch Intern Med 1981;141:716–722.
24. **Brown BG, Josephson MA, Petersen RB, Pierce CD, Wong M, Hecht HS, Bolson E, Dodge HT.** Intravenous dipyridamole combined with isometric handgrip for near maximal acute increase in coronary flow in patients with coronary artery disease. Am J Cardiol 1981;48:1077–1085.
25. **Serruys PW, Stewart R, Booman F, Brand M, Reiber JHC.** Effects of intracoronary nifedipine on coronary vasomobility and left ventricular hemodynamics (abstr). Circulation 1980;62:Suppl III:III-86.
26. **Parodi O, Maseri A, Simonetti I.** Management of unstable angina at rest by verapamil. Br Heart J 1979;41:167–174.
27. **Goldberg S, Reichek N, Wilson J, Hirshfield JW, Muller J, Kastor JA.** Nifepidine in the treatment of Prinzmetal's angina. Am J Cardiol 1979;44: 804–810.
28. **Hugenholtz PG, Michels HR, Serruys PW, Brower RW.** Nifedipine in the treatment of unstable angina, coronary spasm and myocardial ischemia. Am J Cardiol 1981;47:163–173.
29. **Johnson SM, Mauritson DR, Willerson JT, Hillis LD.** A controlled trial of verapamil for Prinzmetal's variant angina. N Engl J Med 1981;304:862–866.
30. **Endo M, Kanda I, Hosada S, Hayashi H, Hirosawa K, Konno S.** Prinzmetal's variant form of angina pectoris: re-evaluation of mechanisms. Circulation 1975;52:33–37.
31. **Antman E, Muller J, Goldberg S, MacAlpin R, Rubenfire M, Tabatznik B, Liang CS, Heupler F, Achuff S, Reichek N, Geltman E, Kerin NZ, Neff RK, Braunwald E.** Nifedipine therapy for coronary artery spasm: experience in 127 patients. N Engl J Med 1980;302:1269–1273.
32. **Gunther S, Green L, Muller J, Mudge G, Grossman W.** Prevention by nifedipine of abnormal coronary vasoconstriction in patients with coronary artery disease. Circulation 1981;63:849–855.
33. **Josephson MA, Hecht HS, Hopkins JM, Singh BN.** Oral verapamil versus propranolol in coronary artery disease: evaluation of left ventricular function by exercise radionuclide ventriculography (abstr). Am J Cardiol 1981;47: 463.

It may be that there are areas of wisdom that he did not penetrate: but I am more interested in trying to understand the wisdom he possessed than to define its limitations. [When a man is a good deal wiser than oneself, one does not complain that he is no wiser than he is.]

T. S. Eliot, "Goethe as the Sage"

# Nifedipine in Chronic Stable Angina: A Double-Blind Placebo-Controlled Crossover Trial

LON G. SHERMAN, MD and CHANG-SENG LIANG, MD, PhD

**Thirty patients with chronic stable angina pectoris were randomized in a double-blind prospective placebo-controlled crossover trial to assess the efficacy of nifedipine (30 to 60 mg/day orally) in controlling symptoms and objective signs of myocardial ischemia using a symptom-limited treadmill exercise test. Adverse effects that occurred during both nifedipine and placebo treatment were minor and generally well tolerated. Twenty-three patients were analyzed from the crossover phase of the study. Nifedipine significantly reduced the frequency of angina by 55% and nitroglycerin consumption by 59%, and increased exercise time by 34%. These changes were significantly greater than those in the placebo group. Hemodynamic evaluation during exercise revealed a significant reduction in systolic and diastolic blood pressures in the nifedipine group at the onset of angina and at maximal exercise without significant differences in heart rate responses in the nifedipine and placebo groups. The pressure-rate product during submaximal exercise was significantly smaller in the nifedipine group than in the placebo group, but did not differ significantly in the 2 groups at the onset of angina or on maximal exercise. Furthermore, S-T segment depressions that occurred during exercise at the same pressure-rate products were smaller in the nifedipine period than in the placebo period. Thus, it appears that the antianginal effects of nifedipine are caused by a reduced myocardial oxygen demand for a specific work load and possibly by an increased blood supply to ischemic myocardium.**

Beta-receptor blocking agents and nitrates are presently the mainstays of treatment for symptomatic coronary artery disease. Nifedipine is a relatively new agent. It does not cause bronchospasm or myocardial depression, both of which are major adverse effects of beta-receptor blockers and limit their use in certain clinical situations. Nifedipine and nitrates, albeit similar in mechanisms of action, differ greatly in that nifedipine has little effect on preload.[1]

Despite enthusiastic acceptance of nifedipine by clinicians, there has been no completed long-term placebo-controlled crossover study to date. Preliminary double-blind studies including some multicenter trials using nifedipine in patients with angina pectoris have demonstrated promising results.[2–7] The present study is a randomized, prospective, double-blind, placebo-controlled crossover trial from a single center. Its purpose was to assess the efficacy of the nifedipine in reducing both subjective and objective signs of myocardial ischemia in symptomatic patients with chronic stable angina pectoris.

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## Methods

Thirty patients were included in the study. All had a history of angina pectoris characterized by chest pain, chest pressure, or distress, usually brought on by exertion or emotional stress, and relieved by nitroglycerin, rest, or removal of emotional stress. These symptoms had been stable without acute myocardial infarction for at least 6 months. All patients had at least 5 episodes/week of angina pectoris or had <5 episodes of angina/week but exhibited >0.2 mV of horizontal or downsloped S-T segment depression during exercise. Coronary artery disease was confirmed by at least 1 of the following: (1) coronary angiography showing ≥70% diameter narrowing of ≥1 major coronary arteries, (2) documentation of a prior transmural myocardial infarction, (3) demonstration of typical angina pectoris during exercise stress testing associated with ischemic electrocardiographic changes. Two patients with stable angina who had undergone aortocoronary bypass surgery 3 and 10 years earlier were included. Informed consent was obtained from all patients. All patients were withdrawn from concomitant therapy with long-acting ni-

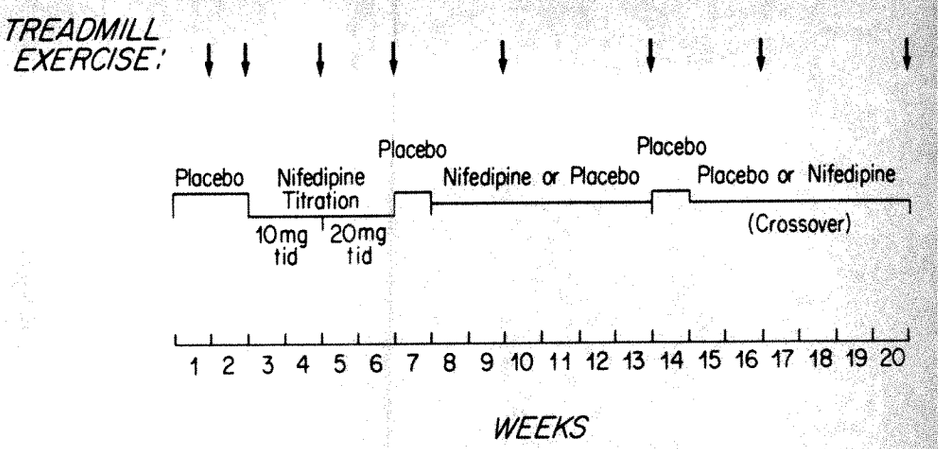



**FIGURE 1.** The weeks during which subjects received either placebo or nifedipine. During the titration phase (weeks 3 to 6), the optimal dose of nifedipine was established which was later given during the double-blind phase of the study (weeks 8 to 13 or weeks 15 to 20). Patients were crossed over from nifedipine to placebo or placebo to nifedipine during the second leg of the double-blind phase (weeks 15 to 20) after a single-blind placebo week. Exercise treadmill tests were performed at specific times denoted by **arrows**.

trates or beta-receptor blocking agents at least 1 week before entering the study. Two patients who had received quinidine, 1 procainamide, and 2 disopyramide for ventricular arrhythmias before the study continued receiving the maintenance therapy. Sixteen patients continued receiving maintenance doses of thiazide diuretics (n = 13) and furosemide (n = 3), and appropriate doses of potassium supplements to prevent hypokalemia. Three of the patients taking diuretics also received maintenance doses of alpha-methyldopa for control of hypertension. Seven patients continued receiving digoxin therapy. None of the patients included had uncontrolled congestive heart failure, forms of heart disease considered to result from causes other than atherosclerotic cornary disease, unstable cardiac arrhythmias, cerebral vascular insufficiency, uncontrolled hypertension, serious hepatic, renal, and hematopoietic diseases, or concomitant disorders with symptoms that could be confused with angina.

The study design consisted of 3 phases (Fig. 1). Initially, all patients underwent a baseline phase during which no long-term antianginal medications were used. During this time, placebo was taken in a single-blind manner. Thereafter, there was a 4-week single-blind titration phase during which nifedipine was administered orally at either 10 or 20 mg 3 times a day to determine the optimal dosage for each patient. This was followed by a 14-week randomized double-blind crossover phase consisting of two 6-week drug periods with 1-week placebo washout periods before each 6-week drug period. The placebo and nifedipine capsules were identical in appearance.

Treadmill exercise testing (12 leads) was done using a modified Balke's procotol,[8] in which patients were exercised on a treadmill with stages of 3 minutes each, initially at 2.0 mph with a 3% grade followed by an increase in speed to 3.3 mph and a 6% grade. The treadmill speed was held constant thereafter with incremental increases of grade by 3% during all subsequent stages. During exercise, times were recorded at the onset of angina and maximal exercise tolerance which was defined by angina pain of moderately severe intensity (primary endpoint). In addition, exercise tests were terminated if any of the following were observed: severe shortness of breath, a significant decrease in systolic blood pressure, or severe fatigue. None of the patients developed significant ventricular arrhythmia during exercise that necessitated termination of the study. Measurements of heart rate, arterial blood pressure by an arm cuff sphygmomanometer, and S-T segment depression were taken every minute during exercise. Systolic arterial pressure and heart rate were multiplied to yield the pressure-rate product. The work performed at each minute of exercise was derived using approximate total body oxygen consumption[8] and expressed in METs. One MET is the energy expenditure at rest, equivalent to approximately 3.5 ml of oxygen/kg body weight/min. The total work performance achieved at the onset of angina and maximal exercise was computed by summing the work performed at each minute of exercise until the specified times. All exercise tests were done 2 hours after intake of nifedipine or placebo, and at least 3 hours after meals. No patient took nitroglycerin within 6 hours before treadmill exercise. Exercise testing was done at the end of weeks 1 and 2. Patients were allowed to continue in the study if exercise times in the 2 baseline testings were discordant by <15%.

At the start of the third week, nifedipine was given single-blinded at a dosage of 10 mg every 8 hours for 2 weeks (weeks 3 and 4) and increased to 20 mg every 8 hours, if tolerated for the next 2 weeks (weeks 5 and 6). Exercise testing was repeated at the end of weeks 4 and 6. The optimal nifedipine dosage was determined by the highest dose tolerated without signs or symptoms related to significant blood pressure reduction, deterioration of myocardial function, or laboratory evidence suggesting adverse effects upon renal, hepatic, or hematopoietic systems.

All patients received placebo during the seventh week. From weeks 8 through 13, patients were given their optimal dose of nifedipine or placebo in a randomized, double-blind manner followed by a week of placebo. Thereafter, from weeks 15 through 20, patients were crossed-over double-blinded to nifedipine or placebo. Patients who had increasing frequency of chest pain during the initial leg of the crossover period could be entered early into the next leg. Exercise tests were done at the end of the second week and the last week of each leg during the double-blind period.

In addition to exercise testing, patients kept a diary of all anginal attacks as well as total nitroglycerin tablets taken during each phase. All patients were periodically examined and tested for observed or laboratory evidence of adverse effects.

Results are expressed as mean ± standard error. The percentage of difference from baseline values during the single-blind titration phase and double-blind crossover phase were compared using the Student's $t$ test for paired comparisons. Because the exercise time was reproducible with a coefficient of variation of 7.7% for the 2 treadmill testings during each leg of the double-blind crossover period, the 2 exercise measurements for each leg were averaged. The crossover periods were assessed using analysis of variance for repeated measures with a crossover design.[9] The S-T segment responses for

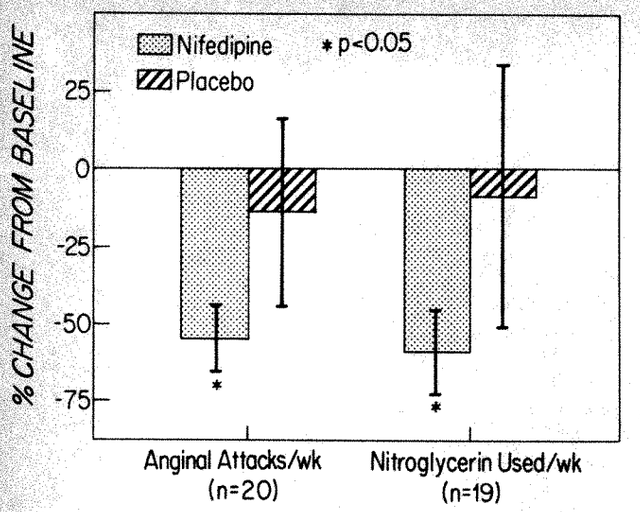



**FIGURE 2.** Changes in frequency of angina and nitroglycerin consumption from baseline by nifedipine and placebo during the double-blind crossover phase. Values are mean ± standard error. **Asterisks** indicate values that differ from placebo at $p < 0.05$, as determined by Student's *t* test for paired comparisons.

specific pressure-rate products were determined from regression analyses for each patient. The values were then averaged for both treatment groups and compared using Student's *t* tests. The incidence of adverse effects in the 2 treatment groups was compared using a chi-square test. Values are considered statistically significant if $p < 0.05$.

## Results

Thirty patients, 19 men and 11 women aged 43 to 70 years, were randomized to the nifedipine-placebo crossover study. No patient had serious cardiovascular complications, prolonged bed rest, or hospitalization. Seven patients, however, were excluded from the crossover statistical analyses. Three were excluded because of early termination during the titration phase due to headache, loss in follow-up, and uneasiness in participating in the research protocol, respectively. Two patients were prematurely crossed-over because of increasing frequency of chest pain during the initial (placebo) leg of the double-blind phase. These patients subsequently improved during the second leg of the study when they received nifedipine. One patient was dropped from the final (placebo) leg of the double-blind crossover phase because of increasing chest pain. One patient was excluded from analysis because of incomplete data collection. When data were not available from some patients, the number of subjects analyzed are indicated in parentheses.

**Anginal episodes and nitroglycerin consumption:** Nifedipine significantly decreased the frequency of anginal attacks during the low-dose (30 mg/day) and high-dose (60 mg/day) titration phases. Anginal attacks significantly decreased from 4.4 ± 0.7 before treatment to 2.8 ± 0.5/week during the lower dosage (n = 25), and from 5.0 ± 0.8 to 2.7 ± 0.5/week with the higher dose (n = 19). Six patients had severe headaches and could not tolerate the higher dosage. Nitroglycerin use also was

**TABLE I Exercise Time, Work Performance, and S-T Segment Depression During Treadmill Exercise**

| | Placebo | Nifedipine |
|---|---|---|
| Time (seconds) | | |
| Onset of angina | 274 ± 21 | 319 ± 25* |
| Maximal exercise | 440 ± 43 | 490 ± 48* |
| Work performance achieved (METs) | | |
| Onset of angina | 17.5 ± 2.3 | 22.3 ± 2.8* |
| Maximal exercise | 38.2 ± 6.6 | 45.3 ± 7.4* |
| S-T segment depression (mV) | | |
| Onset of angina | 0.11 ± 0.02 | 0.09 ± 0.02 |
| Maximal exercise | 0.18 ± 0.02 | 0.14 ± 0.02* |

Values are mean ± standard error. N = 17 for data obtained at the onset of angina and n = 23 for maximal exercise.
* Values that differ from the placebo at $p < 0.05$.

significantly decreased from the baseline (5.1 ± 1.2 tablets/week) to 3.5 ± 0.7 tablets/week during the low-dose titration phase and from 6.2 ± 1.3 to 2.7 ± 0.7 tablets/week during the high-dose phase. In addition, nifedipine but not placebo reduced anginal frequency and nitroglycerin use during the crossover period (Fig. 2).

**Exercise time, work performance, and ischemic S-T segment response:** During the titration phase, patients had angina after 229 ± 29 seconds of exercise before receiving nifedipine, but remained free of angina until 276 ± 36 seconds into exercise while taking the low-dose nifedipine (n = 23). The maximal duration of

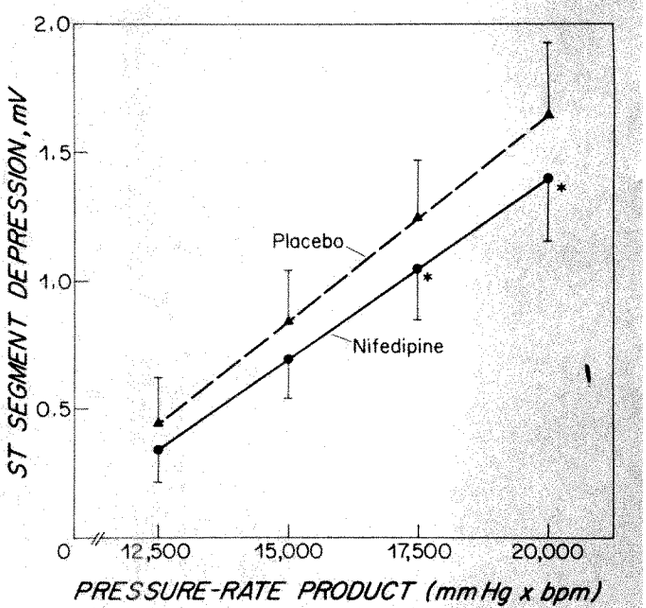



**FIGURE 3.** Comparisons of ischemic S-T segment depressions at specific pressure-rate products in the double-blind nifedipine and placebo periods (n = 17). The values of S-T segment depressions were calculated for each patient by interpolation from the regression lines that correlated S-T segment depressions and pressure-rate products during exercise. **Bars** indicate standard errors. **Asterisks** show values that differ significantly from the corresponding values during the placebo period at $p < 0.05$, as determined by Student's *t* test for paired comparisons.

exercise increased from 368 ± 35 to 434 ± 39 seconds (n = 28). The time to onset of angina and maximal exercise also increased in patients receiving the high-dose nifedipine. Unlike the baseline exercise testing during which all patients stopped exercise because of moderately severe chest pain, 6 patients did not have chest pain and stopped exercise because of fatigue or severe shortness of breath. Of the remaining 17 patients, the time to onset of angina increased from 206 ± 16 to 290 ± 22 seconds. The maximal duration of exercise for all patients increased from 369 ± 37 to 489 ± 55 seconds.

The increase in exercise tolerance was reflected in total work performance achieved at the onset of angina which increased significantly from 14 ± 3 to 19 ± 5 METs during the low-dose nifedipine period (n = 23) and from 11 ± 1 to 19 ± 2 METs with the high dose (n = 17). Total work performance achieved at maximal exercise also increased significantly from baseline during the low-dose nifedipine (29 ± 4 to 37 ± 5 METs) and high-dose nifedipine (29 ± 5 to 46 ± 9 METs).

The amount of S-T segment depression at the onset of angina was not significantly reduced by either the low- or the high-dose nifedipine. At maximal exercise, however, S-T segment depression was significantly reduced by nifedipine, decreasing from 0.18 ± 0.01 at baseline to 0.15 ± 0.02 mV with the low-dose nifedipine, and from 0.17 ± 0.01 to 0.12 ± 0.02 mV with the high dose.

During the crossover period, the time to the onset of angina and the maximal duration of exercise were significantly greater during the nifedipine period (Table I). Similarly, significantly greater work performance was achieved at the onset of angina and at maximal exercise during the nifedipine period than with placebo. The S-T segment depression at the onset of angina did not differ significantly in the nifedipine and placebo periods. However, a significant reduction in S-T segment depression was found at maximal exercise during nifedipine treatment compared with placebo. Furthermore, Figure 3 shows that nifedipine was associated with a reduction in the magnitude of S-T segment depression during exercise-induced increases in pressure-rate products. At pressure-rate products ≥17,500 mm Hg·beats/min, the amount of S-T segment depression was significantly reduced by nifedipine compared with placebo.

**TABLE II Exercise Hemodynamic Values in the Double-Blind Crossover Periods**

| | Placebo | Nifedipine |
|---|---|---|
| Onset of angina | | |
| Heart rate (beats/min) | 122 ± 4 | 123 ± 3 |
| Systolic pressure (mm Hg) | 159 ± 5 | 154 ± 4* |
| Diastolic pressure (mm Hg) | 87 ± 3 | 82 ± 4* |
| Pressure-rate product (mm Hg·beats/min × $10^{-3}$) | 19.5 ± 0.9 | 18.8 ± 0.6 |
| Maximal exercise | | |
| Heart rate (beats/min) | 133 ± 4 | 133 ± 4 |
| Systolic pressure (mm Hg) | 167 ± 6 | 157 ± 5* |
| Diastolic pressure (mm Hg) | 88 ± 4 | 80 ± 3* |
| Pressure-rate product (mm Hg·beats/min × $10^{-3}$) | 22.4 ± 1.2 | 20.9 ± 0.9 |

Values are mean ± standard error; n = 17.
* Values that differ from the placebo at $p < 0.05$.

**Hemodynamics during exercise:** The data reported in Table II include 17 patients whose exercise response was associated with typical anginal pain during both legs of the crossover period. The resting heart rate during the nifedipine phase (79 ± 3 beats/min) was slightly higher than during the placebo phase (75 ± 3 beats/min, n = 23, p = 0.044), but the heart rate response to exercise did not differ in the 2 phases. The lack of differences was noted both at the onset of angina and at maximal exercise. In contrast, the systolic and diastolic blood pressures during exercise were signifi-

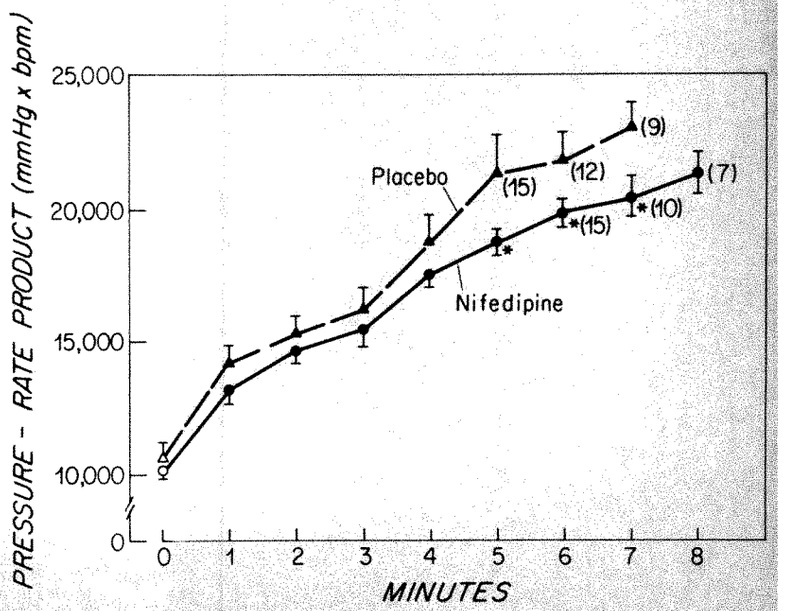



**FIGURE 4.** Temporal changes in pressure-rate product during exercise in double-blind nifedipine and placebo periods. N = 17 unless otherwise indicated in parentheses. **Bars** show standard errors. **Asterisks** indicate values that differ significantly from the corresponding values in the placebo period at $p < 0.05$, as determined by Student's *t* test for paired comparisons.

**TABLE III Incidence of Adverse Effects**

| Adverse Effect | Nifedipine | Placebo |
|---|---|---|
| Headache | 4 | 0* |
| Lack of energy | 4 | 3 |
| Gastrointestinal symptoms | 4 | 1 |
| Dizziness | 2 | 2 |
| Flushing | 1 | 0 |
| Paresthesia | 1 | 1 |
| Palpitations | 1 | 0 |
| Rash | 1 | 0 |
| Restlessness | 0 | 1 |

Total of 30 patients in each treatment group.
* Value that differs significantly from the nifedipine at $p < 0.05$, as determined by chi-square test.

cantly lower with nifedipine than with placebo both at the onset of angina and at maximal exercise.

Figure 4 shows that the pressure-rate product increased progressively as exercise duration lengthened, and that the increase in pressure-rate products beyond 4 minutes of exercise was significantly smaller in patients receiving nifedipine compared with placebo. The pressure-rate products at the onset of angina and maximal exercise, however, did not differ significantly in the nifedipine and placebo groups (Table II).

When the 6 patients who did not experience angina during crossover periods were included in the analysis, similar significant decreases were noted in the systolic and diastolic pressures during nifedipine treatment compared with placebo. Likewise, the maximal exercise pressure-rate product during nifedipine treatment (22,045 ± 1,128 mm Hg·beats/min) was not significantly different from placebo (23,196 ± 1,224 mm Hg·beats/min).

**Adverse effects:** Adverse effects observed in the study were minor and were well tolerated by the patients (Table III). They were present in 16 of the 30 patients studied, 6 of whom were receiving placebo when the adverse effects occurred. No untoward effects were reflected by laboratory data. The most common adverse effects were headaches, lack of energy, and various gastrointestinal symptoms including nausea or vomiting, diarrhea, and flatulence. Lack of energy was the most common complaint of patients receiving placebo. Dizziness was equally common during nifedipine and placebo treatment. Headaches, flushing, palpitation, and a rash were evident only during nifedipine usage and, with the exception of headaches, were uncommon. Only headaches were statistically more common during the nifedipine use compared with placebo. The causal relation between the observed adverse effects and nifedipine usage, however, was not established. No patient had peripheral edema during the study period.

## Discussion

The present study demonstrates that nifedipine improves both symptoms and objective signs of myocardial ischemia in patients with angina pectoris. Nifedipine decreased frequency of anginal episodes and nitroglycerin usage. This is further supported by our findings that unstable angina occurred in 3 patients while receiving placebo. In addition, exercise time until the onset of angina and maximal tolerated exercise was prolonged during nifedipine use compared with placebo. The ischemic S-T segment depression at given pressure-rate products during moderate to maximal tolerated exercise was reduced by nifedipine compared with placebo. Some minor adverse effects occurred during both the nifedipine and placebo treatment, but were generally well tolerated. Headache was the only symptom that occurred more frequently during nifedipine than placebo.

The improvement in patients with ischemic heart disease who were receiving nifedipine is likely related to a favorable shift in the balance between myocardial oxygen supply and demand. Angina pectoris is thought to be inducible when a mismatch develops between myocardial oxygen supply and demand for oxygen during aerobic cardiac metabolism.[10] Our results show that nifedipine, in comparison with placebo, causes a significant decrease in systolic and diastolic arterial pressure due to its vasodilatory effect upon the systemic circulation, without differences in heart rate during exercise. This decrease in systolic blood pressure was reflected in a lower pressure-rate product during exercise when patients were taking nifedipine. Since the pressure-rate product is known to correlate closely with myocardial oxygen consumption during exercise in patients with ischemic heart disease,[11,12] a reduction in the product would imply less myocardial oxygen consumption due to a reduction in oxygen demand. Thus, it appears likely that the blunted response of the systolic blood pressure during exercise is responsible, at least in part, for the longer exertional period that lapses before the pressure-rate product anginal threshold is reached. Since angina occurs reproducibly at specific pressure-rate products for a given patient, the pressure-rate products are similar with nifedipine and placebo at the onset of angina.[13]

Alternatively, nifedipine may favorably affect myocardial oxygen supply by enhancement of coronary flow to ischemic regions. Nifedipine is known to be a direct coronary vasodilator.[14,15] It has also been shown to produce sustained increases in collateral flow during ischemia in animal studies,[16,17] and may induce protective collateralization during chronic ischemia.[18] Recently, it has been shown that in patients with coronary artery disease, nifedipine increases regional myocardial blood flow supplied by vessels with significant coronary obstruction.[19] However, these studies were done with patients in the resting nonischemic states, and most patients were maintained with propranolol. Similarly, during experimental myocardial ischemia, intracoronary nifedipine resulted in increased coronary blood flow at moderate reductions in coronary perfusion pressure.[20] Our finding that nifedipine was associated with a reduction in the ischemic S-T segment depression at given pressure-rate products during moderate to maximal exertion compared with placebo is consistent with increased myocardial oxygen supply. Thus, it appears that nifedipine may also ameliorate the

myocardial oxygen supply-demand ratio by increasing blood flow to hypoperfused myocardium.

*In summary*, our study supports the view that nifedipine may act by reducing myocardial oxygen demand for a given work load through its vasodilator effects upon the peripheral circulation and, in addition, may enhance myocardial oxygen supply by direct coronary vasodilation or increased collateral flow. These hemodynamic changes during exercise are converse to the changes seen in anginal patients exercised during beta-receptor blockade in which a reduction in the pressure-rate product is predominantly attributed to a slowing of heart rate with some contribution due to a diminution in systolic pressure.[21-25] The mechanism by which nifedipine benefits the signs and symptoms of angina pectoris will require invasive hemodynamic studies for validation.

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## References

1. **Stone PH, Antman EM, Muller JE, Braunwald E.** Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II. Hemodynamic effects and clinical applications. Ann Intern Med 1980;93:886–904.
2. **Camerini F, Scardi S.** Nifedipine in angina pectoris: a multicentric clinical trial. In: Lochner W, Braasch W, Kroneberg G, eds. Second International Adalat Symposium. Berlin: Springer-Verlag, 1975:322–328.
3. **Sakuma A, Kimura E.** An interim report on a cooperative double-blind clinical trial with nifedipine. In Ref 2:329–332.
4. **Bidoggia H, Machado R.** Antianginal effect of nifedipine in a double-blind cross-over trial. In: Jatene AD, Lichtlen PR, eds. Third International Adalat Symposium. Amsterdam: Excerpta Medica, 1976;226–232.
5. **Folle LE, Ortiz A, Artucio R, Dihiero J.** Efficacy of Adalat in angina pectoris patients in a controlled clinical trial compared with placebo. In Ref 4: 200–206.
6. **Menna J, Traina M, Ferreirós E, Cassera JC.** Long-term double-blind cross-over study on the antianginal efficacy of Adalat compared with placebo. In Ref 4:272–279.
7. **Mueller HS, Chahine RA.** Interim report of multicenter double-blind placebo-controlled studies of nifedipine in chronic stable angina. Am J Med 1981;71:645–657.
8. Committee on Exercise. Exercise Testing and Training of Apparently Healthy Individuals: A Handbook for Physicians. Dallas, TX: American Heart Association 1972:12–15.
9. **Wallenstein S, Fisher AC.** The analysis of the two-period repeated measurements crossover design with application to clinical trials. Biometrics 1977;33:261–269.
10. **Epstein SE, Redwood DR, Goldstein RE, Beiser GD, Rosing DR, Glancy DL, Reis RL, Stinson EB.** Angina pectoris: pathophysiology, evaluation, and treatment. Ann Intern Med 1971;75:263–296.
11. **Gobel FL, Nordstrom LA, Nelson RR, Jorgensen CR, Wang Y.** The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 1978;57:549–556.
12. **Holmberg S, Wieslaw S, Varnauskas E.** Coronary circulation during heavy exercise in control subjects and patients with coronary heart disease. Acta Med Scand 1971;190:465–480.
13. **Robinson BF.** Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. Circulation 1967;35:1073–1083.
14. **Simonsen S, Nitter-Hauge S.** Effect of nifedipine (Adalat) on coronary haemodynamics in patients with coronary arteriosclerotic disease. Acta Med Scand 1978;204:179–184.
15. **Fleckenstein A.** Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. Annu Rev Pharmacol Toxicol 1977;17:149–166.
16. **Henry PD, Shuchleib R, Borda LJ, Roberts R, Williamson JR, Sobel BE.** Effects of nifedipine on myocardial perfusion and ischemic injury in dogs. Circ Res 1978;43:372–380.
17. **Henry PD, Shuchleib R, Clark RE, Perez JE.** Effects of nifedipine on myocardial ischemia: analysis of collateral flow, pulsatile heat and regional muscle shortening. Am J Cardiol 1979;44:817–824.
18. **Schmier J, Van Ackern K, Brückner UB, Hakimi B, Heger W, Simo J.** Investigations on the development of collaterals, coronary flow, tachyphylaxis and steal phenomenon in dogs after application of Adalat. In Ref 2:92–100.
19. **Malacoff RF, Lorell BH, Mudge GH Jr, Holman BL, Idoine J, Folck B, Cohn PF.** Beneficial effects of nifedipine on regional myocardial blood flow in patients with coronary artery disease. Circulation 1982;65:I:I-32–I-37.
20. **Weintraub WS, Hattori S, Agarwal J, Bodenheimer MM, Banka VS, Helfant RH.** Variable effect of nifedipine on myocardial blood flow at three grades of coronary occlusion in the dog. Circ Res 1981;48:937–942.
21. **Goldbarg AN, Moran JF, Butterfield TK, Nemickas R, Bermudez GA.** Therapy of angina pectoris with propranolol and long-acting nitrates. Circulation 1969;40:847–853.
22. **Pine M, Favrot L, Smith S, McDonald K, Chidsey CA.** Correlation of plasma propranolol concentration with therapeutic response in patients with angina pectoris. Circulation 1975;52:886–893.
23. **Alderman EL, Davies RO, Crowley JJ, Lopes MG, Brooker JZ, Friedman JP, Graham AF, Matlof HJ, Harrison DC.** Dose response effectiveness of propranolol for the treatment of angina pectoris. Circulation 1975;51: 964–975.
24. **Amsterdam EA, Hughes JL III, DeMaria AN, Zelis R, Mason DT.** Indirect assessment of myocardial oxygen consumption in the evaluation of mechanisms and therapy of angina pectoris. Am J Cardiol 1974;33: 737–743.
25. **Sklar J, Johnston GD, Overlie P, Gerber JG, Brammell HL, Gal J, Nies AS.** The effects of a cardioselective (metoprolol) and a nonselective (propranolol) beta-adrenergic blocker on the response to dynamic exercise in normal men. Circulation 1982;65:894–899.

# Effect of Intravenous and Intracoronary Nifedipine on Coronary Blood Flow and Myocardial Oxygen Consumption

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**The effect of intravenous and intracoronary nifedipine on coronary sinus blood flow, coronary vascular resistance, and myocardial oxygen consumption was studied in 20 patients with coronary artery disease. An intravenous infusion of 1.0 mg nifedipine resulted in a decrease in mean aortic pressure, an increase in heart rate and coronary blood flow, and no significant change in myocardial oxygen consumption. In contrast, the intracoronary injection of 0.1 mg nifedipine led to a moderate reduction in mean aortic pressure, no change in heart rate, an increase in coronary blood flow, and a significant reduction in myocardial oxygen consumption. During rapid atrial pacing before and approximately 6 minutes after the intracoronary nifedipine injection, coronary blood flow and myocardial oxygen consumption reached identical levels. Thus, only intracoronary injection of nifedipine increases coronary flow in the presence of reduced myocardial oxygen consumption. After intravenous administration, reflex tachycardia counteracts the direct myocardial effect of nifedipine and the potential oxygen-saving effect of afterload reduction. There is no evidence of a prolonged oxygen-sparing effect after cessation of the immediate effects.**

Nifedipine is increasingly being used in the treatment of angina pectoris.[1-4] Based on experimental studies, nifedipine is believed to inhibit calcium ion influx across muscle cell membranes.[5] In vascular smooth muscle, this results in relaxation with subsequent vasodilation. In cardiac muscle, there is less contraction and a negative inotropic effect.[5,6] The following mechanisms might therefore contribute to the antianginal properties of nifedipine: (1) a reduction in myocardial oxygen consumption by a direct myocardial effect, (2) a decreased myocardial oxygen demand due to afterload reduction resulting from the dilation of peripheral resistance vessels, and (3) an increased coronary blood flow with a subsequent improved oxygen supply due to coronary vasodilation. These effects have never been verified in the intact resting heart in man. We therefore studied the effect of intravenous and intracoronary nifedipine on coronary sinus blood flow, coronary vascular resistance, and myocardial oxygen consumption in patients with chronic stable angina due to coronary artery disease.

A prolonged anti-ischemic activity of nifedipine during stress was recently reported in the absence of altered hemodynamic function. These data suggested a reduction in myocardial oxygen requirements without a change in the usual indexes of myocardial energy demand.[7] In order to evaluate this hypothesis, coronary sinus blood flow and myocardial oxygen consumption were measured during rapid atrial pacing before and after intracoronary nifedipine administration.

## Methods

**Patients:** The study was performed on 20 patients, 19 men and 1 woman, undergoing routine cardiac catheterization for chronic stable angina. Coronary artery disease was defined as >60% diameter reduction of 1 or more major coronary arteries. Patient data are summarized in Table I.

**Protocol:** Drug treatment was withheld for 48 hours before study. Cardiac catheterization was performed with the patient in the fasting state without premedication. Right- and left-sided heart catheterization, single-plane ventriculography, and selective coronary angiography in multiple projections were performed by way of the femoral route. A preshaped coronary sinus catheter with 2 thermistors and bipolar pacing

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**TABLE I Clinical and Diagnostic Data**

| Patient | Age (yr) & Sex | LVEDP (mm Hg) | CI (liters/min/m$^2$) | EF (%) | CAD Ventriculography |
|---|---|---|---|---|---|
| | | | Intravenous Nifedipine | | |
| 1 | 62M | 12 | 2.6 | 44 | LAD, LC, RC Ant aneur |
| 2 | 60M | 14 | 2.6 | 50 | LAD, LC, RC Diff hyp |
| 3 | 57M | 8 | 4.1 | 79 | LAD N |
| 4 | 65M | 16 | 2.8 | 52 | LAD, LC, RC Ant hyp |
| 5 | 52M | 14 | 2.8 | 45 | LAD Ant ak |
| 6 | 49M | 9 | 3.5 | 70 | LAD N |
| 7 | 47M | 8 | 3.0 | 69 | LAD N |
| 8 | 57M | 8 | 3.2 | 68 | LAD, LC N |
| 9 | 52M | 5 | 2.7 | 69 | LAD, LC N |
| 10 | 51M | 10 | 3.1 | 56 | LAD, LC Inf hyp |
| | | | Intracoronary Nifedipine | | |
| 11 | 45M | 11 | 2.6 | 60 | LAD, RC Inf hyp |
| 12 | 62M | 12 | 3.8 | 75 | LAD N |
| 13 | 60M | 8 | 3.1 | 63 | LAD, RC N |
| 14 | 52M | 9 | 3.4 | 74 | LAD, LC N |
| 15 | 52M | 16 | 3.0 | 55 | LAD, LC, RC Inf hyp |
| 16 | 63M | 16 | 2.9 | 69 | LAD, RC N |
| 17 | 53F | 13 | 2.9 | 57 | LAD, RC Inf hyp |
| 18 | 44M | 8 | 3.5 | 65 | LAD N |
| 19 | 45M | 15 | 3.8 | 60 | LAD Ant hyp |
| 20 | 56M | 10 | 3.2 | 60 | LAD, LC, RC N |

Ant aneur = anterior aneurysm; Ant hyp = anterior hypokinesia; CAD = coronary artery disease; CI = cardiac index; Diff hyp = diffuse hypokinesia; EF = ejection fraction; Inf hyp = inferior hypokinesia; LAD = left anterior descending coronary artery; LC = left circumflex artery; LVEDP = left ventricular end-diastolic pressure; N = normal; RC = right coronary artery.

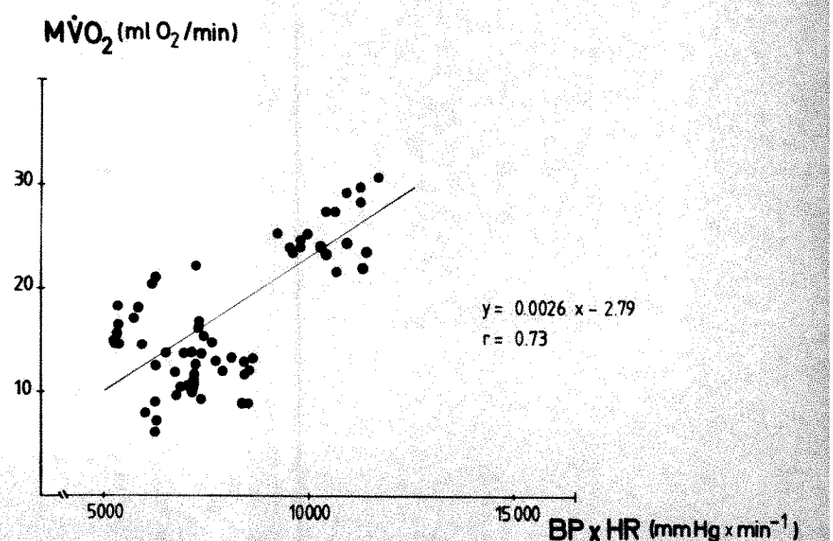



**FIGURE 1.** Correlation between myocardial oxygen consumption ($MVO_2$) and pressure-rate product before and after the intravenous infusion of 1.0 mg nifedipine. Four or 5 comparisons were obtained in each patient. $MVO_2$ values are not corrected for heart weight. BP × HR = peak systolic pressure times heart rate.

**TABLE II Response to Intravenous Nifedipine**

| | CSBF (ml/min) | CVR (mm Hg/ml/min) | $MVO_2$ (ml $O_2$/min) | $P_{AO}$ (mm Hg) | HR (beats/min) | BP × HR (mm Hg/min) |
|---|---|---|---|---|---|---|
| R | 131 ± 53 | 0.96 ± 0.40 | 17.1 ± 6.7 | 107 ± 10 | 74 ± 12 | 11,932 ± 2,426 |
| 2* | 186 ± 69† | 0.54 ± 0.19† | 16.5 ± 6.3 | 89 ± 10† | 88 ± 14† | 11,271 ± 2,472 |
| 4* | 154 ± 61‡ | 0.72 ± 0.27§ | 15.7 ± 7.0 | 99 ± 10† | 81 ± 14§ | 11,703 ± 2,576 |
| 6* | 124 ± 53 | 0.89 ± 0.32 | 16.0 ± 7.0 | 97 ± 10§ | 76 ± 14 | 11,167 ± 2,475 |
| 12* | 127 ± 47 | 1.00 ± 0.41 | 16.0 ± 7.1 | 102 ± 10‡ | 75 ± 13 | 11,825 ± 2,802 |

BP × HR = peak systolic pressure times heart rate; CSBF = coronary blood flow; CVR = coronary vascular resistance; HR = heart rate; $MVO_2$ = myocardial oxygen consumption; $P_{AO}$ = mean aortic pressure; R = at rest.
* Minutes after intravenous nifedipine infusion.
† $p = 0.001$.
‡ $p = 0.05$.
§ $p = 0.01$.

electrodes (type CCS- 7U-90B, Wilton Webster Laboratories, Altadena, California) was inserted from the right antecubital vein and placed in the coronary sinus so that the external thermistor was about 2 to 3 cm inside the coronary sinus. Catheter positions were frequently documented on videotape throughout the study. Changes in catheter position could therefore be ruled out. There was at least a 15-minute interval between the last injection of contrast medium for diagnostic coronary angiography and coronary sinus flow measurements.

The effect of intravenous nifedipine was studied on the first 10 patients. Coronary sinus blood flow and myocardial oxygen consumption were determined at rest. One mg of nifedipine in a 10 ml solution was continuously infused within 2 minutes.

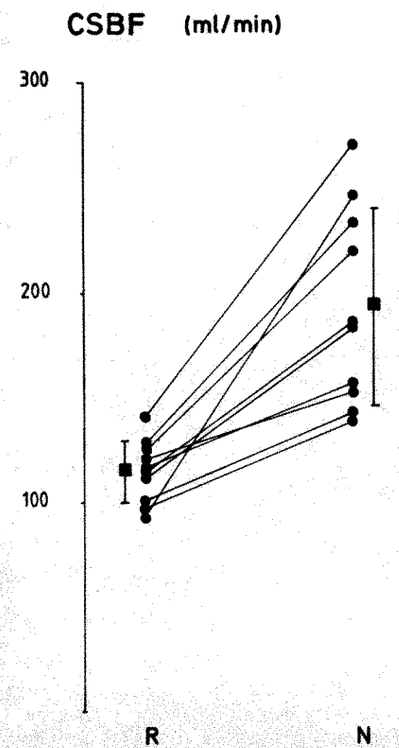



**FIGURE 2.** Coronary sinus blood flow (CSBF) before (R) and 1 minute after the intracoronary injection of 0.1 mg nifedipine (N). Each patient's individual response is shown.

Coronary sinus flow and the corresponding oxygen saturations were measured immediately after the infusion and after 4, 6, and 12 minutes. Heart rate and aortic pressure were continuously monitored.

The second group of 10 patients received intracoronary nifedipine. Coronary sinus flow and myocardial oxygen consumption were again determined at rest. The patients were then paced beyond the angina pectoris threshold or until a frequency-dependent atrioventricular block appeared. The mean pacing rate was 118 ± 6 beats/min. Right atrial pressure did not change during pacing. Coronary sinus reflux could therefore be excluded.[8] After determining coronary sinus flow and myocardial oxygen consumption, there was a brief recovery period for the heart rate to return to basal levels. Thereafter, 0.1 mg nifedipine was injected into the left coronary artery within 10 seconds and coronary sinus flow and myocardial oxygen consumption were measured after 1, 3, and 5 minutes. Patients were then paced with their individual preinjection pacing rates and coronary sinus flow and myocardial oxygen consumption measurements repeated.

**Calculations:** Coronary sinus blood flow was measured by the constant infusion thermodilution technique.[9] Arterial and coronary sinus blood samples were simultaneously drawn for the determination of oxygen saturation and content. Oxygen saturation was measured using an AO-Oximeter (American Optical, Bedford, Massachusetts). The coronary arteriovenous oxygen difference ($AVO_2$) was calculated as follows: $AVO_2 = (SAO_2 - SCSO_2) \times 1.34 \times Hb$, where $SAO_2$ = arterial oxygen saturation, $SCSO_2$ = coronary sinus blood oxygen saturation, 1.34 = oxygen carrying capacity of hemoglobin, and Hb = hemoglobin concentration. Myocardial oxygen consumption was calculated as the product of coronary sinus blood flow and the coronary arteriovenous oxygen difference. Coronary vascular resistance was derived from the ratio of mean aortic pressure to coronary sinus blood flow.

## Results

**Intravenous nifedipine:** Coronary sinus blood flow increased from 131 ± 53 to 186 ± 69 ml/min after completing the infusion of 1.0 mg nifedipine ($p < 0.001$). Coronary vascular resistance decreased from 0.96 ± 0.40 to 0.54 ± 0.19 mm Hg/ml/min ($p < 0.001$). Mean aortic pressure decreased from 107 ± 10 to 89 ± 10 mm Hg ($p < 0.001$) and the heart rate increased from 74 ± 12 to 88 ± 14 beats/min ($p < 0.001$). Six minutes after initiation of the infusion, coronary sinus blood flow, coronary vascular resistance, and heart rate had returned to preinfusion values. Mean aortic pressure remained low for 12 minutes ($p < 0.05$). Myocardial oxygen con-

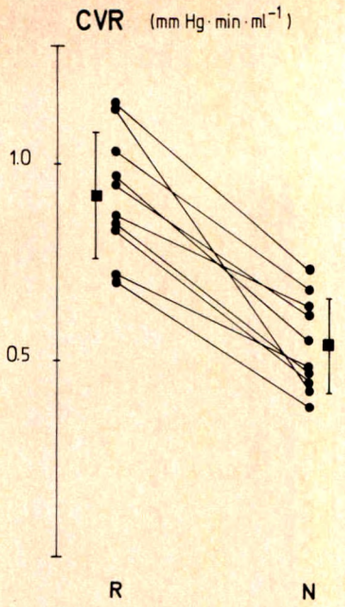



**FIGURE 3.** Coronary vascular resistance (CVR) before (R) and 1 minute after the intracoronary injection of 0.1 mg of nifedipine (N).

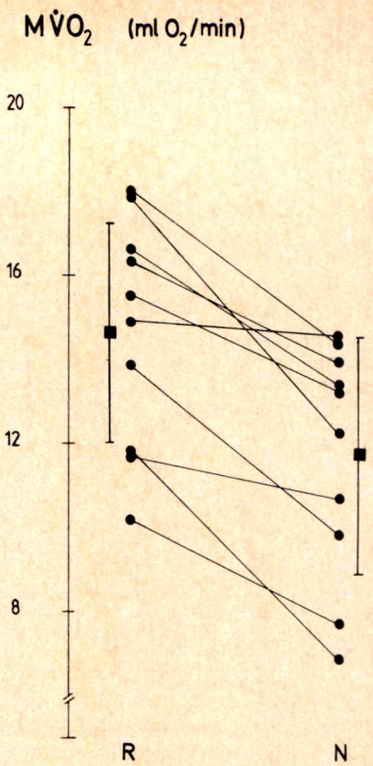



**FIGURE 4.** Myocardial oxygen consumption ($MVO_2$) before (R) and 1 minute after the intracoronary injection of 0.1 mg of nifedipine (N).

sumption decreased slightly from 17.1 ± 6.7 to 16.5 ± 6.3 ml $O_2$/min ($p < 0.3$). There were no significant changes in the rate-pressure product. Mean values are shown in Table II. There was a linear correlation between myocardial oxygen consumption and the rate-pressure product ($r = 0.73$, Fig. 1).

**Intracoronary nifedipine:** One minute after the intracoronary injection of 0.1 mg nifedipine, coronary sinus blood flow increased from 115 ± 15 to 193 ± 47 ml/min ($p < 0.001$) and coronary vascular resistance decreased from 0.92 ± 0.16 to 0.54 ± 0.12 mm Hg/ml/min ($p < 0.001$). A reduction in coronary vascular resistance with a subsequent increase in flow occurred in all patients studied (Fig. 2 and 3).

Intracoronary injection led to a significant reduction in myocardial oxygen consumption (from a mean of 14.6 ± 2.6 to 11.7 ± 2.8 ml $O_2$/min, $p < 0.05$, Fig. 4). This was accompanied by a decrease in mean aortic pressure from 107 ± 5 to 99 ± 3 mm Hg ($p < 0.01$). There were no significant changes in heart rate (72 ± 9 versus 74 ± 12 beats/min). In 6 of 10 patients, coronary sinus blood flow and myocardial oxygen consumption had returned to resting values 3 minutes after the intracoronary injection. After 5 minutes, coronary flow (113 ± 18 ml/min) and myocardial oxygen consumption (14.9 ± 3.1 ml $O_2$/min) stabilized at preinjection levels. Mean aortic pressure was not significantly different from control values after 3 (108 ± 6 mm Hg) and 5 minutes (108 ± 13 mm Hg).

**Atrial pacing:** During rapid atrial pacing (mean rate 118 ± 6 beats/min), coronary sinus blood flow and myocardial oxygen consumption increased to 172 ± 62 ml/min and 19.8 ± 5.0 ml $O_2$/min, respectively. Similar coronary sinus flow (177 ± 69 ml/min) and myocardial oxygen consumption values (20.6 ± 7.3 ml $O_2$/min) were obtained when the patients were paced at their individual preinjection pacing rates approximately 6 minutes after the intracoronary nifedipine administration (Fig. 5 and 6). There were no differences in the mean aortic pressure during the 2 pacing periods (108 ± 6 versus 109 ± 7 mm Hg).

## Discussion

**Coronary effects of nifedipine:** Intracoronary and intravenous nifedipine resulted in a marked increase in coronary flow. The increase in blood flow was more pronounced after the intracoronary injection of 0.1 mg nifedipine than after the intravenous infusion of 1.0 mg (a mean of 70 versus 44%). Both intravenous and intracoronary nifedipine reduced coronary vascular resistance to almost the same level. Differences in flow are due to different coronary perfusion pressures. Intravenous nifedipine produced a marked and sustained decrease in mean aortic pressure, while intracoronary nifedipine only resulted in moderate and transient pressure changes. Since only changes in the entire left ventricular outflow can be detected by the thermodilution technique,[10] our data do not permit an analysis of regional perfusion patterns or a correlation between individual responses to nifedipine and the severity and distribution of coronary arterial stenoses.

The changes in coronary vascular resistance observed in this study represent the combined effect of nifedipine on large epicardial conductance vessels and small intramural resistance vessels. In the presence of eccentric stenosis, resistance in the extramural conductance vessels may be a combination of the luminal narrowing

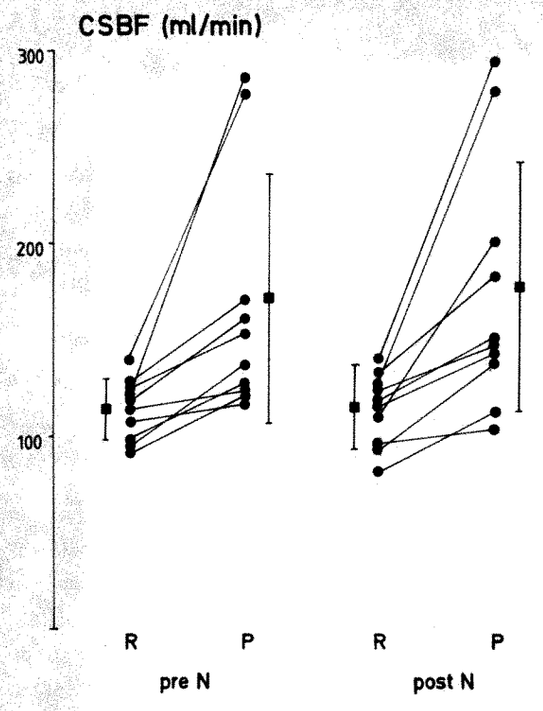



**FIGURE 5.** Coronary sinus blood flow (CSBF) at rest (R) and during rapid atrial pacing (P) before (pre N) and about 6 minutes after the intracoronary injection of 0.1 mg nifedipine (post N). Individual pacing rates were identical during the 2 pacing periods.

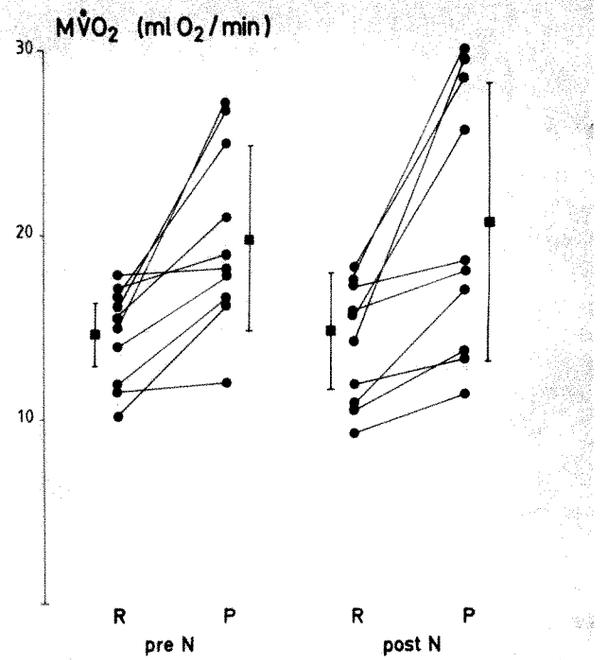



**FIGURE 6.** Myocardial oxygen consumption ($M\dot{V}O_2$) at rest (R) and during rapid atrial pacing (P) before (pre N) and about 6 minutes after the intracoronary injection of 0.1 mg of nifedipine (post N).

caused by the fixed lesion and the degree of coronary artery constriction in the normal arterial wall opposite the organic lesion. Recent data indicate that the degree of stenosis can be influenced pharmacologically.[11] This effect might contribute to the increase in poststenotic coronary blood flow after nifedipine administration.[12] Coronary flow returned to basal levels within about 5 minutes after intracoronary nifedipine administration. However, prolonged dilation of large epicardial coronary arteries after the intracoronary injection of 0.1 mg nifedipine has been documented by angiography.[13] This implies that nifedipine predominantly results in a sustained relaxation of the epicardial conductance vessels, while intramural arterioles are only transiently dilated.

**Nifedipine and myocardial oxygen consumption:** There were no significant changes in myocardial oxygen consumption after the intravenous infusion of 1 mg of nifedipine. The rate-pressure product, generally accepted as a reliable predictor of myocardial energy requirements,[14] also did not change significantly. There was a linear correlation between myocardial oxygen consumption and the double product. The potential oxygen-saving effect of nifedipine due to an afterload reduction was therefore counteracted by a reflex tachycardia.

This mechanism is potentially dangerous in patients with severely stenosed coronary arteries. A detrimental effect of high doses of nifedipine on regional myocardial perfusion has been observed in animals with subtotally occluded coronary arteries.[15] This is explained by a decrease in diastolic perfusion pressure, a shortening of the diastolic perfusion time, and an exhaustion of the poststenotic coronary vascular reserve at basal levels.

In contrast to this, the intracoronary injection of 0.1 mg nifedipine resulted in a significant reduction of myocardial oxygen consumption. Since intravenous injection of the same dose did not induce any hemodynamic changes,[7] the decrease in myocardial oxygen consumption results from a direct negative inotropic effect of nifedipine, which is unmasked by the absence of indirect peripheral effects. A higher local concentration of nifedipine might also be important. In accordance with this, selective intrabypass injections in patients with successful aortocoronary bypass grafting revealed a delay in shortening in regional wall motion in areas directly supplied by the injected bypass, while contraction in normally perfused areas remained unchanged.[16]

**Nifedipine and stress:** A significant reduction in exercise-induced S-T segment depression has been reported in patients with severe coronary artery disease after intracoronary infusion of 0.1 mg nifedipine.[7] Earlier studies on different calcium-channel blockers during pacing-induced angina also revealed antianginal activity without altered hemodynamic function.[17] These findings suggested a reduced myocardial oxygen consumption without changes in the usual indexes of myocardial oxygen demand. Myocardial oxygen consumption was not assessed directly in these studies.

Our data contradict this hypothesis. Both coronary sinus blood flow and myocardial oxygen consumption reached identical levels during atrial pacing before and

6 minutes after intracoronary injection. There was no evidence of a metabolically mediated, sustained oxygen-saving effect of nifedipine after the cessation of its immediate effects.

**Implications:** The intracoronary administration of nifedipine will be increasingly used during routine coronary angiography and reperfusion of acute myocardial infarction. It permits us to distinguish an organic lesion from a functional one and to determine to what extent a functional component contributes to the significance of a critical lesion.[13] It enables us to rule out coronary arterial spasm as the cause of acute myocardial ischemia.[4] Intracoronary nifedipine provides antiischemic action by decreasing myocardial oxygen consumption while increasing coronary flow. After systemic administration, nifedipine has comparable effects on coronary vascular resistance. However, a reduction in myocardial oxygen consumption can only be expected when an increase in heart rate does not take place.

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## References

1. **Goldberg S, Reichek N, Wilson J, Hirshfeld JW, Muller J, Kaster JA.** Nifedipine in the treatment of Prinzmetal's (variant) angina. Am J Cardiol 1979;44:804–810.
2. **Moskowitz RM, Piccini PA, Nacarelli GV, Zelis R.** Nifedipine therapy for stable angina pectoris: preliminary results of effects on angina frequency and treadmill exercise response. Am J Cardiol 1979;44:811–816.
3. **Lynch P, Dargie H, Krikler S, Krikler D.** Objective assessment of antianginal treatment: a double blind comparison of propranolol, nifedipine and their combination. Br Med J 1980;281:184–187.
4. **Hugenholtz PG, Michels HR, Serruys PW, Brower RW.** Nifedipine in the treatment of unstable angina, coronary spasm and myocardial ischemia. Am J Cardiol 1981;47:163–173.
5. **Fleckenstein A.** On the basic pharmacological mechanism of nifedipine and its relation to therapeutic efficacy. In: Jatene AD, Lichtlen PR, eds. New Therapy in Ischemic Heart Disease. Amsterdam: Excerpta Medica, 1976:1–13.
6. **Vater W.** Myocardial oxygen consumption under the influence of nifedipine in the anesthetized dog. In: Lochner W, ed. Second International Nifedipine Symposium. Heidelberg, West Germany: Springer, 1975:77–81.
7. **Kaltenbach M, Schulz W, Kober G.** Effects of intravenous and intracoronary administration of nifedipine. Am J Cardiol 1979;44:832–836.
8. **Mathey DG, Chatterje K, Tyberg IV, Cekvon J, Brundoge B, Parmley W.** Coronary sinus reflux. Circulation 1978;57:778–786.
9. **Ganz W, Tamura K. Marcus H, Konoso R, Yoshida S, Sevan H.** Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971;44:181–195.
10. **Klocke FJ.** Coronary blood flow in man. Prog Cardiovasc Dis 1976;19: 117–166.
11. **Brown BG, Bolson E, Petersen RB, Pierce CD, Dodge HD.** The mechanism of nitroglycerin action: stenosis vasodilatation as a major component of the drug response. Circulation 1981;64:1089–1097.
12. **Lichtlen PR, Engel HJ, Wolf R, Amende I.** The effect of the calciumantagonistic drug nifedipine on coronary and left ventricular dynamics in patients with coronary heart disease. In: Fleckenstein A, Roskamm H, eds. Calcium-Antagonismus. Heidelberg, West Germany: Springer, 1980: 270–281.
13. **Schulz W, Kober G, Krauss G, Kaltenbach M.** Influence of intracoronary and intravenous nifedipine on diameters of coronary vessels and stenoses. In: Raffienbeul W, Lichtlen RR, Balcon R, eds. Unstable angina pectoris. Stuttgart, West Germany: Georg Thieme, 1981:259–265.
14. **Klocke FJ, Ellis AK.** Control of coronary blood flow. Ann Rev Med 1980; 31:489–508.
15. **Selwyn AP, Jonathan A, Fox KM, Pratt T.** The use of nifedipine in myocardial ischemia and angina pectoris. In: Puech P, Koch R, eds. New Therapy of Ischemic Heart Disease. Amsterdam: Excerpta Medica, 1980:207–211.
16. **Serruys PW, Brower RW, den Katen HJ, Born AH, Hugenholtz PG.** Regional wall motion from radiopaque markers after intravenous and intracoronary injection of nifedipine. Circulation 1981;63:584–591.
17. **Pepine C, Schang S, Bemiller C.** Alteration of left ventricular response to ischemia with oral perhexiline. Postgrad Med J 1973;49(Suppl 3):43–46.

# Electrocardiographic Criteria for the Diagnosis of Combined Inferior Myocardial Infarction and Left Anterior Hemiblock

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**New electrocardiographic (ECG) criteria for diagnosing the combination of inferior myocardial infarction and left anterior hemiblock are proposed. The proposed criteria are based upon the relations between portions of the vectorcardiographic QRS loop in the frontal plane and the corresponding portions of the QRS complexes recorded by the limb leads. The application of the proposed criteria requires that the tracings be obtained with 3-channel ECG machines. The proposed criteria for the diagnosis of inferior myocardial infarction and left anterior hemiblock are as follows: (1) leads aVR and aVL both end in R waves, with the peak of the terminal R wave in lead aVR occurring later than the peak of the terminal R wave in lead aVL, and (2) a Q wave of any magnitude is present in lead II. The performance of the proposed criteria was superior to that of 10 combinations of traditional ECG criteria for inferior myocardial infarction and left anterior hemiblock.**

The diagnosis of the combination of inferior myocardial infarction and left anterior hemiblock is difficult when traditional methods of electrocardiographic (ECG) analysis are used. However, several groups of investigators have shown the vectorcardiogram to be more reliable than the electrocardiogram for this purpose.[1–6] This is because each of the 2 abnormalities is associated with a characteristically different contour of the vectorcardiographic (VCG) QRS loop in the frontal plane. Whereas both inferior myocardial infarction and left anterior hemiblock produce deviations of portions of the loop superiorly, the former results specifically in clockwise rotation of the initial forces.[7–10] Since the latter causes counterclockwise rotation of the loop, the combination of the 2 abnormalities is manifested by clockwise rotation of the initial portion, followed by counterclockwise rotation of the terminal portion of the QRS loop in the frontal plane.[1–6]

In the present study, new electrocardiographic criteria for diagnosing inferior myocardial infarction and left anterior hemiblock are described. The proposed criteria are based upon the relations between the limb leads of the scalar electrocardiogram and the VCG loop in the frontal plane and permit important features of the contour of the VCG loop to be inferred from the electrocardiogram. Applying the proposed criteria requires that the tracings be obtained using 3-channel ECG machines. These machines, which have been widely used for several years, permit analysis of the temporal relations among corresponding portions of simultaneously recorded QRS complexes.

## Methods

### Selection of Patients

Two groups of patients were selected to evaluate the performance of the proposed criteria for inferior myocardial infarction and left anterior hemiblock. The patients in Group I were selected on the basis of angiographic and VCG evidence

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of inferior myocardial infarction or left anterior hemiblock, or both. The patients in Group II were selected on the basis of serial ECG changes that were obtained under clinical circumstances in which the development of, respectively, inferior myocardial infarction alone, left anterior hemiblock alone, and inferior myocardial infarction and left anterior hemiblock was likely.

**Group I:** A total of 163 male patients, aged 26 to 82 years (mean 61), who had undergone both vectorcardiography and cardiac catheterization at the Syracuse Veterans Administration Medical Center between April 17, 1978 and March 1, 1982 were included in this group. Of these, 30 patients (Subgroup IA) had angiographic and VCG evidence of inferior myocardial infarction and VCG evidence of left anterior hemiblock. The 133 patients in Subgroup IB had either angiographic and VCG evidence of inferior myocardial infarction without left anterior hemiblock (29 patients), angiographic and VCG evidence of left anterior hemiblock without inferior myocardial infarction (53 patients), or angiographic and VCG evidence of the absence of both inferior myocardial infarction and left anterior hemiblock (51 patients).

The angiographic evidence of inferior myocardial infarction consisted of a ≥75% obstruction of the dominant coronary artery and either asyneresis, akinesia, or dyskinesia of the inferior wall of the left ventricle. The VCG criteria for inferior myocardial infarction that were used were those of Starr et al.[7] These VCG criteria were chosen because they were shown in a recent report to have the highest overall accuracy for diagnosing inferior myocardial infarction of 3 sets of criteria tested.[9] The VCG criteria used for diagnosing left anterior hemiblock were those of Benchimol et al.[11] Although all of the patients in Group 1 also had scalar electrocardiograms obtained, the patients were assigned to either Subgroup IA or IB only on the basis of their angiographic and VCG findings.

**Group II:** In order to confirm the high degrees of sensitivity and specificity exhibited by the proposed criteria when the data from Group I were analyzed (see later), serial electrocardiograms from an additional group of 185 patients (136 men and 49 women, aged 28 to 84 years) were studied. The patients in Group II had been patients at 1 of the following hospitals in Syracuse, New York between July 1, 1975 and March 1, 1982: the Veterans Administration Medical Center, the State University Hospital, or the Crouse-Irving Memorial Hospital.

*Subgroup IIA:* This subgroup consisted of 35 patients with acute anterior myocardial infarction manifested by a typical clinical history, elevation of cardiac enzymes, and the development of S-T segment elevation and Q waves in ECG leads $V_1$ through $V_4$, but without concomitant S-T segment elevation or Q waves in leads II, III, or aVF. During the evolution of the ECG changes of anterior infarction, each patient developed leftward deviation of the frontal plane QRS axis which was not initially present. In each patient, atrioventricular block also occurred in the course of the evolution of the infarction. The QRS complexes analyzed were those of supraventricular beats recorded after leftward deviation of the axis had occurred, but before they had become longer than 100 ms in duration. Therefore, artificially paced complexes, idioventricular complexes, and complexes showing right or left bundle branch block were excluded.

*Subgroup IIB:* This subgroup consisted of 133 patients with acute inferior myocardial infarction manifested by a typical history, elevation of cardiac enzymes, and the development of S-T segment elevation and Q waves in ECG leads II, II, and aVF, but without the concomitant appearance of S-T segment elevation or Q waves in leads $V_1$, $V_2$, $V_3$, or $V_4$. In the tracings obtained before the changes of inferior myocardial infarction, none of the patients had QRS complexes in leads aVR and aVL that both ended in R waves. The electrocardiograms analyzed were those of each patient that showed the greatest degree of leftward deviation of the frontal plane QRS axis that developed in the evolution of the changes of inferior myocardial infarction.

*Subgroup IIC:* This subgroup consisted of 17 patients who met the same criteria for selection as those of Subgroup IIB, except for the following: in the tracings obtained before the changes of inferior myocardial infarction, each of the patients of Subgroup IIC had QRS complexes in leads aVR and aVL that both ended in R waves, with the peak of the terminal R wave in lead aVL preceding the peak of the terminal R wave in lead aVR.

## Collection of Data

The vectorcardiograms were recorded using the Frank lead system and an Instruments for Cardiac Research model 1001 vectorcardiograph. The electrocardiograms were recorded using 12 standard leads and either a Marquette MAC 1-T or Hewlett-Packard model 1517-A electrocardiograph at a paper speed of 25 mm/s. These machines use 3 channels and simultaneously record leads I, II, and III; then leads aVR, aVL, and aVF; then leads $V_1$, $V_2$, and $V_3$; and finally leads $V_4$, $V_5$, and $V_6$. All recordings were made at a paper speed of 25 mm/s. In order to be certain that all 3 channels were operating simultaneously, the relative times of onset of the 1.0 mV standardization marks were inspected. If the times of onset of the standardization marks were not identical, a correction for the discrepancy was made when the QRS complexes were analyzed. For example, if the standardization mark in channel 2 began 10 ms before the marks in channels 1 and 3, the QRS complexes in leads II and aVL were considered to have actually begun 10 ms later than they appeared on the tracing.

## Rationale for the Proposed Criteria

The relations between the VCG QRS loop in the frontal plane and the scalar electrocardiogram in a typical patient with inferior myocardial infarction and left anterior hemiblock are shown in Figure 1. The figure shows that important features of the contour of the VCG loop can be inferred by analyzing the simultaneously-recorded pairs of ECG leads. On the basis of the illustrated relations, new ECG criteria for diagnosing inferior myocardial infarction and left anterior hemiblock are proposed; these are listed in Table I.

## Comparison of Electrocardiographic Criteria

In order to provide a comprehensive basis for evaluating the proposed criteria, the electrocardiograms were also interpreted according to 5 sets of traditional criteria for diagnosing inferior myocardial infarction and 2 sets of traditional criteria for diagnosing left anterior hemiblock. The comparison criteria for inferior myocardial infarction that were chosen are as follows: (1) Q waves of at least 30 ms duration in leads II, III, and aVF (2, 3, aVF criterion)[7]; (2) Q wave of at least 30 ms duration in lead aVF without regard to leads II and III (aVF criterion)[7]; (3) the criteria of Myers et al[12]; (4) the criteria of Walsh et al[13]; and (5) the criteria of the New York Heart Association.[14]

The comparison criteria for diagnosing left anterior hemiblock were as follows: (1) frontal plane QRS axis between −30° and −90° < −30° criterion; and (2) frontal plane QRS axis between −45° and −90° < −45° criterion.

Because the electrocardiograms were interpreted according to each of 5 sets of comparison criteria for inferior myocardial infarction in addition to each of 2 comparison criteria for left anterior hemiblock, a total of 10 combinations of comparison criteria were used.

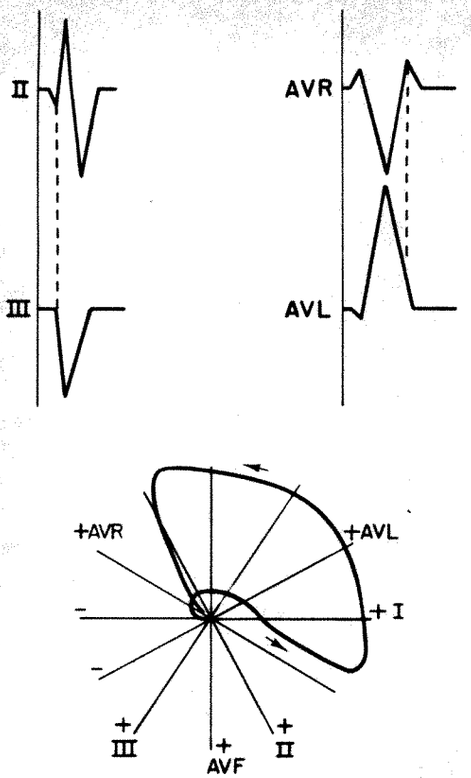



**FIGURE 1.** Diagram of a VCG QRS loop in the frontal plane of a tracing that reveals the combination of inferior infarction and left anterior hemiblock, with the hexaxial reference figure superimposed upon it. The **arrows** show that the initial portion of the loop is clockwise and the terminal portion is counterclockwise. The initial portion of the loop is maximally represented on the negative half of the axis of lead II before it is maximally represented on the negative half of the axis of lead III. Therefore, the nadir of the Q wave in lead II occurs before the nadir of the Q wave lead III. If the initial clockwise portion of the VCG loop were to travel inferiorly and to the right for a short time before going superior to the E point (thus still meeting the VCG criteria for inferior infarction of Starr et al), lead III would begin with a small R wave rather than with a Q wave. In the latter case, the peak of the initial R wave in lead III would precede the nadir of the Q wave in lead II. The terminal portion of the loop is maximally represented on the positive half of the axis of lead aVL before it is maximally represented on the positive half of the axis of lead aVR. Therefore, the peak of the R wave in lead aVL occurs before the peak of the R wave in lead aVR.

## Analysis of Data

The relative odds, that is, the odds of being a case among patients who have positive results relative to the odds among those who have negative results, were chosen to measure the diagnostic capabilities of the proposed and comparison ECG criteria. The measurement of relative odds incorporates both the sensitivity and specificity of a test and is not affected by the prevalence of cases in the population being evaluated. It is defined by the following formula: Relative odds = [(sensitivity) (specificity)]/[(1 − sensitivity) (1 − specificity)]. When the sensitivity and/or specificity = 1, the denominator of the expression is assigned a value of 1.

In addition, for patients with discordant predictions by the proposed versus traditional criteria, the hypothesis of no difference in performance was evaluated by the sign test corrected for continuity.[15] In order to control the type I error for multiple tests, two-tailed p values <0.01 were taken to indicate statistical significance at the joint 5% level.

**TABLE I Proposed Electrocardiographic Criteria for the Diagnosis of the Combination of Inferior Myocardial Infarction and Left Anterior Hemiblock**

1. Leads aVR and aVL both end in R waves, with the peak of the terminal R wave in lead aVR occurring later than the peak of the terminal R wave in lead aVL

AND

2. A Q wave of any magnitude is present in lead II

## Results

The performances of the proposed and all the combinations of comparison criteria in Groups I and II are summarized in Table II. As Table II shows, the proposed criteria were positive in all patients in Subgroups IA and IIC and were negative in all patients in Subgroups IB, IIA, and IIB. The comparison criteria that exhibited the best diagnostic performances (as indicated by having the highest values of relative odds) were the inferior myocardial infarction criteria of Walsh et al combined with the left anterior hemiblock criteria of $< -30°$ and $< -45°$, respectively. Therefore, it was these 2 combinations of criteria that were chosen for a more detailed comparison with the proposed criteria using the sign test corrected for continuity. The superiority of the proposed criteria over the Walsh et al $< -30°$ and the Walsh et al $< -45°$ criteria is significant at the $p < 0.005$ level in each case.

In all of the patients with left anterior hemiblock with or without inferior myocardial infarction, leads aVR and aVL ended in R waves and the peak of the R wave in lead aVL preceded the peak of the R wave in lead aVR. In all the patients with left anterior hemiblock alone, the QRS complexes in both leads II and III began with R waves. Only when inferior myocardial infarction was also present did any patient with left anterior hemiblock have a Q wave in lead II. Of the total of 162 patients with inferior myocardial infarction alone, 161 (99%) had Q waves in both leads II and III and, in each instance, the nadir of the Q wave in lead II preceded the nadir of the Q wave in lead III. Of the total of 47 patients with inferior myocardial infarction and left anterior hemiblock, 33 (70%) also had Q waves in both leads II and III with the nadir of the Q wave in lead II preceding the nadir of the Q wave in lead III. Of the remaining patient with inferior myocardial infarction alone and the remaining 14 patients with inferior myocardial infarction and left anterior hemiblock, the Q waves in lead II were associated with small initial R waves in lead III, with the peak of the latter preceding the nadir of the former. Thus, using the method of analysis shown in Figure 1, we could infer from the electrocardiogram that in all patients with inferior myocardial infarction either alone or in combination with left anterior hemiblock, the initial forces of ventricular depolarization were clockwise and predominantly superior. Similarly, we could infer that in all patients with left anterior hemiblock alone or in

**TABLE II Performances* of Criteria for the Diagnosis of the Combination of Inferior Infarction and Left Anterior Hemiblock**

| | | Percentage Correctly Identified by | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2, 3, aVF | | aVF | | Myers et al[12] | | Walsh et al[13] | | NYHA | |
| Subgroup | n | Proposed Criteria | < −30° | < −45° | < −30° | < −45° | < −30° | < −45° | < −30° | < −45° | < −30° | < −45° |
| IA cases | 30 | 100 | 10 | 7 | 30 | 23 | 20 | 13 | 43 | 30 | 23 | 17 |
| IB noncases | 133 | 100 | 98 | 99 | 98 | 99 | 98 | 99 | 98 | 99 | 98 | 99 |
| Relative odds | | 10,000:1 | 5.4:1 | 7.5:1 | 21:1 | 30:1 | 12:1 | 15:1 | 37:1 | 42:1 | 15:1 | 20:1 |
| IIC cases | 17 | 100 | 12 | 12 | 18 | 12 | 18 | 12 | 24 | 18 | 18 | 12 |
| IIA & B noncases | 168 | 100 | 93 | 96 | 93 | 96 | 95 | 96 | 93 | 96 | 93 | 96 |
| Relative odds | | 10,000:1 | 1.8:1 | 3.3:1 | 2.9:1 | 3.3:1 | 4.2:1 | 3.3:1 | 4.2:1 | 5.3:1 | 2.9:1 | 3.3:1 |

* The tabulated percentages are the sensitivities and specificities for the observed cases and noncases, respectively.

combination with inferior myocardial infarction, the terminal forces of ventricular depolarization were counterclockwise and superior.

## Discussion

One reason that it is difficult to diagnose inferior myocardial infarction and left anterior hemiblock using traditional methods of ECG analysis is that both abnormalities can result in deviation of the frontal plane QRS axis to the left. Another reason is that the presence of left anterior hemiblock commonly modifies the ECG manifestations of inferior myocardial infarction.[1,5,6] This is because left anterior hemiblock tends to direct the initial forces of ventricular depolarization inferiorly by way of the intact posterior fascicle.[5,6,16] Therefore, unless the inferior myocardial infarction happens to involve that portion of the left ventricular myocardium which is activated early by the posterior fascicle, the hemiblock reduces the propensity of the infarction to produce Q waves in the inferior leads. Our data support the contention that left anterior hemiblock tends to obscure some of the traditional manifestations of inferior myocardial infarction. Whereas 30% of our patients with inferior myocardial infarction and left anterior hemiblock did not have a Q wave in lead III, only 1% with inferior myocardial infarction alone failed to have a Q wave in that lead.

Several groups of investigators have described the importance of the respective contours of the initial and terminal portions of the VCG QRS loop in the frontal plane for diagnosing inferior myocardial infarction and left anterior hemiblock.[1–6] The data from the patients in Group I indicate that our method of analyzing the electrocardiogram permits us to infer the VCG findings that are important for making this diagnosis. The data from Group II confirm the high degrees of sensitivity and specificity of our criteria. Serial electrocardiograms obtained during the evolution of isolated acute anterior myocardial infarction that show the development of left axis deviation and subsequently of atrioventricular block (Subgroup IIA) make it likely that the left axis deviation is due to left anterior hemiblock. Conversely, patients with isolated inferior myocardial infarction (Subgroup IIB) would not be expected to have left anterior hemiblock during the evolution of acute infarction. All the patients in Subgroup IIA and none of the patients in Subgroup IIB developed terminal R waves in both leads aVR and aVL with the peak of the R wave in aVL preceding the peak of the R wave in lead aVR. We therefore used this set of findings in leads aVR and aVL as a marker of left anterior hemiblock. In a recent study of left anterior hemiblock unassociated with inferior myocardial infarction, our group used data from the same patients who comprise Subgroups IIA and IIB of the present study in addition to other data to show that the above marker of left anterior hemiblock was not also produced by other conditions reported to lead to false-positive diagnoses of left anterior hemiblock, namely isolated inferior myocardial infarction, left ventricular enlargement, alteration of the position of the heart within the thorax, or pulmonary emphysema.[17]

Hurd et al,[9] in a comparison of VCG and traditional ECG criteria for inferior myocardial infarction, demonstrated the diagnostic importance of the "contour information" provided by the vectorcardiogram.[9] The findings of the present study show that this "contour information" can also be obtained from the electrocardiogram. Our group has used similar principles of analysis to develop new ECG criteria for diagnosing inferior myocardial infarction in the absence of left anterior hemiblock.[18]

We evaluated the performance of the proposed criteria for inferior myocardial infarction and left anterior hemiblock using electrocardiograms that were recorded at standard paper speed and without comparing the electrocardiograms with tracings obtained previously from the same patients. The proposed ECG criteria duplicate the performance of the vectorcardiogram for detecting inferior myocardial infarction and left anterior hemiblock and therefore permit this diagnosis to be made reliably even when the vectorcardiogram is not readily available.

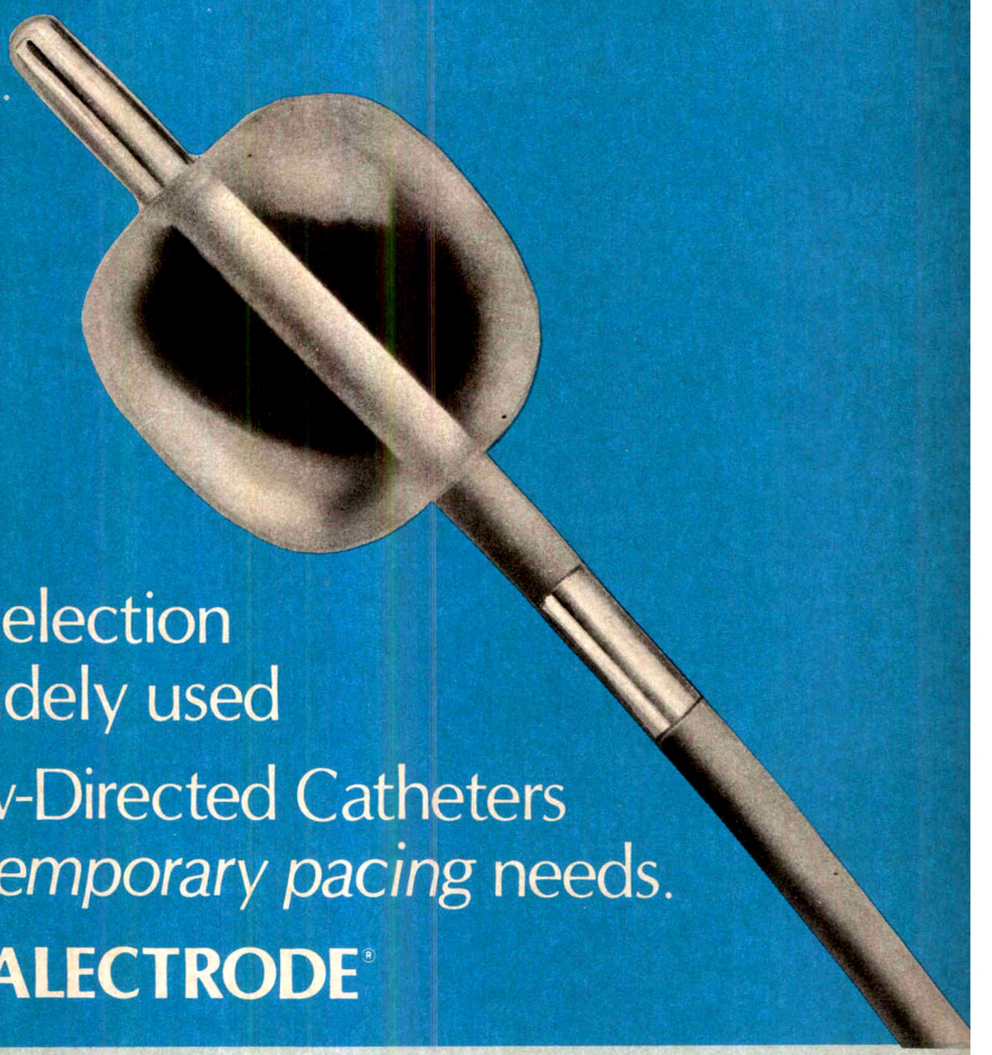
## References


1. **Benchimol A, Desser KB, Schumacher J.** Value of the vectorcardiogram for distinguishing left anterior hemiblock from inferior infarction with left axis deviation. Chest 1972;61:74–76.
2. **Benchimol A, Desser KB, Massey BJ.** Coexisting left anterior hemiblock and inferior wall myocardial infarction. Am J Cardiol 1972;29:7–14.
3. **Kulbertus HE, Collignon P, Humblet L, Deleval-Rutten F.** Left axis deviation in inferior infarction; vectorcardiographic recognition of concomitant left anterior hemiblock. Chest 1971;60:362–366.
4. **Kohn PM, Harris AH.** Vectorcardiographic analysis of left axis deviation

in the differentiation of diaphragmatic infarction and parietal block. Dis Chest 1965;47:492–502.
5. **Castellanos A, Lemberg L, Sung RJ, Myerburg RJ.** Dynamic vectorcardiography in the evaluation of left hemiblocks. In: Hoffman I, Hamby RI, eds. Vectorcardiography 3. Amsterdam: North-Holland, 1976:99–111.
6. **Castellanos A, Chahine RA, Chapunoff E, Gomez J, Portillo B.** Diagnosis of left anterior hemiblock in the presence of inferior wall myocardial infarction. Chest 1971;60:543–551.
7. **Starr JW, Wagner GS, Behar VS, Walston A, Greenfield JC.** Vectorcardiographic criteria for the diagnosis of inferior myocardial infarction. Circulation 1974;49:829–836.
8. **Young E, Williams C.** The frontal plane vectorcardiogram in old inferior myocardial infarction. Circulation 1968;37:604–623.
9. **Hurd HP, Starling MR, Crawford MH, Diabal PW, O'Rourke RA.** Comparative accuracy of electrocardiographic and vectorcardiographic criteria for inferior myocardial infarction. Circulation 1981;63:1025–1029.
10. **Witham AC.** VCG patterns of myocardial scarring in the absence of diagnostic Q waves. In: Schlant RC, Hurst JW, eds. Advances in Electrocardiography. Vol 2. New York: Grune & Stratton, 1976;245–262.
11. **Benchimol A, Barreto EC, Pedraza A.** The Frank vectorcardiogram in left anterior hemiblock. J Electrocardiol 1971;4:116–128.
12. **Myers GB, Klein HA, Hiratzka TV.** Correlation of electrocardiographic and pathologic findings in posterior infarction. Am Heart J 1949;38:547–592.
13. **Walsh TJ, Tiongson PM, Stoddard EA, Massie E.** The vectorcardiographic QRS E-loop findings in inferoposterior myocardial infarction. Am Heart J 1962;63:516–527.
14. The Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Heart Vessels. 8th ed. Boston: Little, Brown, 1979:91–95.
15. **Steel RGD, Torrie JH.** Principles and Procedures of Statistics. 2nd ed. New York: McGraw-Hill, 1980;538–539.
16. **Rosenbaum MB, Elizari MV, Lazzari JO.** The Hemiblocks. Oldsmar, FL: Tampa Tracings, 1970;73,223,227.
17. **Warner RA, Hill NE, Mookherjee S, Smulyan H.** Improved electrocardiographic criteria for the diagnosis of left anterior hemiblock. Am J Cardiol 1983;51:723–726.
18. **Warner R, Hill NE, Sheehe PR, Mookherjee S, Fruehan CT, Smulyan H.** Improved electrocardiographic criteria for the diagnosis of inferior myocardial infarction. Circulation 1982;66:422–428.

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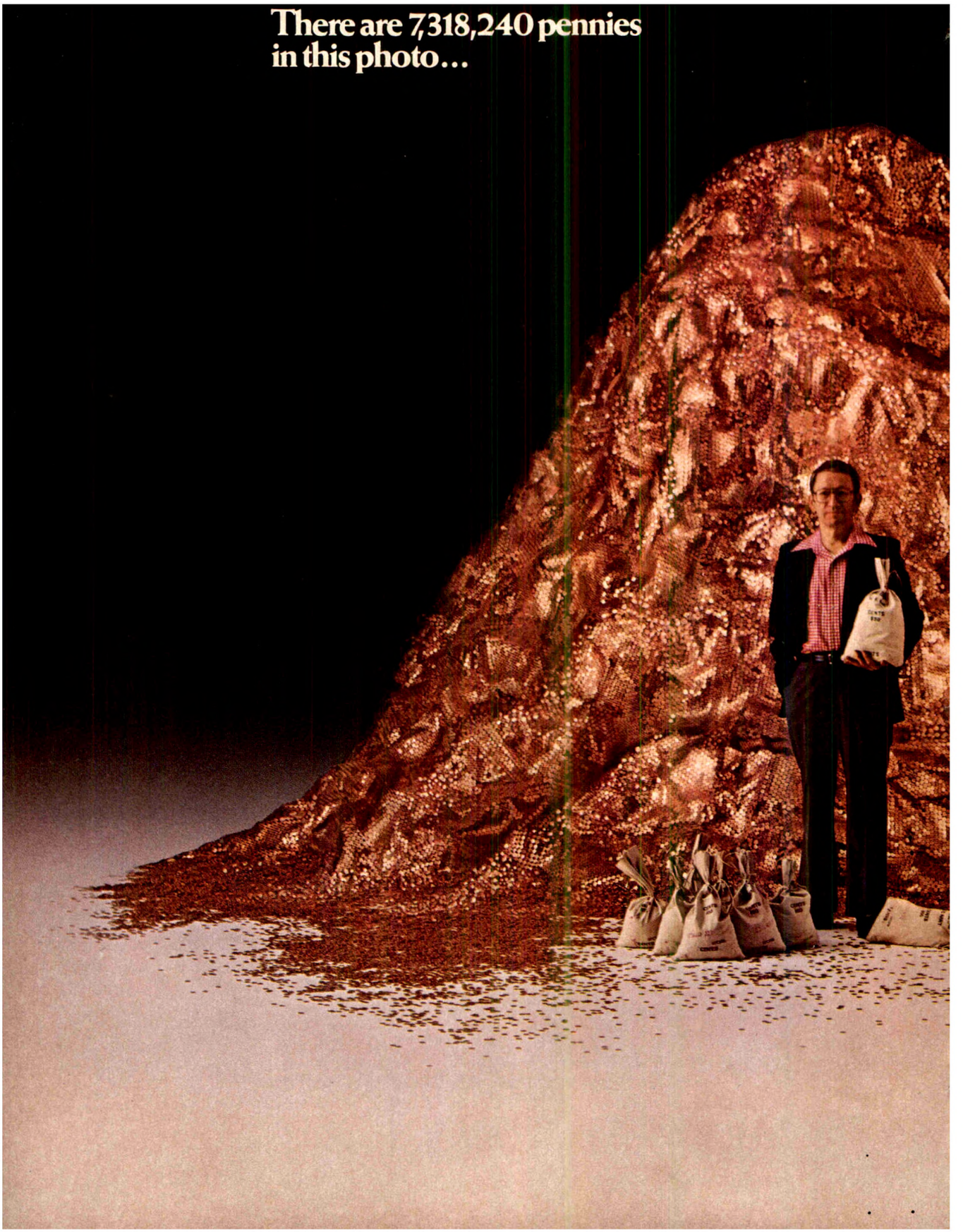
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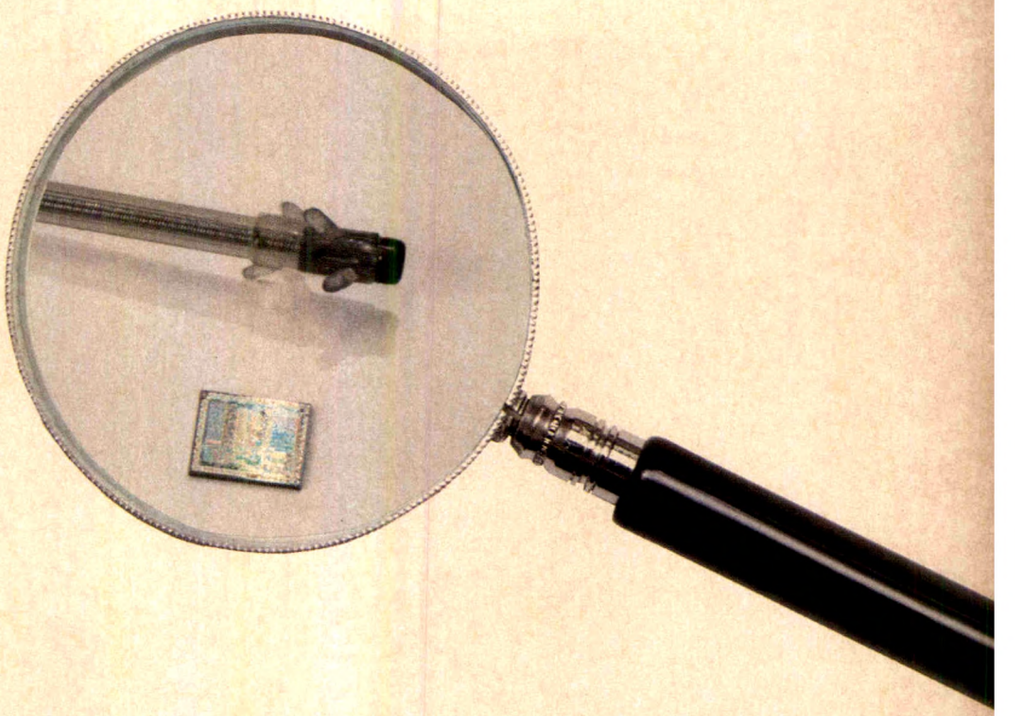
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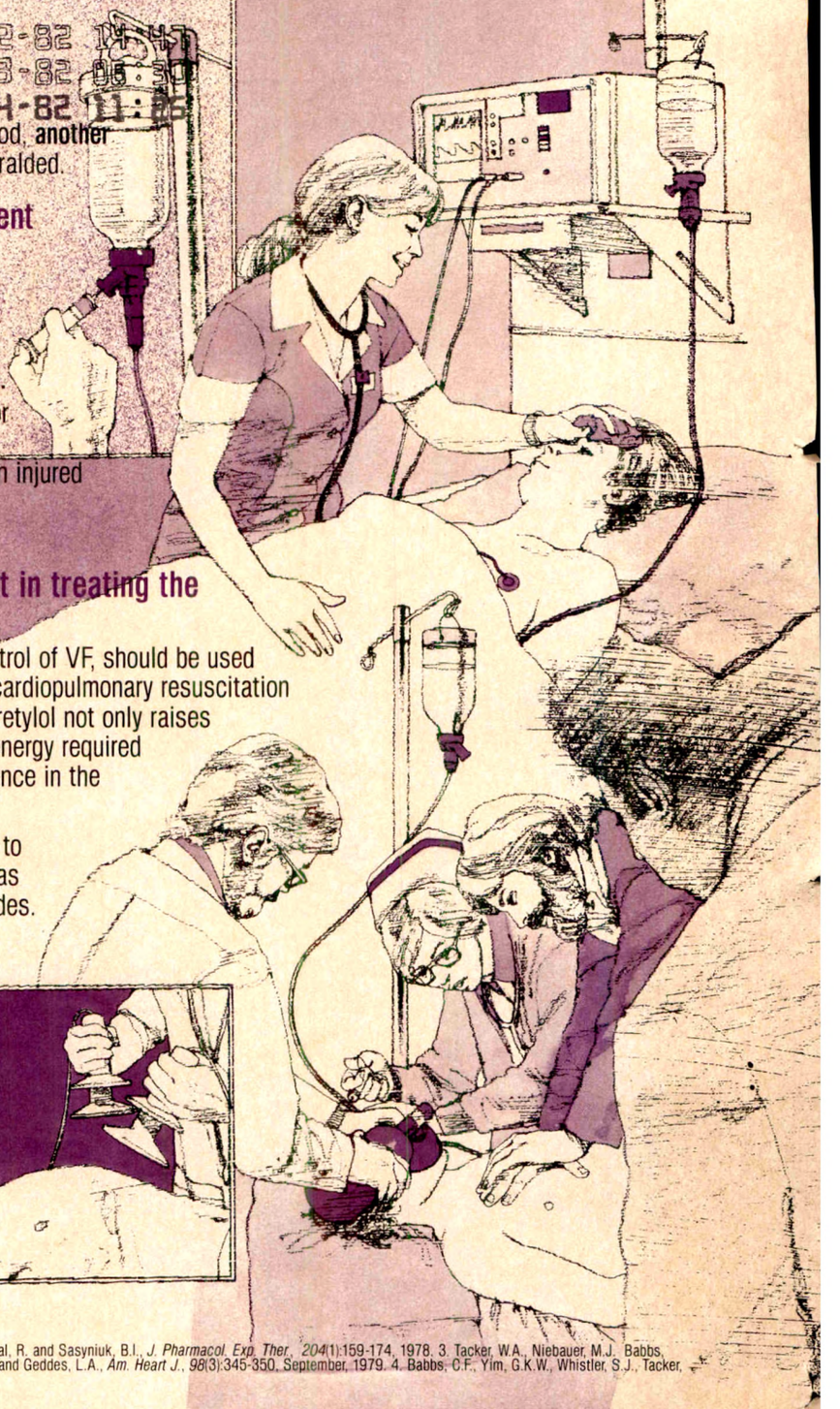
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During the two or three days **after** conversion of ventricular fibrillation, the patient may still be electrically unstable. During this critical high risk period, **another** episode of VF may occur, completely unheralded.




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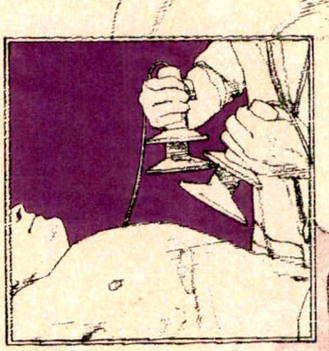
1. Bretylol raises the VF threshold almost three times control, protecting the heart from fibrillation.[1]*
   **No other agent has this dramatic effect.**
2. Bretylol also suppresses reentry, a major cause of VF by helping to equalize the electrophysiological differences between injured and normal ventricular tissue.[2]*
   **No other agent can do this.**

### And, Bretylol offers added benefit in treating the acute episode, too.

Bretylol, a first-line agent in the acute control of VF, should be used in the very first stages of VF, as soon as cardiopulmonary resuscitation and countershock have been attempted. Bretylol not only raises the fibrillation threshold...it reduces the energy required for defibrillation.[3,4]* Another critical difference in the Bretylol mechanism of action.

That's why it makes sense to use Bretylol to maintain stabilization in the CCU, as well as in the first few minutes of acute VF episodes.

There are no contraindications to the use of Bretylol in VF. Hypotension and postural hypotension have been the most frequently reported adverse reactions. Consult brief summary of prescribing information on the following page.



For further information, please contact the Medical Services Department, American Critical Care, a division of American Hospital Supply Corporation, 1600 Waukegan Road, McGaw Park, IL 60085, Phone 312/473-3000.

*based on laboratory animal studies

1. Bacaner, M.B., *Am. J. Cardiol.*, *21*(4):504-512, April, 1968. 2. Cardinal, R. and Sasyniuk, B.I., *J. Pharmacol. Exp. Ther.*, *204*(1):159-174, 1978. 3. Tacker, W.A., Niebauer, M.J., Babbs, C.F., Combs, W.J., Hahn, B.M., Barker, M.A., Seipel, J.F., Bourland, J.D. and Geddes, L.A., *Am. Heart J.*, *98*(3):345-350, September, 1979. 4. Babbs, C.F., Yim, G.K.W., Whistler, S.J., Tacker, W.A. and Geddes, L.A., *Am. Heart J.*, *98*(3):345-350, September, 1979.

**Bretylol...adds a different and unique dimension in control of ventricular fibrillation**

**American Critical Care**

# Bretylol®
## (bretylium tosylate)

**Brief summary of prescribing information**

**INDICATIONS**—BRETYLOL is indicated in the prophylaxis and therapy of ventricular fibrillation.

BRETYLOL is also indicated in the treatment of life-threatening ventricular arrhythmias, such as ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

**CONTRAINDICATIONS**—There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

**WARNINGS—1. Hypotension:** Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, lightheadedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

**2. Transient Hypertension and Increased Frequency of Arrhythmias:** Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

**3. Caution During Use with Digitalis Glycosides:** The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL (bretylium tosylate) should be avoided.

**4. Patients with Fixed Cardiac Output:** In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

**USE IN PREGNANCY**—The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

**USE IN CHILDREN**—The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

**PRECAUTIONS—1. Dilution for Intravenous Use:** BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

**2. Use of Various Sites for Intramuscular Injection:** When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

**3. Reduce Dosage in Impaired Renal Function:** Since BRETYLOL is excreted principally via the kidney, the dosage interval should be increased in patients with impaired renal function.

**ADVERSE REACTIONS**—Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

**HOW SUPPLIED**—NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, non-pyrogenic.

Oct. 1980

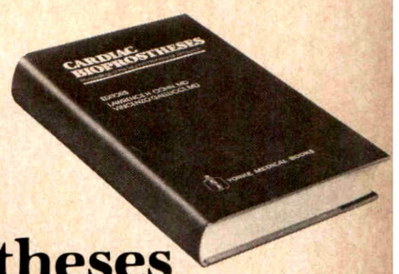
Please refer to complete prescribing information prior to use.

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**The most up-to-date presentation of the latest data on the entire range of clinical, bioengineering, pathology, and long-range follow-up issues on cardiac tissue valves.**




# Cardiac Bioprostheses

**Proceedings of the Second International Symposium**
**Rome, Italy, May 17-19, 1982**

**edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD**
**ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $65.00**

An international program committee organized this symposium on a strictly competitive abstract basis. It was held less than six months ago. One-hundred-eighty abstracts were submitted and 45 in 8 categories were accepted. Virtually every major cardiovascular center in the world that has any meaningful experience with cardiac bioprosthetic valves was represented. Nowhere will you find between two covers as much *current* information on the field of cardiac valves.

Almost 20 years have gone by since the first reports of homograft valve replacement by Drs. Donald Ross and Brian Barratt-Boyes and almost 10 years since the first reports began to appear about commercially available, quality-controlled porcine bioprosthetic and bovine pericardial valves. This book brings you completely up-to-date on what has happened since and what is happening *today*.

If your interests include the clinical, pathological and bioengineering aspects of cardiac bioprostheses then this book is a *must buy!* It should not be missing from your own professional library.

## Who are the editors?

**Lawrence H. Cohn, MD,** is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

**Vincenzo Gallucci, MD,** is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

**• Section 1 CLINICAL ANALYSIS • Section 2 HEMODYNAMICS • Section 3 THROMBOEMBOLISM • Section 4 PEDIATRIC VALVE REPLACEMENT • Section 5 EXPERIMENTAL PATHOLOGY • Section 6 EXPLANT PATHOLOGY • Section 7 BIOPROSTHETIC BIOENGINEERING • Section 8 LONG-TERM FOLLOW-UP • Section 9 SUMMING UP • AUTHOR INDEX • SUBJECT INDEX**

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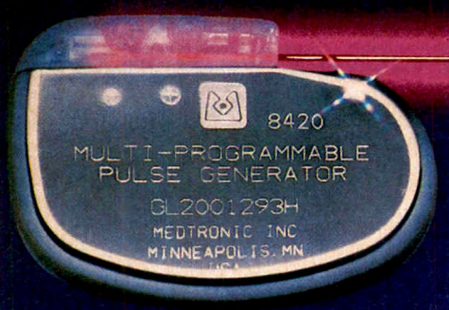
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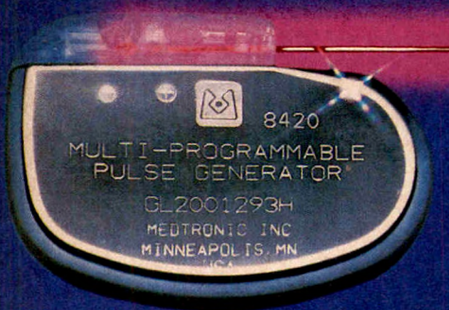
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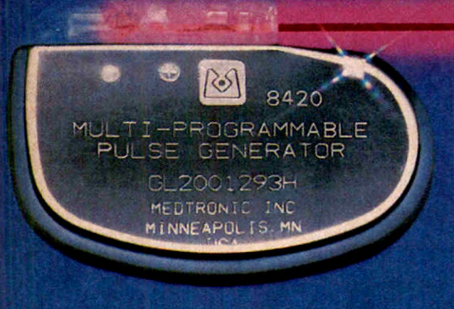
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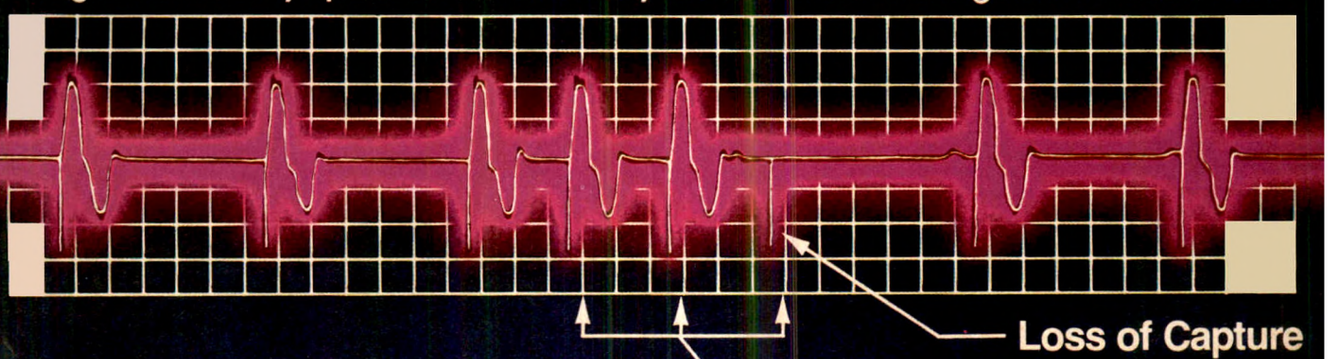
**(EOL). 3 distinct warnings signal elective replacement.**

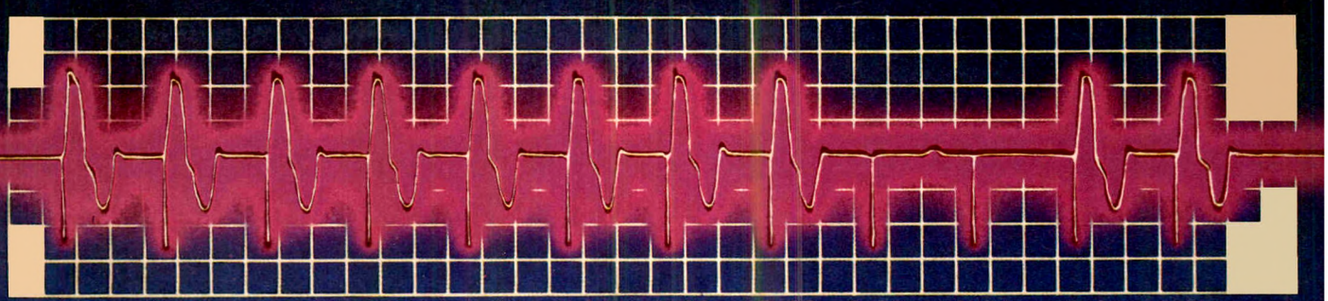



Your 70 year old female patient has rushed to your office in alarm. During her routine pulse self-check test, she determined that her pacemaker had dropped 10% in rate. The implanted unit is a Spectrax SXT though, and you are able to reassure her. This rate change is simply a safeguard warning signalling elective replacement. Pulse width on the Spectrax SXT automatically increases to compensate for the gradual decline in battery voltage. She is in no danger of pacemaker battery failure or loss of capture. This fact is easily and visibly confirmed with Spectrax SXT's noteworthy telemetry which prints out battery status on command. In this case the print out has changed from **"Battery OK"** to **Elec. Replace Time!** Seeing is believing. You and your patient have several months in which to make her surgery decision. You can confidently relieve her anxiety.

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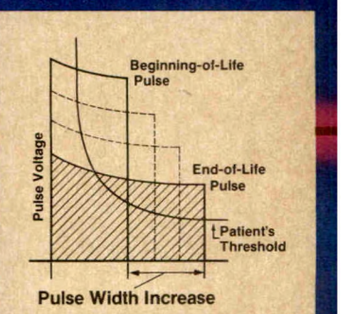
**Stimulus Pulse Width (MS)**

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SPECTRAX-SXT 8420-23

*TELEMETRY READOUT:*
*     BATTERY OK     *
*         RATE= 70PPM*
*           PW=0.50MS*
*        SENSE= 2.5MV*
*         AMPL=FULL   *
*         HYST=NONE   *
*MAGNET ASYNC MODE    *
*         REFR=325MS  *
*PERM    DEMAND MODE  *
```

```
SPECTRAX-SXT 8420-23

*TELEMETRY READOUT:*
ELECT. REPLACE TIME!
*         RATE= 70PPM*
*           PW=0.50MS*
*        SENSE= 2.5MV*
*         AMPL=FULL   *
*         HYST=NONE   *
*MAGNET ASYNC MODE    *
*         REFR=325MS  *
*PERM    DEMAND MODE  *
```




## DISCOVER THE REMARKABLE CLINICAL BENEFITS OF SPECTRAX SXT FOR YOURSELF

(Turn this page over for more information)

**Medtronic**

## Medtronic Implantable Pulse Generators and Leads

### Intended Uses

Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems. Cardiac pacing using an implantable A-V sequential pulse generator is for long-term therapeutic control of heart rate in patients where restoration of A-V synchrony is indicated to improve cardiac output or to protect against arrhythmias related to sequence of cardiac impulse propagation.

### Contraindications

There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

### Warnings

Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. See the specific precautions and warnings in the technical manuals included with the pulse generator.

### Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

### Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

**For complete Spectrax SXT information ☐ clinical reprints ☐ or a convenient demonstration ☐ return this form for immediate action.**

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Specialty or practice_____

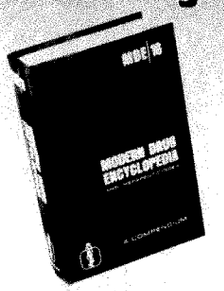
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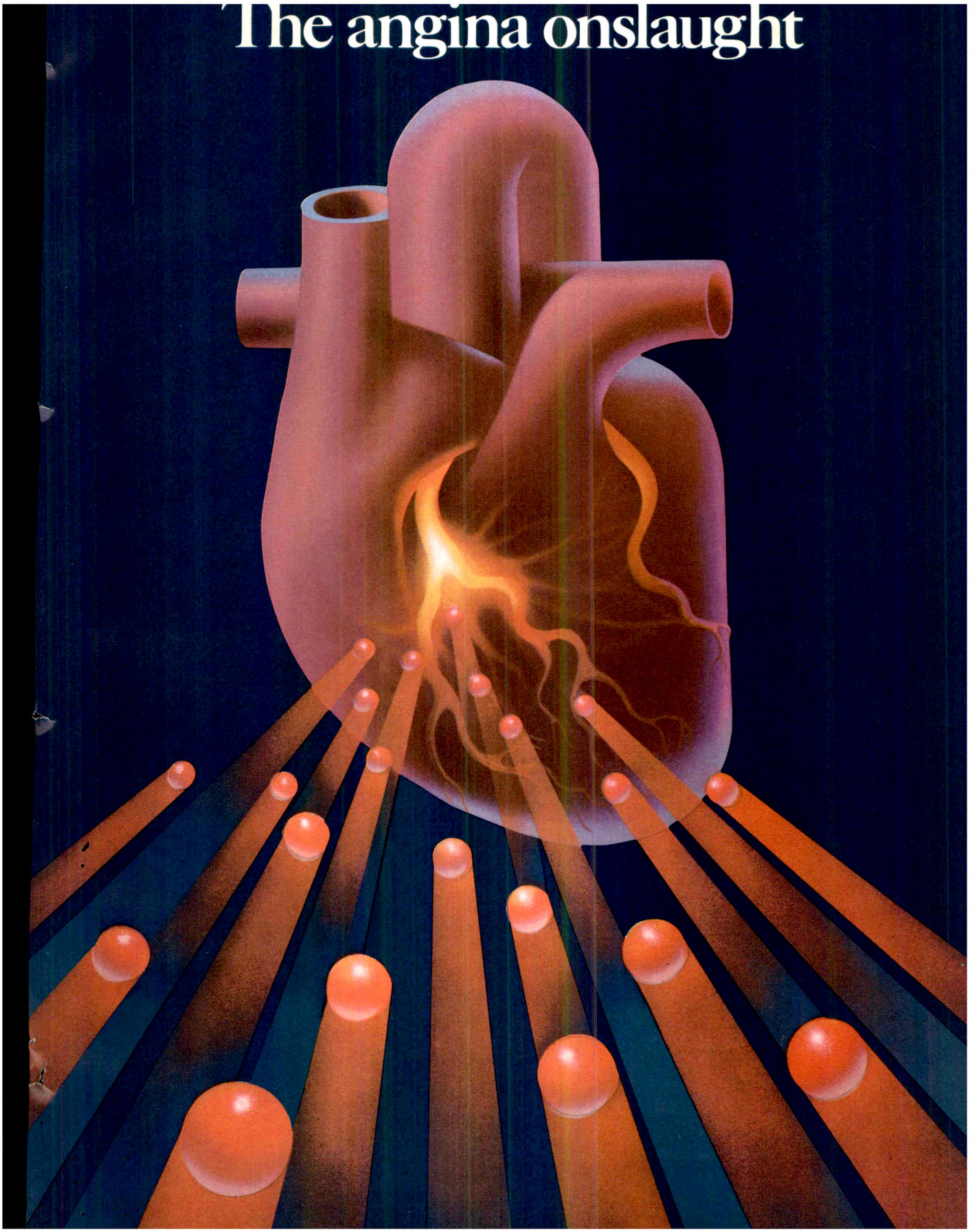
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# The angina onslaught



# The angina shield:
# CORGARD®
# (nadolol tablets)




SQUIBB®




# Reliable 24-hour-a-day protection...

Physical exertion, emotional strain, and the unexpected crises of daily life — these can unleash an anginal attack at any time. So it's important to be certain that your patients are protected continuously. Unlike other beta-blockers, Corgard provides this protection around the clock with a once-daily dose — reducing the anginal attack rate, increasing work capacity, and decreasing the dependence on nitroglycerin.

# with convenient once-a-day dosage

A single daily dose of Corgard controls angina all day, every day. And since Corgard is associated with a low incidence of side effects,* your patients can lead more comfortable lives. An added convenience of Corgard is that it can be taken at any time of day, regardless of meals, because its absorption is not affected by food.

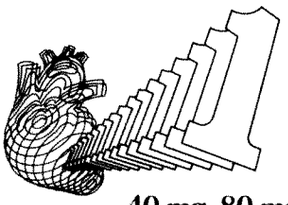
*For a full discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary on next page.

# CORGARD® (nadolol tablets)

## The only once-a-day beta-blocker for both angina pectoris and hypertension

*Please see next page for brief summary.*

# The only once-a-day beta-blocker for both angina pectoris and hypertension



# CORGARD® (nadolol tablets)

**40 mg, 80 mg, 120 mg, and 160 mg scored tablets available in a variety of bottle sizes and in Convenience Packages of 40 mg and 80 mg tablets**

**CORGARD® TABLETS**
**Nadolol Tablets**

**DESCRIPTION:** Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

**CONTRAINDICATIONS:** Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

**WARNINGS: Cardiac Failure** — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal** — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)** — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

**Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

**Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

**Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

**PRECAUTIONS: Impaired Hepatic or Renal Function** — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

**Information for Patients** — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

**Drug Interactions** — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

**Carcinogenesis, Mutagenesis, Impairment of Fertility** — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

**Pregnancy** — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

**Nursing Mothers** — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

**Pediatric Use** — Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

**Cardiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

**Potential Adverse Effects:** Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

**OVERDOSAGE:** Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

**Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

**Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

**Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

**Bronchospasm** — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

**DOSAGE:** For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

**HOW SUPPLIED:** In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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# Improved Electrocardiographic Criteria for the Diagnosis of Left Anterior Hemiblock

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**New electrocardiographic (ECG) criteria for the diagnosis of left anterior hemiblock are proposed. The proposed criteria are based upon the relation between portions of the vectorcardiographic (VCG) QRS loop in the frontal plane and the corresponding portions of the ECG QRS complexes recorded by the limb leads. The application of the proposed criteria requires that the tracings be obtained with 3-channel ECG machines so that the temporal relation between the QRS complexes in simultaneously recorded limb leads can be inspected. This type of analysis of the electrocardiogram permits prediction of features of the VCG QRS loop that are important for the diagnosis of left anterior hemiblock. The proposed ECG criteria for the diagnosis of left anterior hemiblock are (1) the QRS complexes in leads aVR and aVL each end in an R wave (terminal R wave), and (2) the peak of the terminal R wave in lead aVR occurs later than the peak of the terminal R wave in lead aVL. The sensitivity and specificity of the proposed criteria were empirically evaluated using series of electrocardiograms obtained under clinical circumstances during which the occurrence of left anterior hemiblock was, respectively, likely and unlikely. The performance of the proposed criteria was statistically superior to that of 2 sets of frontal plane QRS axis criteria.**

The electrocardiographic (ECG) diagnosis of left anterior hemiblock has depended largely upon the identification of marked left axis deviation in the frontal plane. Because various investigators disagree as to the magnitude of the axis deviation required for the diagnosis and because other conditions can also result in left axis deviation, the ECG diagnosis of left anterior hemiblock is often uncertain.[1–18] The vectorcardiogram (VCG) has been found useful in the diagnosis of left anterior hemiblock because the frontal plane QRS loop exhibits a characteristic pattern of counterclockwise rotation with superior deviation of the mid and terminal forces.[2,5,7,8,10,11,13,14,16,17,19–23]

In the present study, we describe a new method for diagnosing left anterior hemiblock using the scalar electrocardiogram. Because this method is based upon the relations between the limb leads of the electrocardiogram and the VCG loop in the frontal plane, it more closely approximates the accuracy of the vectorcardiogram in diagnosing left anterior hemiblock than does examination of the frontal plane QRS axis alone. An important feature of the present method is the examination of the temporal relations between corresponding portions of the QRS complexes in a pair of simultaneously recorded limb leads. Therefore, the application of the method requires that the tracings be obtained using 3-channel ECG machines. These machines, which simultaneously record leads I, II, and III and then leads aVR, aVL, and aVF, have been in widespread clinical use for several years.

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## Methods

**Selection of patients:** The principal group of patients selected for study consisted of patients who had serial ECG findings elicited during clinical circumstances that permitted us to assess empirically the sensitivity and specificity of our ECG criteria for left anterior hemiblock.

A total of 168 patients (122 men and 46 women) aged 28 to 84 years (mean 55) comprised the study group. They had been patients at 1 of the following hospitals in Syracuse, New York between July 1, 1975 and January 1, 1982: the Veterans Administration Medical Center, the State University Hospital, or the Crouse-Irving Memorial Hospital.

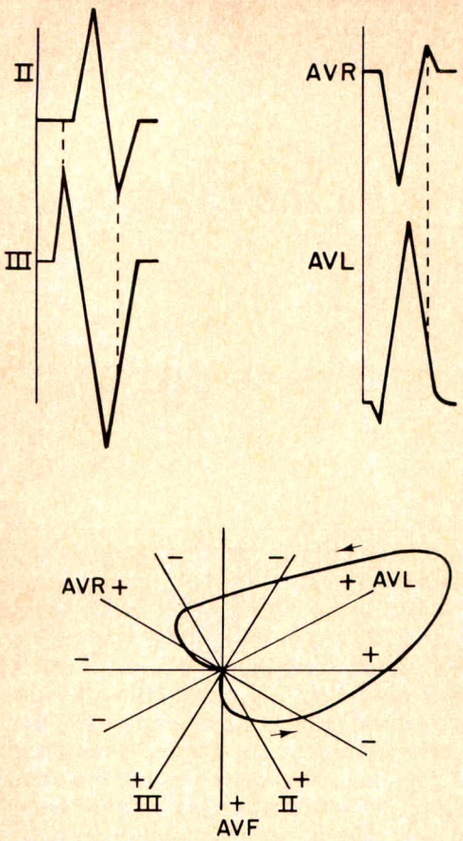



**FIGURE 1.** Diagram of a VCG QRS loop in the frontal plane of a tracing that shows left anterior hemiblock. The hexaxial reference figure is superimposed upon the loop. The **arrows** show that the loop is inscribed in a counterclockwise direction. Above the loop are diagrams of the QRS complexes recorded by 2 pairs of scalar leads—II and III and aVR and aVL—that correspond to the loop. The complexes in each of the 2 pairs were recorded simultaneously by a 3-channel ECG machine. The initial portion of the loop is maximally represented on the positive half of the axis of lead III before it is maximally represented on the positive half of the axis of lead II. Therefore, the peak of the R wave in lead III occurs before the peak of the R wave in lead II. The terminal portion of the loop is maximally represented on the negative half of the axis of lead III before it is maximally represented on the negative half of the axis of lead II and maximally represented on the positive half of the axis of lead aVL before it is maximally represented on the positive half of the axis of lead aVR. Therefore, the nadir of the S wave in lead III occurs before the nadir of the S wave in lead II and the peak of the R wave in lead aVL occurs before the peak of the R wave in lead aVR.

*Group A:* This group consisted of 35 patients with isolated acute anterior myocardial infarction consisting of a typical history, elevation of cardiac enzymes, and the development of S-T segment elevation and Q waves in ECG leads $V_1$ through $V_4$, but without the concomitant appearance of S-T segment elevation or Q waves in ECG leads II, III, or aVF. During the evolution of the ECG changes of anterior infarction, each patient had leftward deviation of the frontal plane QRS axis that was not present initially. In each patient, third-degree or Mobitz type II second-degree atrioventricular block subsequently occurred in the course of the evolution of the infarction. The QRS complexes that were analyzed in this group were those of supraventricular beats that were recorded after leftward deviation of the axis in the frontal plane had occurred, but before they had become >100 ms in duration. Therefore, artifically paced complexes, idioventricular complexes, and complexes showing right or left bundle branch block were excluded. In 8 (23%) of the patients in Group A, the preinfarction electrocardiograms showed left ventricular enlargement by the criteria of Romhilt and Estes.[24] In each of the patients in Group A, left ventricular enlargement was present on ECG findings obtained before as well as after infarction had occurred.

**TABLE I Proposed ECG Criteria for the Diagnosis of Left Anterior Hemiblock**

1. The QRS complexes in leads aVR and aVL each end in an R wave (terminal R wave)

AND

2. The peak of the terminal R wave in lead aVR occurs later than the peak of the terminal R wave in lead aVL

*Group B:* This group consisted of 133 patients with isolated acute inferior myocardial infarction manifested by a typical history, elevation of cardiac enzymes, and the development of S-T segment elevation and Q waves in ECG leads II, III, and aVF, but without the concomitant appearance of S-T segment elevation or Q waves in leads $V_1$, $V_2$, $V_3$, or $V_4$. The ECG findings that were analyzed were those of each patient's series that showed the greatest degree of leftward deviation of the frontal plane QRS axis that developed in the evolution of the changes of inferior infarction. In 14 (11%) of the ECG results that were analyzed in Group B, the Romhilt and Estes criteria for left ventricular enlargement were met.

Because the leftward deviation of the frontal plane QRS axis that occurred in Group A is likely to have been due to the development of left anterior hemiblock, the ECG findings analyzed in this group are designated as cases of left anterior hemiblock. Conversely, because left anterior hemiblock is unlikely to have developed in the patients in Group B, the ECG results analyzed in this group are designated as noncases of left anterior hemiblock. Therefore, the ECG findings of Group A were used to assess the sensitivity, and those of Group B the specificity, of the criteria for left anterior hemiblock.

*Confirmatory series:* In order to further evaluate the specificity exhibited by the proposed criteria, an additional series of patients was studied. These patients were selected to show whether a noncardiac condition that might produce superior deviation of the QRS axis in the frontal plane would result in false-positive diagnoses of left anterior hemiblock by the proposed criteria. The confirmatory series consisted of 43 patients who had electrocardiograms obtained during the third trimester of pregnancy and again 4 to 6 weeks postpartum. At the time that the first of the pairs of electrocardiograms was taken, the mean week of gestation of the patients was 33 (range 27 to 36) and the mean abdominal girth of the patients was 99.5 cm (range 80 to 124). In order to maximize the degree of superior displacement of the diaphragm, and therefore of the heart overlying it, the electrocardiograms obtained during pregnancy were recorded during full expiration. The tracings obtained during the postpartum period were recorded during normal respiration.

**Collection of data:** The ECG findings were obtained in each patient using 12 standard leads and either a Marquette MAC 1-T or Hewlett-Packard model 1517-A electrocardiograph. These machines use 3 channels and simultaneously record leads I, II, and III, then leads aVR, aVL, and aVF, then leads $V_1$, $V_2$, and $V_3$, and finally leads $V_4$, $V_5$, and $V_6$. All recordings were made at a paper speed of 25 mm/s. In order to

**TABLE II Distribution of Frontal Plane QRS Axes in Groups A and B**

| | n | <−60° | −46° to −60° | −31° to −45° | −16° to −30° | −1° to −15° | 0° to +15° | +16° to +30° | >+30° |
|---|---|---|---|---|---|---|---|---|---|
| Group A (cases) | 35 | 8 | 7 | 3 | 9 | 4 | 0 | 4 | 0 |
| | ... | 23% | 20% | 9% | 26% | 11% | 0% | 11% | 0% |
| Group B (noncases) | 133 | 3 | 3 | 5 | 12 | 6 | 33 | 26 | 45 |
| | ... | 2% | 2% | 4% | 9% | 5% | 25% | 20% | 34% |

be certain that all 3 channels were operating simultaneously, the relative times of onset of the 1.0 mV standardization marks were inspected. In most cases, the standardization marks were inscribed simultaneously. However, when the times of onset of the standardization marks were not identical, a correction for the discrepancy was made in the analysis of the QRS complexes. For example, if the standardization mark in channel 2 began 10 ms before the marks in channels 1 and 3, the QRS complexes in leads II and aVL were considered to have actually begun 10 ms later than they appeared on the tracing.

**Rationale for the proposed criteria:** The vectorcardiographic features of left anterior hemiblock have been described by Benchimol et al.[13] The relations between the VCG QRS loop in the frontal plane and the scalar ECG findings in patients with left anterior hemiblock are illustrated in Figure 1. As the figure shows, important features of the contour of the VCG loop can be inferred by analyzing simultaneously recorded pairs of ECG leads. On the basis of the illustrated relations, new ECG criteria for the diagnosis of left anterior hemiblock are proposed and are listed in Table I.

**Comparison ECG criteria:** In order to provide a basis by which to evaluate the performance of our proposed criteria, the ECG results of all the patients were also interpreted with respect to the following 2 sets of comparison criteria for the diagnosis of left anterior hemiblock: (1) frontal plane QRS axis between −30° and −90° (<−30° criterion), and (2) frontal plane QRS axis between −45° and −90° (<−45° criterion).

**Analysis of data:** For patients with discordant predictions by the proposed versus each set of comparison ECG criteria, the hypothesis of no difference in performance was evaluated by Fisher's exact test.[25] This is a rigorous test of comparative performance which is not affected by the level of case prevalence. In order to control the type I error for multiple tests, 2-tailed p values <0.01 were taken to indicate statistical significance at the joint 5% level.

## Results

In Group A, the proposed criteria were met in all the patients after anterior infarction had occurred and in none of the patients before infarction had occurred. In Group B, the proposed criteria were met in none of the patients either before or after inferior infarction occurred. The distribution of the values of the frontal plane QRS axes is shown in Table II. The performances of the proposed and comparison ECG criteria for the diagnosis of left anterior hemiblock are summarized in Table III. The superiority of the proposed over the <−30° and the <−45° criteria is significant at the p <0.001 level in each case.

Of the 8 patients in Group A and the 14 patients in Group B who met the ECG criteria for left ventricular enlargement, only those in Group A met the proposed criteria for left anterior hemiblock, and these only after anterior infarction had occurred.

*Confirmatory series:* In none of the 43 patients in this series did either the proposed or the comparison criteria become positive with pregnancy.

## Discussion

The traditional ECG criteria for the diagnosis of left anterior hemiblock require that some degree of left axis deviation be present. In diagnosing left anterior hemiblock, some investigators have demanded that the frontal plane QRS axis be −45° or less.[9,10,12,13] Others have advocated the less stringent criterion of an axis of ≤−30° for the diagnosis.[1,4,5,7,8,11,16] Still others have recognized that left anterior hemiblock may be present even though the QRS axis is less negative than −30° in the frontal plane.[2,3,6] However, since conditions other than left anterior hemiblock, such as inferior myocardial infarction, left ventricular enlargement, pulmonary emphysema, Wolff-Parkinson-White syndrome, hyperkalemia, and an altered position of the heart within the thorax, also have been reported to result in left axis deviation, relatively liberal axis criteria for diagnosing left anterior hemiblock are likely to be less specific.[7,10,11,14,15,17,18] Because of these considerations, Rosenbaum et al[10] described the choice of a particular value of the frontal plane QRS axis to identify patients with left anterior hemiblock as "arbitrary."

Various groups have emphasized the importance of the characteristic contour of the VCG QRS loop in the frontal plane for diagnosing left anterior hemiblock.[2,5,7,8,10,11,13,14,16,17,19–23] Several types of studies have confirmed that the features of the VCG findings described in the present report indicate that left anterior hemiblock is present. Vectorcardiographic loops similar to those upon which we based the rationale for

**TABLE III Performances* of the Criteria for the Diagnosis of Left Anterior Hemiblock**

| | | % Correctly Identified by: | | |
|---|---|---|---|---|
| Group | n | Proposed Criteria | <−30° Criterion | <−45° Criterion |
| A (cases) | 35 | 100 | 71 | 51 |
| B (noncases) | 133 | 100 | 92 | 95 |

* The tabulated percentages are the sensitivities and specificities of the cases and noncases, respectively.

our proposed electrocardiographic criteria have been observed after angiography of the left coronary artery,[14,23] after surgical interruption of the anterior fascicle in both experimental animals,[14,26] and humans,[7,14,19] during spontaneously occurring intermittent conduction disturbances,[2,5,7,14,19] and in conduction disturbances caused by inducing premature atrial contractions.[27]

When the proposed criteria are positive, it indicates not only that the terminal forces of the ventricular depolarization are deviated superiorly, but also that they are inscribed in a counterclockwise direction. This makes the proposed criteria especially useful for distinguishing left anterior hemiblock from inferior myocardial infarction, since the latter produces superior deviation and clockwise rotation of the initial forces in the frontal plane.[28] In this regard, the authors have recently described improved ECG criteria for the diagnosis of inferior myocardial infarction which use a method of ECG analysis similar to that employed in the present investigation.[29]

The clinical context in which the ECG findings of the patients in Group A developed leftward deviation of the frontal plane QRS axis (isolated acute anterior infarction and subsequent atrioventricular block) makes it highly probable that this change in axis can be attributed to the occurrence of left anterior hemiblock. Therefore, the patients in this subgroup were used to evaluate the sensitivities of the proposed and comparison criteria. The development of high degree atrioventricular block in the patients in Group A illustrates that the proposed electrocardiographic criteria can accurately identify left anterior hemiblock that is functionally significant.

Conversely, the clinical circumstances during which the ECG changes of the patients in Group B were recorded (acute inferior without concomitant anterior infarction) make it unlikely that left anterior hemiblock occurred in this group. Because, as noted above, clinical entities other than inferior infarction have also been reported to produce false-positive evidence of left anterior hemiblock, the specificity of the proposed criteria was evaluated in additional ways. First, the presence of abdominal distension associated with the third trimester of pregnancy failed to produce false-positive evidence of left anterior hemiblock, even though the tracings were obtained in full expiration to maximize the superior displacement of the left hemidiaphragm and the heart overlying it. Second, of 22 patients with ECG evidence of left ventricular enlargement, the proposed criteria for left anterior hemiblock became positive only in the patients in Group A, and only after anterior infarction had occurred. Third, although no patients with Wolff-Parkinson-White Syndrome were included in our study, it is unlikely that this disorder would affect the terminal portions of leads aVR and aVL. This is because, in patients in sinus rhythm, conduction over accessory pathways alters the morphology of only the initial portion of the QRS complex. Finally, the ECG findings of patients with hyperkalemia sufficiently severe to influence the appearance of the QRS complexes can be identified by the characteristic alterations of P and T waves associated with this disorder.[17]

The present study shows that ECG criteria based on features of the VCG QRS loop in left anterior hemiblock diagnose this abnormality more reliably than do traditional frontal plane QRS axis criteria. Therefore, the accuracy with which left anterior hemiblock is diagnosed may be increased without resorting to the less widely available, costly, and time-consuming vectorcardiogram.

## References


1. **Maytin O, Castillo C, Castellanos A.** The genesis of QRS changes produced by selective coronary arteriography. Circulation 1970;41:247–255.
2. **Rosenbaum MB, Elizari MV, Levi RJ, Nau GJ, Pisani N, Lazzari JO, Halpern MS.** Five cases of intermittent left anterior hemiblock. Am J Cardiol 1969;24:1–7.
3. **Okuma K.** ECG and VCG changes in experimental hemiblock and bifascicular block. Am Heart J 1976;92:473–480.
4. **Kulbertus HE, Coyne JJ, Hallidie-Smith KA.** Conduction disturbances before and after surgical closure of ventricular septal defect. Am Heart J 1969; 77:123–131.
5. **Kulbertus H, Collignon P, Humblet L.** Vectorcardiographic study of the QRS loop in patients with left anterior focal block. Am Heart J 1970;79:293–304.
6. **Fernandez F, Scebat L, Lenegre J.** Electrocardiographic study of left intraventricular hemiblock in man during selective coronary arteriography. Am J Cardiol 1970;26:1–5.
7. **Castellanos A, Lemberg L, Sung RJ, Myerburg RJ.** Dynamic vectorcardiography in the evaluation of left hemiblocks. In: Hoffman I, Hamby RI, eds: Vectorcardiography 3. Amsterdam: North Holland Publishing, 1976:99–11.
8. **Lemberg L, Castellanos A, Arcebal AG.** Re-evaluation of septal activation in the human heart with special reference to the spatial orientations of the initial QRS vectors in intermittent left hemiblocks. In: Hoffman I, Hamby RI, Glassman E, eds. Vectorcardiography 2. Amsterdam: North Holland Publishing, 1971:257–263.
9. **Chung EK.** Electrocardiography: Practical Applications with Vectorial Principles. Hagerstown: Harper and Row, 1980:81.
10. **Rosenbaum MB, Elizarai MV, Lazzari JO.** The Hemiblocks. Oldsmar, FL: Tampa Tracings, 1970:73.
11. **Kohn PM, Harris AH.** Vectorcardiographic analysis of left axis deviation, in the differentiation of diaphragmatic infarction and parietal block. Dis Chest 1965;47:492–502.
12. **Rosenbaum MB, Corrado G, Olivberi R, Castellanos A, Elizari MV.** Right bundle branch block with left anterior hemiblock surgically-induced in tetralogy of Fallot. Am J Cardiol 1979;26:12–19.
13. **Benchimol A, Barreto EC, Pedraza A.** The Frank vectorcardiogram in left anterior hemiblock. J Electrocardiol 1971;4:116–128.
14. **Hoffman I.** Clinical vectorcardiography in adults. Part 2. Am Heart J 1980;100:373–396.
15. **Corne RA, Parkin TW, Brandenburg RO, Brown AL.** Significance of marked left axis deviation. Am J Cardiol 1965;15:605–610.
16. **Kulbertus HE, Collignon PG, Humblet L.** Right bundle branch block with left axis deviation. In: Ref 8:272–276.
17. **Pryor R, Blount SG.** The clinical significance of true left axis deviation. Am Heart J 1966;72:391–413.
18. **Grant RP.** Left axis deviation. Circulation 1956;14:233–249.
19. **Lemberg L, Castellanos A, Arcebal AG.** The vectorcardiogram in acute left anterior hemiblock. Am J Cardiol 1971;28:483–489.
20. **Benchimol A, Desser KB, Massey BJ.** Coexisting left anterior hemiblock and inferior wall myocardial infarction. Am J Cardiol 1972;29:7–14.
21. **Kulbertus H, Collignon P, Humblet L.** Vectorcardiographic study of QRS loop in patients with left superior axis deviation and right bundle branch block. Br Heart J 1970;32:386–392.
22. **Rothfeld EL, Zucker IR, Tiu R, Parsonnet V.** The electrocardiographic syndrome of superior axis deviation and right bundle branch block. Dis Chest 1969;55:306–309.
23. **Fernandez F, Heller J, Trevi GP, Rabenou S, Scebat L, Lenegre J.** The QRS loop in left anterior and posterior hemiblocks. Am J Cardiol 1972; 29:337–343.
24. **Romhilt DW, Estes EH.** A point-score system for ECG diagnosis of left ventricular hypertrophy. Am Heart J 1968;75:752–758.
25. **Steel RGD, Torrie JH.** Principles and Procedures of Statistics. 2nd ed. New York: McGraw-Hill, 1980:504–506.
26. **Uhley HN, Rivkin LM.** Electrocardiographic patterns following interruption of the main and peripheral branches of the canine left bundle of His. Am J Cardiol 1964;13:41–47.
27. **Cohen SI, Lau SH, Stein E, Young MW, Damato AN.** Variations of aberrant ventricular conduction in man: evidence of isolated and combined block within the specialized conduction system. Circulation 1968;38:899–916.
28. **Starr JW, Wagner GS, Behar VS, Walston A, Greenfield JC Jr.** Vectorcardiographic criteria for the diagnosis of inferior myocardial infarction. Circulation 1974;49:829–836.
29. **Warner RA, Hill NE, Sheehe PR, Mookherjee S, Fruehan CT, Smulyan H.** Improved electrocardiographic criteria for the diagnosis of inferior myocardial infarction. Circulation 1982;66:422–428.

# Effects of Provocation on Transcardiac Thromboxane in Patients With Coronary Artery Disease

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**Thromboxane $A_2$ exerts powerful effects on vascular smooth muscle tone and platelet aggregability. Previous studies have demonstrated increases in transcardiac thromboxane $B_2$ (a stable thromboxane $A_2$ metabolite) in patients with unstable angina and recent chest pain. To determine whether these increases in transcardiac thromboxane $B_2$ are unique to the unstable anginal syndrome or are merely a consequence of ongoing myocardial ischemia, simultaneous ascending aortic and coronary sinus blood samples were obtained for quantitation of thromboxane $B_2$ in 52 patients with a history of chest pain. Provocation was performed with (1) rapid cardiac pacing in 23 patients, (2) cold pressor stress in 19 patients, and (3) sustained isometric exertion in 10 patients. Of the 52 patients, only 5 had a substantial (>3-fold) increase in coronary sinus thromboxane $B_2$ in response to provocation: 1 had unstable angina and chest pain during the previous 48 hours and 4 had a myocardial infarction within the previous 6 weeks. Similarly, only 7 had a >3-fold increase in the coronary sinus/aortic thromboxane $B_2$ ratio in response to provocation: 1 had unstable angina and recent chest pain, 5 had a recent myocardial infarction, and 1 had both of these. There were no other clinical features unique to these patients. The remaining patients with similar diagnoses did not develop a marked increase in coronary sinus thromboxane $B_2$ or the coronary sinus/aortic thromboxane $B_2$ ratio with provocation. None of the 35 patients with stable ischemic heart disease or nonischemic chest pain syndromes had a substantial increase in coronary sinus thromboxane $B_2$ or the coronary sinus/aortic thromboxane $B_2$ ratio ($p < 0.001$ for both coronary sinus thromboxane $B_2$ and the coronary sinus/aortic thromboxane $B_2$ ratio in comparison with the 17 patients with recent unstable angina or myocardial infarction). Thus, generous amounts of thromboxane $B_2$ are released into the coronary circulation after provocation in some patients with unstable angina or recent myocardial infarction but not in those with stable ischemic heart disease or nonischemic chest pain syndromes.**

Since thromboxane $A_2$ exerts potent effects on vascular smooth muscle tone and platelet aggregability,[1] there has been speculation about its etiologic role in ischemic heart disease. We previously reported[2] that transcardiac ratios (coronary sinus/ascending aorta) of thromboxane $B_2$ (the stable nonenzymatic metabolite of thromboxane $A_2$) were elevated in patients with unstable angina pectoris and recent chest pain but not in those with stable angina or other cardiac disorders. Although transcardiac thromboxane $B_2$ ratios are increased in patients with unstable angina and recent chest pain, it is unknown whether these increases are a consequence of ongoing myocardial ischemia. Previous studies have suggested that most patients with coronary artery disease have increases in thromboxane $B_2$ during myocardial ischemia.[3] Therefore, this study was performed to determine whether the transcardiac thromboxane $B_2$ increases that occur in association with unstable angina are unique to this syndrome or are merely a result of recent myocardial ischemia. To accomplish this, we examined the effects of an increase in myocardial oxygen demand by rapid cardiac pacing, cold pressor stimulation, and isometric handgrip exertion on transcardiac thromboxane $B_2$ levels in patients with and without coronary artery disease.

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**TABLE I Effects of Rapid Cardiac Pacing**

| Patient Diagnosis | Thromboxane $B_2$ | | | | Diseased Coronary Arteries (n) | Medications | Pacing-Induced | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | Provocation | | | | % Lactate Extraction ≤3.0 | ECG Changes* | Chest Pain |
| | AO | CS | AO | CS | | | | | |
| Unstable AP & recent MI | 66 | 95 | 118 | 124 | 3 | N,B | 0 | + | + |
| Unstable AP | 54 | 530 | 137 | 6,877 | 2 | N,B | 0 | + | + |
| Unstable AP | 31 | 41 | 22 | 28 | 2 | N | + | + | 0 |
| Recent MI | 56 | 103 | 25 | 509 | 1 | C,N,B | 0 | 0 | + |
| Recent MI | 134 | 160 | 103 | 182 | 1† | N | 0 | + | + |
| Recent MI | 152 | 375 | 75 | 246 | 1 | N | + | + | + |
| Recent MI | 30 | 39 | 37 | 308 | 2 | C,N,B | 0 | 0 | + |
| Stable AP | 68 | 55 | 68 | 100 | 1 | B | + | + | 0 |
| Stable AP | 28 | 33 | 27 | 40 | 3 | N,B | + | 0 | 0 |
| Stable AP | 54 | 176 | 77 | 145 | 1 | N,B | + | 0 | 0 |
| Stable AP | 33 | 34 | 38 | 46 | 2 | N | + | 0 | + |
| Stable AP | 13 | 19 | 7 | 13 | 1 | C,N | + | + | 0 |
| Stable AP | 66 | 136 | 85 | 136 | 2 | N | + | 0 | + |
| Stable AP | 27 | 18 | 25 | 34 | ‡ | N | 0 | 0 | + |
| Stable AP | 267 | 350 | 298 | 325 | 3 | N,B | + | + | + |
| Stable AP | 47 | 139 | 64 | 146 | 1 | N,B | + | + | + |
| Stable AP | 66 | 74 | 72 | 116 | 1 | N | + | + | 0 |
| Stable AP | 43 | 62 | 71 | 103 | 2 | N | + | + | + |
| Stable AP | 89 | 96 | 99 | 136 | 2 | N | 0 | + | + |
| NICPS | 165 | 128 | 152 | 172 | 0 | N,B | 0 | 0 | + |
| NICPS | 73 | 161 | 216 | 142 | 0 | N,B | 0 | 0 | + |
| NICPS | 41 | 59 | 53 | 56 | 0 | N | 0 | 0 | 0 |
| NICPS | 46 | 43 | 37 | 56 | 0 | C,N | 0 | 0 | + |

* One mm or more horizontal or downsloping S-T depression 0.08 second after the J point.
† Concomitant coronary arterial spasm.
‡ Previous myocardial infarction with normal coronary arteriograms.
AO = ascending aorta; AP = angina pectoris; B = beta blockers; C = cyclooxygenase inhibitors; CS = coronary sinus; ECG = electrocardiographic; MI = myocardial infarction; N = long-acting nitrates; NICPS = nonischemic chest pain syndrome. + = present; 0 = absent.
All values are in picograms per milliliter.

## Methods

From May to December 1980, 52 patients (22 women and 30 men, aged 31 to 75 years) undergoing cardiac catheterization for the evaluation of chest pain at Parkland Memorial Hospital, Dallas, Texas, were studied after informed consent was obtained. In all patients, a 7Fr or 8Fr woven Dacron® (Goodale-Lubin) catheter was advanced from a brachial vein to the coronary sinus and its position was confirmed fluoroscopically and oximetrically. Similarly, a 7Fr or 8Fr polyurethane (pigtail) catheter was introduced percutaneously into the femoral artery and positioned in the ascending aorta adjacent to the coronary ostia. All blood samples were obtained before systemic heparinization or injection of iodinated contrast material. There was no attempt to control or alter the patients' medications before catheterization, but careful records were maintained of all medications administered within 1 week of study.

Provocation-induced ischemic electrocardiographic alterations were said to be present if there was ≥1 mm of horizontal or downsloping S-T segment depression 0.08 second after the J point in comparison with the baseline tracing.[4] After provocation, all patients underwent single plane left ventriculography and selective coronary arteriography.

**Techniques of provocation:** *Rapid cardiac pacing:* In 23 patients, a 6Fr pacing catheter was advanced to the right ventricular apex from the femoral vein. After aorta and coronary sinus specimens were obtained for quantitation of thromboxane $B_2$ and lactate and a baseline 12-lead electrocardiogram was recorded, ventricular pacing was initiated at 100 beats/min. Every 3 minutes, pacing was discontinued for 15 seconds. A 12-lead electrocardiogram was recorded, and then pacing was reinstituted at a rate 10 to 15 beats/min faster. Pacing was continued until the occurrence of angina, marked S-T segment depression on a nonpaced electrocardiogram, or a peak pacing rate of 160 beats/min, at which time blood specimens again were obtained from the aorta and coronary sinus. Immediately after blood sampling, pacing was discontinued, and a 12-lead electrocardiogram was recorded. Five and 10 minutes after the discontinuation of pacing, aorta and coronary sinus specimens again were obtained and a 12-lead electrocardiogram was recorded. Thus, in these 23 patients, aorta and coronary sinus blood specimens for measurement of thromboxane $B_2$ and lactate were obtained before, during, and after rapid cardiac pacing.

*Cold pressor stimulation:* In 19 patients, baseline aorta and coronary sinus blood specimens were obtained for quantitation of thromboxane $B_2$, and a 12-lead electrocardiogram was recorded. Then, the patient's hand was immersed in crushed ice for 3 minutes. During the final 20 seconds of exposure to cold, aorta and coronary sinus blood sampling was repeated, as was the 12-lead electrocardiogram.

*Isometric exercise:* In 10 patients, baseline aorta and coronary sinus blood specimens were obtained for measurement of thromboxane $B_2$, and a 12-lead electrocardiogram was recorded. Then, after the patient's maximal hand strength was determined with a hand dynamometer (Stoelting), the patient maintained 30% of this maximal force for 3 minutes. As with cold pressor stimulation, aorta and coronary sinus blood specimens, as well as a 12-lead electrocardiogram, were obtained during the final 20 seconds of handgrip exertion.

**Chemical analyses:** The blood specimens for thromboxane analysis were drawn into heparinized plastic syringes and transferred quickly into iced 10 ml tubes containing indomethacin (10 μg) and heparin (1,000 U). They were immediately centrifuged at 2,000 *g* for 15 minutes at 4°C. The su-

**TABLE II Effects of Cold Pressor Stress**

| Patient Diagnosis | Thromboxane $B_2$ | | | | Diseased Coronary Arteries (n) | Medications |
|---|---|---|---|---|---|---|
| | Baseline | | Provocation | | | |
| | AO | CS | AO | CS | | |
| Unstable AP & recent MI | 106 | 1,044 | 79 | 1,044 | 3 | N,B |
| Unstable AP & recent MI | 18 | 72 | 30 | 98 | 1 | N,B |
| Unstable AP | 39 | 700 | 29 | 542 | * | N |
| Unstable AP | 18 | 12 | 33 | 17 | 3 | N,B |
| Recent MI | 10 | 13 | 12 | 9 | 3 | C,N |
| Stable AP | 110 | 77 | 85 | 69 | 2† | N |
| Stable AP | 87 | 86 | 119 | 138 | 2 | |
| Stable AP | 60 | 60 | 139 | 56 | 3 | N,B |
| Stable AP | 111 | 131 | 73 | 147 | 1 | B |
| Stable AP | 26 | 13 | 14 | 30 | 3 | N,B |
| Stable AP | 43 | 39 | 39 | 42 | * | |
| Stable AP | 127 | 153 | 48 | 112 | 2 | N,B |
| Stable AP | 125 | 247 | 117 | 139 | * | |
| NICPS | 27 | 41 | 31 | 71 | 0 | C,N |
| NICPS | 66 | 69 | 77 | 53 | 0 | N |
| NICPS | 72 | 100 | 71 | 117 | 0 | N |
| NICPS | 274 | 245 | 240 | 223 | 0 | N |
| NICPS | 18 | 31 | 32 | 42 | 0 | C,N,B |
| NICPS | 61 | 72 | 108 | 102 | 0 | N,B |

Abbreviations as in Table I.
* Previous myocardial infarction with normal coronary arteriograms.
† Concomitant coronary arterial spasm.

pernatants were separated and stored at −20°C for subsequent analysis. Thromboxane was measured by radioimmunoassay.[2]

The blood samples for lactate determination were immediately deproteinated in iced perchloric acid, centrifuged, decanted, and stored frozen. Lactate concentration was assayed enzymatically with the Sigma Chemical kit (St. Louis, Missouri); spectrophotometric measurements were performed at 340 nm.

**Analysis of data:** For each of the 52 patients, thromboxane $B_2$ values before, during, and after (in the case of rapid pacing) provocation were expressed as the ratio of coronary sinus to aorta. Previous studies from our laboratory[2] have demonstrated that the normal thromboxane $B_2$ coronary sinus/aorta ratio is $\leq 3.0$. Thus, for the purposes of this study, an increase in the thromboxane $B_2$ coronary sinus/aorta ratio with provocation from within the normal range to $>3.0$, or an increase in the ratio by $\geq 3.0$, was considered abnormal. Similarly, a 3-fold increase in the absolute coronary sinus thromboxane $B_2$ level with provocation was considered abnormal. Baseline and provocation thromboxane $B_2$ coronary sinus/aorta ratios were compared using the Wilcoxon paired-sample test.[5] The frequency of provocation-induced increases in coronary sinus and transcardiac thromboxane $B_2$ levels among patients with (1) unstable angina (with recent chest pain) and recent myocardial infarction, (2) stable angina, and (3) nonischemic chest pain syndromes were analyzed using the Fisher exact test.[5] Baseline and provocation heart rates and blood pressures were compared using the paired-sample $t$ test.[5] The aortic thromboxane $B_2$ concentrations in patients with and without recent ingestion of cyclooxygenase inhibitors were compared using the Mann-Whitney test.[5] A p value $<0.05$ was considered significant. All values are expressed as the mean ± standard deviation.

The percent myocardial lactate extraction was calculated with the formula $100 \times (AO_L - CS_L)/AO_L$, where $AO_L$ represents the aortic lactate concentration and $CS_L$ represents the coronary sinus lactate concentration. Using this formula, a value less than zero indicates myocardial lactate production.[6] Since this assay in our laboratory has a variability of 3%, we accepted a percent myocardial lactate extraction of $\leq -3.0$ as evidence of myocardial lactate production.

## Results

**Rapid cardiac pacing:** Of the 23 patients subjected to rapid pacing (Table I), 16 had chest pain and 12 had S-T segment depression consistent with ischemia (8 with and 4 without concomitant chest pain). Pacing was continued to 160 beats/min in 3 patients without the occurrence of pain or electrocardiographic changes. Myocardial lactate production occurred during pacing in 12 patients. Subsequently, selective coronary arteriography revealed that 18 of the 23 patients had atherosclerotic coronary artery disease.

In 3 of the 23 patients, coronary sinus thromboxane $B_2$ increased abnormally during or immediately after rapid cardiac pacing. Of these 3 patients, all had chest pain, 1 had ischemic electrocardiographic alterations, none had myocardial lactate production, and all 3 had atherosclerotic coronary artery disease. One had unstable angina[7] and chest pain within the previous 48 hours, and the other 2 had a myocardial infarction within 6 weeks of study. Four patients with unstable angina or recent infarction did not have an increase in transcardiac thromboxane $B_2$ in response to pacing (1 with unstable angina, 2 with a recent infarction, and 1 with both). Among these 4, 3 had chest pain, all 4 had ischemic electrocardiographic changes consistent with ischemia, and 2 had myocardial lactate production.

Of the 23 patients subjected to rapid cardiac pacing, 16 had neither unstable angina nor a recent infarction. Of these, 10 had chest pain during pacing, 7 had electrocardiographic changes consistent with myocardial

ischemia, 10 had myocardial lactate production, and 11 had underlying atherosclerotic coronary artery disease. However, none of these patients developed a pacing-induced abnormal increase in coronary sinus thromboxane $B_2$.

Among the 12 patients who had pacing-induced myocardial lactate production, none had a concomitant abnormal elevation in coronary sinus thromboxane $B_2$.

**Cold pressor stimulation:** Of the 19 patients provoked with exposure to cold, none developed chest pain or S-T segment alterations indicative of myocardial ischemia (Table II). Before cold pressor provocation, heart rate was 68 ± 9 (mean ± standard deviation) beats/min, and during cold pressor, it was 71 ± 9 beats/min (p = NS [not significant]). Systolic arterial pressure increased from 153 ± 25 mm Hg before cold pressor to 188 ± 40 mm Hg during cold pressor (p <0.01). None of the 19 patients demonstrated an abnormal increase in the coronary sinus thromboxane $B_2$ level in response to cold pressor stimulation. Five patients had unstable angina or recent infarction (2 with unstable angina and chest pain within 48 hours of study, 1 with a myocardial infarction within 6 weeks of study, and 2 with both of these), and 14 had stable angina or nonischemic chest pain syndromes.

**Isometric exercise:** During sustained handgrip, 1 of the 10 patients had chest pain, and none had S-T segment changes suggestive of ischemia (Table III). During the 3 minutes of handgrip, heart rate increased from 78 ± 16 to 88 ± 19 beats/min (p = 0.02), and systolic arterial pressure increased from 135 ± 15 to 175 ± 14 mm Hg (p <0.01). In 2 of the 10 patients, isometric exercise induced an abnormal increase in the coronary sinus thromboxane $B_2$ level (from 24.7 and 132.0 at baseline to 86.3 and 862.0, respectively, at peak handgrip). Both of these patients had had a myocardial infarction within the previous 6 weeks; neither had chest pain during handgrip exertion. The coronary sinus level remained unchanged in the remaining 3 patients with unstable angina and recent pain (1 patient) or recent myocardial infarction (2 patients). The 5 patients with stable angina pectoris or nonischemic chest pain syndromes demonstrated no substantial change in coronary sinus thromboxane $B_2$ in response to handgrip.

**Effects of provocation in patients with unstable angina or recent myocardial infarction:** Seventeen of the 52 patients subjected to provocation had unstable angina and chest pain within 48 hours of study (5 patients), a myocardial infarction within 6 weeks of study (9 patients), or both (3 patients). In 5 of these 17 patients (29%), the coronary sinus thromboxane $B_2$ level increased abnormally (>3-fold) with provocation (3 with pacing and 2 with isometric exertion), whereas it remained unchanged in the other 12 patients. Of the 5 patients with a substantial increase in coronary sinus thromboxane $B_2$, 1 had unstable angina and 4 had recent infarctions. Therefore, 1 of 8 patients with unstable angina and recent chest pain and 4 of 12 patients with recent myocardial infarctions had a marked increase in coronary sinus thromboxane $B_2$ in response to an increase in myocardial oxygen demand. In contrast, of the 35 patients with stable angina or nonischemic chest pain syndromes, none demonstrated a 3-fold increase in the coronary sinus thromboxane $B_2$ level with provocation (p <0.001) (Fig. 1).

In terms of transcardiac changes in thromboxane $B_2$, a ratio of the coronary sinus/ascending aortic thromboxane $B_2$ concentrations can provide a useful index of intracoronary thromboxane $B_2$ production.[2] Expressing the present data in this fashion demonstrates that a significant increase in the thromboxane $B_2$ coronary sinus/ascending aortic ratio occurred with provocation in 7 of the 52 patients (13%). Of these 7, 4 were provoked with pacing, 1 with cold pressor stress, and 2 with isometric exertion. One of these 7 had recent unstable angina, 5 had recent infarctions, and 1 had both. Of the 52 patients in the entire study population, the 7 with provocable increases were among 17 patients (41%) with similar diagnoses, whereas none of the remaining 35 patients had significant increases in the thromboxane $B_2$ coronary sinus/aortic ratio (p <0.001). Thus, in this study, similar results were obtained by evaluation of changes in coronary sinus/aortic ratios.

**Effect of medications:** Of the 52 patients, 45 (87%) were receiving long-acting nitrates, 21 (40%) were receiving propranolol (mean daily dose 140 mg, range 30

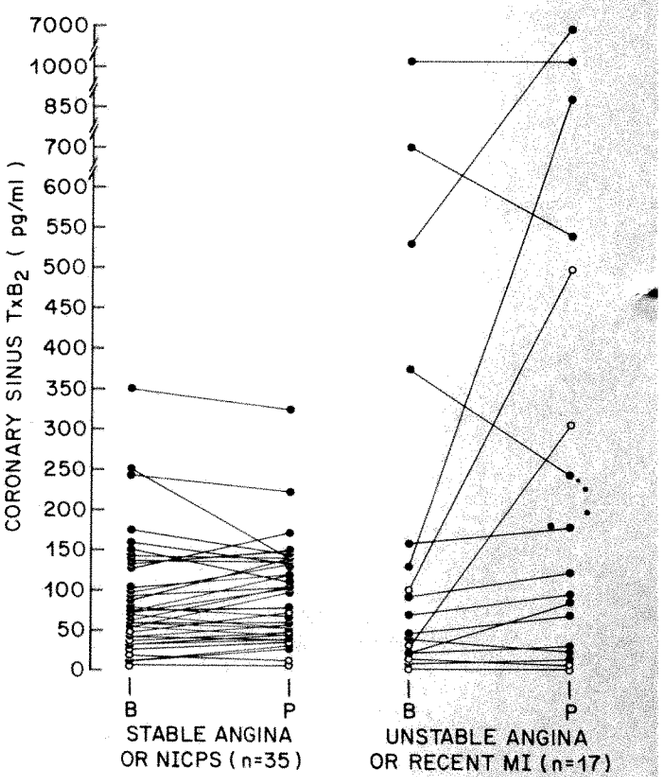



**FIGURE 1.** Baseline (B) and provocation (P) thromboxane $B_2$ coronary sinus plasma concentrations in 52 patients with (**right**) and without (**left**) unstable angina pectoris or recent myocardial infarction (MI). Provocation was performed with rapid cardiac pacing (n = 23), cold pressor stress (n = 19), or sustained isometric exertion (n = 10). Each line represents the data from 1 patient. **Open circles** identify the 9 patients with recent cyclooxygenase inhibitor ingestion (4 patients with and 5 without unstable angina or recent myocardial infarction). NICPS = nonischemic chest pain syndrome.

**TABLE III Effects of Sustained Isometric Exertion**

| Patient Diagnosis | Thromboxane $B_2$ | | | | Diseased Coronary Arteries (n) | Medications |
|---|---|---|---|---|---|---|
| | Baseline | | Provocation | | | |
| | AO | CS | AO | CS | | |
| Unstable AP | 26 | 48 | 45 | 72 | 3 | N,B |
| Recent MI | 30 | 34 | 39 | 42 | 1 | N,B |
| Recent MI | 19 | 25 | 23 | 86 | 3 | |
| Recent MI | 39 | 132 | 68 | 862 | 2 | N |
| Recent MI | 9 | 8 | 7 | 9 | 3 | C,N,B |
| Stable AP | 61 | 92 | 51 | 102 | 3 | N,B |
| NICPS | 42 | 74 | 40 | 79 | 0 | N |
| NICPS | 141 | 54 | 128 | 45 | 0 | N |
| NICPS | 28 | 42 | 84 | 59 | 0 | |
| NICPS | 11 | 8 | 12 | 13 | 0 | C |

Abbreviations as in Table I.

to 320), and 4 (8%) were receiving metoprolol (100 to 200 mg/24 hours). Nitrates and propranolol did not appear to influence the thromboxane $B_2$ concentrations (Tables I to III). Nine patients received cyclooxygenase inhibitors at some time within 5 days of study (aspirin in 4, ibuprofen in 1, aspirin plus ibuprofen in 1, indomethacin in 1, sulfinpyrazone in 1, and sulindac in 1); these 9 patients had lower plasma concentrations of these hormones (baseline aortic thromboxane $B_2$ concentration 24.5 ± 17.1 pg/ml) than the 44 patients who had not received them (74.9 ± 57.8 pg/ml) ($p < 0.001$). The exclusion of the 9 patients who had recently received cyclooxygenase inhibitors did not influence the overall results of the study (Tables I to III). Interestingly, 2 of these patients had an abnormal increase in the coronary sinus thromboxane $B_2$ level with provocation (Table I, Group 1, Patients 4 and 7).

## Discussion

Recent studies have suggested that unstable angina pectoris is a syndrome characterized by spontaneous reductions in coronary blood flow[8,9] induced by either coronary arterial spasm or intracoronary platelet aggregation with the transient formation of platelet "plugs." Since thromboxane $A_2$ is a powerful promoter of increased vascular tone and platelet aggregation,[10] it is of interest that its stable metabolite, thromboxane $B_2$, is elevated in the coronary circulation of patients with unstable angina.[2] In contrast, stable (exertional) angina is a syndrome characterized by episodic increases in myocardial oxygen demand in the setting of limited oxygen supply due to coronary atherosclerosis. Although it is unknown whether coronary arterial spasm or enhanced platelet aggregation is of etiologic importance in this syndrome, previous studies from our laboratory have demonstrated that patients with stable (exertional) angina do not have increased transcardiac levels of thromboxane $B_2$.[2] Thus, there is inferential evidence that unstable angina and stable (exertional) angina differ in pathogenesis and, consequently, in their association (or lack of association) with transcardiac thromboxane levels.

In the present study, marked (>3-fold) increases in coronary sinus thromboxane $B_2$ or the coronary sinus/aortic thromboxane $B_2$ ratio in response to provocation were observed in only 5 (10%) or 7 (13%) of the patients, respectively. In a retrospective attempt to ascertain common features among these patients, it was apparent that substantial provocation-induced thromboxane $B_2$ elevations occurred only in 2 types: those with unstable angina and recent chest pain (within 48 hours of study) and those with recent myocardial infarction (within 6 weeks of study). Such increases in thromboxane $B_2$ were not observed in those with stable (exertional) angina or nonischemic chest pain syndromes. There were no other clinical features unique to those who developed such an increase in thromboxane $B_2$.

Rapid cardiac pacing, cold pressor stimulation, and isometric exertion were used in the present study to induce myocardial ischemia. Cardiac pacing increases heart rate, exposure to cold increases systemic arterial pressure, and sustained handgrip increases both heart rate and systemic arterial pressure.[11–13] Thus, all 3 methods of provocation increase the rate-pressure product, thereby augmenting myocardial oxygen demand.[14] In addition, activation of the sympathetic nervous system with alpha-adrenergic stimulation (induced by cold pressor stress and isometric exercise) causes an increase in coronary vascular resistance.[15,16] This coronary vasoconstriction in patients with coronary artery disease may result in myocardial ischemia, which is demonstrable at times even in the absence of chest pain and electrocardiographic changes.[17,18] Aside from their effects on myocardial oxygen demand and coronary vascular resistance, these methods of provocation activate platelets in patients with ischemic heart disease.[19–21] In addition, it has been suggested that rapid cardiac pacing in individuals with atherosclerotic coronary artery disease may increase the production of prostaglandins E and F[22] as well as thromboxane $B_2$.[3,23]

Lewy et al[3] performed cardiac pacing in 14 patients with unstable or accelerated angina. They concluded that thromboxane $A_2$ was produced during pacing-induced myocardial ischemia and that fluctuations in thromboxane $A_2$ levels paralleled alterations in lactate production. Our results are at variance with their conclusions. Specifically, our data suggest that provocation causes a marked increase in coronary sinus thromboxane $B_2$ in some patients with myocardial ischemia but

not in others, and that this increase in thromboxane $B_2$ is unrelated to myocardial lactate production. In the present study, there was a substantial increase in thromboxane $B_2$ with provocation in some patients with unstable angina and chest pain within 48 hours of study and in some with a recent myocardial infarction (within 6 weeks of study). In contrast, thromboxane $B_2$ did not increase markedly with provocation in those with stable ischemic heart disease, even though ischemia (as suggested by chest pain, electrocardiographic alterations, and myocardial lactate production) was produced in both groups of patients. Thus, in the present study, an abnormal increase in coronary sinus thromboxane $B_2$ during provocation appears to be related to the presence of clinical instability or recent myocardial infarction rather than to provoked myocardial ischemia per se.

The apparent lack of objective signs of ischemia in some patients with thromboxane $B_2$ production during provocation may reflect limitations inherent to this type of clinical study. In our experience, chest pain is an unreliable indicator of myocardial ischemia. Nevertheless, we are reluctant to provoke patients with coronary artery disease beyond the onset of chest pain. Furthermore, provocation-induced electrocardiographic alterations and net myocardial lactate production are specific but not sensitive indicators of myocardial ischemia; that is, their absence in some patients with coronary sinus thromboxane $B_2$ elevations does not exclude the presence of ischemia concomitantly in these patients.[24–27] Therefore, further investigation into the relation between myocardial ischemia and intracoronary thromboxane $B_2$ release is needed to resolve this issue.

The question of why some patients with unstable angina (and recent chest pain) and recent myocardial infarction increase their coronary sinus thromboxane $B_2$ in response to provocation, whereas others with these syndromes do not, remains unanswered. At least part of the answer may be a function of the different degrees of ischemia induced in these patients. Alternatively, 3 of 8 patients with unstable angina pectoris had resting coronary sinus thromboxane $B_2$ levels >500 pg/ml. Of these 3, 2 did not have a further increase in the coronary sinus thromboxane $B_2$ concentration. Therefore, patients with an elevated resting coronary sinus thromboxane $B_2$ level may be less affected (in terms of thromboxane $B_2$ production) by an increase in myocardial oxygen demand than those with a "normal" resting level.

The range of thromboxane $B_2$ values obtained in this study is large. However, many factors (such as the presence of ischemic heart disease,[28,29] atherosclerosis,[30,31] and stress[32,33]) affect thromboxane $A_2$ levels and platelet thromboxane $A_2$ generation. Thus, it is not surprising that 52 patients with and without atherosclerotic vascular disease and its associated risk factors have a wide range of aortic and coronary sinus thromboxane $B_2$ concentrations. However, the observed increases in coronary sinus thromboxane $B_2$ could have occurred (1) in the coronary circulation, or (2) in the coronary sinus catheter itself; the present study cannot distinguish between these 2 possibilities. Despite this, there is reason to believe that the release of thromboxane $A_2$ is an intracoronary event, since intracoronary platelet aggregates have been observed in association with several ischemic cardiac syndromes.[34–36] Other recent studies have demonstrated an increase in platelet-specific proteins in peripheral blood samples in patients with unstable angina pectoris, suggesting again that platelets may be involved in the pathophysiology of this syndrome.[37,38] In addition, recent studies from our laboratory have demonstrated no consistent alteration in thromboxane $B_2$ attributable to sampling through long catheters.[39]

*In summary*, provocation with rapid cardiac pacing, cold pressor stimulation, and isometric exercise caused a marked increase in coronary sinus thromboxane $B_2$ levels in some patients with unstable angina pectoris or a recent myocardial infarction. In contrast, patients with a similar degree of coronary artery disease but without unstable angina or a recent myocardial infarction, as well as patients with a nonischemic chest pain syndrome, demonstrated no substantial increase in coronary sinus thromboxane $B_2$ with provocation. The increases in coronary sinus thromboxane $B_2$ during cardiac pacing did not correlate with the presence of objective signs of myocardial ischemia. Although the present study cannot distinguish between cause and effect, thromboxane $A_2$ may play a role in the mediation of unstable ischemic coronary events, such as unstable angina pectoris, acute myocardial infarction, and sudden cardiac death. Further studies are needed to clarify the precise role of thromboxane $A_2$ in these clinical syndromes, as well as the physiologic significance, if any, of the coronary sinus and transcardiac changes in thromboxane $B_2$ observed in this study. Whether provocative testing can identify a subset of patients with unstable ischemic heart disease at risk for thromboxane $A_2$-mediated catastrophic events (which might be prevented by prophylactic treatment with a thromboxane synthetase inhibitor or receptor antagonist) remains to be determined.

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## References

1. **Moncada S, Vane JR.** Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane $A_2$, and prostacyclin. Pharmacol Rev 1979;30:293–331.
2. **Hirsh PD, Hillis LD, Campbell WB, Firth BG, Willerson JT.** Release of prostaglandins and thromboxane into the coronary circulation in patients with ischemic heart disease. N Engl J Med 1981;304:685–691.
3. **Lewy RI, Wiener L, Walinsky P, Lefer AM, Silver MJ, Smith JB.** Thromboxane release during induced angina pectoris: possible vasoconstrictor influence on the coronary vasculature. Circulation 1980;61:1165–1171.
4. **Chou TC.** Electrocardiography in Clinical Practice. New York: Grune & Stratton, 1979:216–241.
5. **Zar JH.** Biostatistical Analysis. Englewood Cliffs, NJ: Prentice-Hall, 1974.
6. **Gertz EW, Wisneski JA, Neese R, Houser A, Korte R, Bristow JD.** Myocardial lactate extraction: multi-determined metabolic function. Circulation 1980;61:256–261.
7. **Fowler NO.** "Preinfarctional" angina: a need for an objective definition and for a controlled clinical trial of its management. Circulation 1971;44:755–785.

8. **Chierchia S, Brunelli C, Simonetti I, Lazzari M, Maseri A.** Sequence of events in angina at rest: primary reduction in coronary flow. Circulation 1980;61:759–768.
9. **Neill WA, Wharton TP Jr, Fluri-Lundeen J, Cohen IS.** Acute coronary insufficiency—coronary occlusion after intermittent ischemic attacks. N Engl J Med 1980;302:1157–1162.
10. **Hamberg M, Svensson J, Samuelsson B.** Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. Proc Natl Acad Sci USA 1975;72:2994–2998.
11. **Godden JO, Roth GM, Hines EA.** The changes in intra-arterial pressure during immersion of the hand in ice-cold water. Circulation 1955;12: 963–973.
12. **Lind AR, Taylor SH, Humphreys PW, Kennelly BM, Donald KW.** The circulatory effects of sustained voluntary muscle contraction. Clin Sci 1964;27:229–244.
13. **Forrester JS, Helfant RH, Pasternac A, Amsterdam EA, Most AS, Kemp HG, Gorlin R.** Atrial pacing in coronary heart disease. Effects on hemodynamics, metabolism and coronary circulation. Am J Cardiol 1971;27: 237–243.
14. **Gobel FL, Nordstrom LA, Nelson RR, Jorgenson CR, Wang Y.** The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 1978;57:549–556.
15. **Mudge GH, Grossman W, Mills RM, Lesch M, Braunwald E.** Reflex increase in coronary vascular resistance in patients with ischemic heart disease. N Engl J Med 1976;295:1333–1337.
16. **Aung-Din R, Mitchell JH, Longhurst JC.** Reflex alpha adrenergic coronary vasoconstriction during hindlimb static exercise in dogs. Circ Res 1981; 48:502–507.
17. **Bodenheimer MM, Banka VS, Fooshee CM, Gillespie JA, Helfant RH.** Detection of coronary heart disease using radionuclide determined regional ejection fraction at rest and during handgrip exercise: correlation with coronary arteriography. Circulation 1978;58:640–648.
18. **Wainwright RJ, Cueni TA, Brennand-Roper DA, Sowton E, Hilson AJW, Maisey MN.** Cold pressor test in detection of coronary heart disease and cardiomyopathy using technetium-99m gated blood-pool imaging. Lancet 1979;2:320–323.
19. **Fitchett DH, Toth E, Ehrman M, Marpole D, Gilmore N.** Platelet activation within the coronary circulation in patients with atherosclerotic coronary disease (abstr). Clin Res 1980;28:659A.
20. **Sano T, Motomiya T, Yamazaki H.** Platelet release reaction *in vivo* in patients with ischaemic heart disease after isometric exercise and its prevention with dipyridamole. Thromb Haemost 1979;42:1589–1597.
21. **Mehta J, Mehta P, Pepine CJ.** Platelet aggregation in aortic and coronary venous blood in patients with and without coronary disease. III. Role of tachycardia stress and propranolol. Circulation 1978;58:881–886.
22. **Berger HJ, Zaret BL, Speroff L, Cohen LS, Wolfson S.** Cardiac prostaglandin release during myocardial ischemia induced by atrial pacing in patients with coronary artery disease. Am J Cardiol 1977;39:481–486.
23. **Lewy RI, Wiener L, Smith JB, Walinsky P, Silver MJ, Saia J.** Comparison of plasma concentrations of thromboxane $B_2$ in Prinzmetal's variant angina and classical angina pectoris. Clin Cardiol 1979;2:404–406.
24. **Corbett J, Dehmer GJ, Lewis SE, Woodward W, Henderson E, Parkey RW, Blomquist CG, Willerson JT.** The prognostic value of submaximal exercise testing with radionuclide ventriculography before hospital discharge in patients with recent myocardial infarction. Circulation 1981;64:535–544.
25. **Gertz EW, Wisneski JA, Neese R, Bristow JD, Searle GL, Hanlon JT.** Myocardial lactate metabolism: evidence of lactate release during net chemical extraction in man. Circulation 1976;63:1273–1279.
26. **Karlsson J, Lobstein P, Templeton GH, Willerson JT.** Lactate metabolism and acute canine myocardial ischemia. Proceedings of the Symposium of the International Society for Cardiac Metabolism. In: Dhalla NS, ed. Recent Advances in Studies in Cardiac Structure and Metabolism, vol 3. Baltimore: University Park Press, 1972:713–720.
27. **Karlsson JK, Templeton GH, Willerson JT.** Relationship between epicardial ST segment changes and myocardial metabolism during acute coronary insufficiency. Circ Res 1973;32:725–730.
28. **Szczeklik A, Gryglewski RJ, Musial J, Grodzinska L, Serwonska M, Marcinkiewicz E.** Thromboxane generation and platelet aggregation in survivals of myocardial infarction. Thromb Haemost 1978;40:66–74.
29. **Mehta J, Mehta P, Conti CR.** Platelet function studies in coronary heart disease. IX. Increased platelet prostaglandin generation and abnormal platelet sensitivity to prostacyclin and endoperoxide analog in angina pectoris. Am J Cardiol 1980;46:943–947.
30. **Zmuda A, Dembinska-Kiec A, Chytkowski A, Gryglewski RJ.** Experimental atherosclerosis in rabbits: platelet aggregation, thromboxane $A_2$ generation and anti-aggregatory potency of prostacyclin. Prostaglandins 1977;14: 1035–1042.
31. **Dembinski-Kiec A, Rucker W, Schoenhofer PS,** Prostacyclin-dependent differences in $TxA_2$ formation by platelets from normal and atherosclerotic rabbits. Atherosclerosis 1979;33:217–226.
32. **Haft JI, Arkel YS.** Effect of emotional stress on platelet aggregation in humans. Chest 1976;70:501–505.
33. **Arkel YS, Haft JI, Kreutner W, Sherwood J, Williams R.** Alteration in second phase platelet aggregation associated with an emotionally stressful activity. Thromb Haemost 1977;38:552–561.
34. **Haerem JW.** Platelet aggregates in intramyocardial vessels of patients dying suddenly and unexpectedly of coronary artery disease. Atherosclerosis 1972;15:199–213.
35. **El-Maraghi N, Genton E.** The relevance of platelet and fibrin thromboembolism of the coronary microcirculation with special reference to sudden cardiac death. Circulation 1980;62:936–944.
36. **Folts JD, Crowell EB, Rowe GG.** Platelet aggregation in partially obstructed vessels and its elimination with aspirin. Circulation 1976;54:365–370.
37. **Sobel M, Salzman EW, Davies GC, Handin RI, Sweeney J, Ploetz J, Kurland G.** Circulating platelet products in unstable angina pectoris. Circulation 1981;63:300–6.
38. **Smitherman TC, Milam M, Woo J, Willerson JT, Frenkel EP.** Elevated beta-thromboglobulin in peripheral venous blood of patients with acute myocardial ischemia: direct evidence for enhanced platelet reactivity in vivo. Am J Cardiol 1981;48:395–402.
39. **Hirsh PD, Firth BG, Campbell WB, Willerson JT, Hillis LD.** Influence of blood sampling site and technique on thromboxane concentration in patients with ischemic heart disease. Am Heart J 1982;104:234–237.

# Precordial S-T Segment Depression in Inferior Myocardial Infarction

## Evaluation by Quantitative Thallium-201 Scintigraphy And Technetium-99m Ventriculography

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**The relation of initial precordial S-T segment depression to anterior ischemia and eventual prognosis was studied in 70 patients with acute inferior myocardial infarction (MI). Early quantitative thallium-201 scintigraphy and technetium-99m ventriculography were used to evaluate anterior ischemia. In comparison with patients without S-T segment depression, those with depression had lower global ejection fraction (EF), 45 ± 10 versus 52 ± 7 ($p < 0.01$), lower inferoposterior regional EF, 40 ± 14 versus 52 ± 13 ($p < 0.005$), and larger thallium-201 defect index, 21 ± 7 versus 16 ± 6 ($p < 0.005$). In contrast, anteroseptal regional EFs were similar in the 2 groups, 54 ± 13 versus 56 ± 12 (p not significant [NS]), and the frequency of anteroseptal thallium-201 defects or redistribution abnormalities was not significantly different, 17 of 47 versus 5 of 23 and 8 of 31 versus 4 of 11 (p = NS). The predictive value of precordial S-T segment depression for mortality was low (21%) compared with the Killip class (75%), chest radiographs (67%), and EF (60%). Multiple logistic regression confirmed that the presence of S-T segment depression did not significantly improve the prediction of mortality when considered with these other risk factors. Thus, *precordial S-T segment depression is a marker of larger MI size and not of anterior ischemia.* When examined with other variables reflecting MI size and left ventricular function, precordial S-T segment depression was not a significant independent risk factor.**

A large proportion of patients with acute inferior wall myocardial infarction present with simultaneous S-T segment elevation in the inferior leads and S-T segment depression in the anterior precordial leads. These patients appear to have a higher morbidity and mortality than those presenting with inferior S-T segment elevations alone.[1,2] It has been proposed that this S-T segment depression may be an indication of simultaneous anterior ischemia or subendocardial infarction, thus accounting for the increased risk seen in these patients.[2] In support of this hypothesis, increased anterior and septal wall motion abnormalities have been noted in this subset of patients.[2] However, others, have noted primarily increased posterior wall motion abnormalities in association with this electrocardiographic finding.[3] Thus, the presence or absence of "distant" ischemia in these patients is not entirely clear. The analysis of regional wall motion may not be sufficiently specific to resolve this issue because wall motion abnormalities in experimental myocardial infarction (MI) without other evidence of ischemia can occur adjacent to, and remote from, the site of MI.[4]

It has also been suggested that precordial S-T segment depression constitutes an important risk factor for post-MI morbidity and mortality. However, when precordial S-T segment depression is evaluated as an independent prognostic factor, it becomes apparent that patients with this finding also demonstrate greater release of creatine kinase and lower left ventricular (LV) ejection fraction (EF).[2,3] Therefore, the apparent prognostic value of these anterior precordial changes may be due to the indirect influence of other variables

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reflecting increased MI size and greater LV dysfunction. This proposed risk factor has not been systematically evaluated while controlling for these confounding variables.

In this study, the relation of precordial S-T segment depression in acute inferior MI to distant anterior wall ischemia was examined by 2 independent methods: quantitative thallium-201 scintigraphy and technetium-99m radionuclide ventriculography. Subsequently, the independent prognostic significance of this electrocardiographic risk factor was compared with that of other risk factors using univariate and multivariate techniques.

## Methods

**Patient population:** Seventy patients with acute inferior MI were studied. Myocardial infarction was confirmed by clinical history, by Q-wave formation (>0.04 ms) with S-T segment elevation in at least 2 of 3 electrocardiographic leads (2, 3, or aVF), and by a typical increase and decrease in serum creatine kinase levels. Exclusion criteria included (1) the presence of pulmonary edema or cardiogenic shock, (2) previous anterior wall MI by history or electrocardiogram, and (3) the presence of a bundle branch block pattern.

Patients were classified according to the clinical degree of LV failure on admission (Killip class)[5] after review of the chart by 2 of the authors. Class I was defined as the absence of any signs or symptoms of LV failure. Class II included patients with mild to moderate failure as denoted by the presence of rales or LV gallop. Patients were considered to have significant radiographic evidence of failure if pulmonary congestion, such as vascular redistribution or interstitial edema, was present on initial chest X-ray. Patients also were classified according to the presence or absence of precordial S-T segment depression in electrocardiographic leads $V_1$ through $V_4$. Patients with at least 1 mm S-T segment depression in at least 2 of these leads on admission electrocardiography were classified as Group A. Those without these changes were classified as Group B.

In each patient, serial blood samples were taken for serum creatine kinase determination on admission and every 4 to 6 hours thereafter until levels returned to baseline. Total serum creatine kinase activity was determined according to the method of Rosalki.[6]

Quantitative thallium-201 perfusion scintigraphy and technetium-99m equilibrium-gated radionuclide ventriculography were performed in all patients within 48 hours of the onset of chest pain (mean 11 ± 8 [standard deviation]). Thallium-201 imaging was performed in the anterior and left anterior oblique 45° views 20 to 30 minutes after intravenous injection of 1.6 mCi of thallium-201. Initial studies were acquired with 500,000 counts per view, using a low energy converging hole collimator. In 42 patients, delayed views were obtained 3 hours after injection using the same acquisition time as the corresponding initial view. Images were acquired in a 128 × 128 matrix and processed using a dedicated PDP 11/60 computer (Digital Equipment). After interpolative background subtraction,[7] the perimeter of the myocardial image was circumscribed in a rectangular region manually. Using algorithms, 8 equal rectangular segments designed to fit the left ventricle in each projection were automatically generated and superimposed on the image (Fig. 1). On each image, the segment with the highest average count density was used as a relative index of normal. Using this system, we found a threshold of 25% reduction in thallium-201 activity from normal to optimally distinguish normal from abnormal segments in patients undergoing cardiac catheterization. A perfusion defect in the anteroseptal region was present if >2 abnormal segments were found in segments 1 to 3 of the anterior view or 6 to 8 of the left anterior oblique 45° view (Fig. 1). A thallium-201 defect index (TI) was constructed to assess defect size using the formula:

$$TI = \frac{\sum_{i=1}^{N} \%\,ADPi}{16}$$

where N = the total number of abnormal segments and % ADPi = the percent reduction in thallium-201 activity of the $i$th abnormal segment. This index has been reproducible in our laboratory with a high correlation between duplicate intra- and interobserver determinations (r = 0.97 and 0.96, respectively; n = 15).

In the 42 patients with sequential studies, an increase of ≥15% in thallium-201 activity for a given segment was considered evidence of thallium-201 redistribution. In a group of 17 patients with previous inferior MI undergoing cardiac catheterization, we found the presence of significant (≥2 segments) resting thallium-201 redistribution to have a sensitivity of 67% and a specificity of 100% in detecting multivessel disease.[8]

Multiple gated blood pool imaging of the left ventricle was accomplished immediately after completion of thallium-201 scintigraphy. Studies were performed with the patient in the modified left anterior oblique 45° position. According to the procedure of Pavel et al,[9] patients received an initial intravenous injection of 7.7 mg of stannous pyrophosphate (Mallinckrodt) in 1 ml of physiologic saline solution. Twenty minutes later the patient received an intravenous injection of 20 mCi of technetium-99m pertechnetate (Union Carbide). Data collection in the gated synchronized mode was begun 10 minutes after administration of the radionuclide.

Data analysis was accomplished using algorithms that were modifications of those described by Green et al[10] and Maddox et al.[11] Scintillation X-Y coordinates were sorted additively

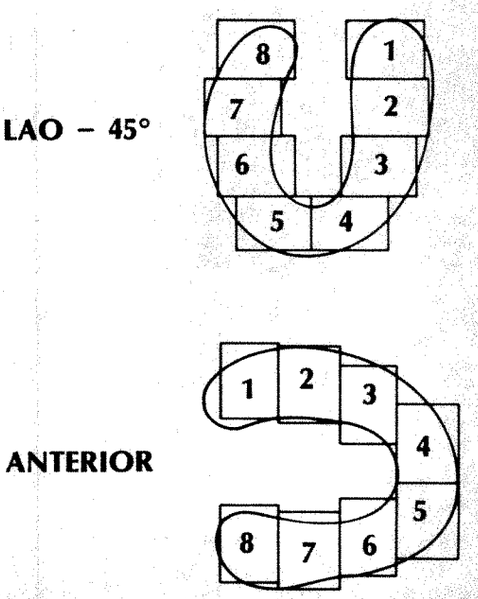



**FIGURE 1.** For computer scoring of each set of scintigraphic views, each view was divided into 8 segments, as shown. LAO = left anterior oblique.

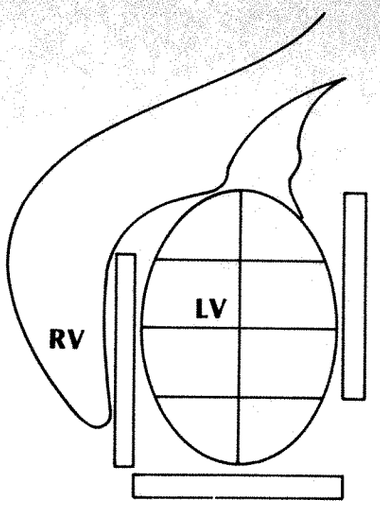



**FIGURE 2.** For calculation of regional ejection fractions, the left ventricular region of interest in the left anterior oblique projection was automatically divided into regions, as shown. LV = left ventricle; RV = right ventricle.

in forty-two 64 × 64 matrix frames after each R wave for approximately 900 cardiac cycles. Data collection continued until 8 million counts had been accumulated (15,000 to 30,000 counts per frame within the region of interest). A time-activity curve was generated from the 42 frames and the end-systolic and end-diastolic frames were identified. A left ventricular region of interest was defined with a user-dependent, irregular region-of-interest program. An automated computer macroalgorithm was then used to find the greatest vertical and horizontal dimensions of the region of interest and to construct the associated rectangle by which it would be circumscribed. The circumscribing rectangle was divided into 8 segments and superimposed on the region of interest. Portions of the rectangle that were outside the region of interest were erased. Three rectangular background areas were defined by computer and placed at the region of interest's lateral, septal, and apical sides (Fig. 2). The 2 segments overlying the cardiac base were discarded because of proximity to the atria and great vessels. The remaining 6 segments were combined into 3 larger segments representing the anteroseptal, apical, and inferoposterior regions. Regional EFs were calculated from the corresponding time-activity curve using weighted background subtraction, as described by Maddox et al.[11]

In 12 hospitalized patients with healed previous MI, the coefficient of variation for replicate EFs obtained 3 or more days apart in each patient was 3.5%. In these same patients, the coefficient of variation for regional ejection fractions ranged from 4 to 10% with this technique. In addition, our laboratory previously reported high correlations between radionuclide-derived regional EFs and corresponding angiographically determined segmental wall motion (r = 0.70 to 0.88).[12]

**Patient follow-up and mortality:** Fourteen of the 70 patients died, 7 during hospitalization and 7 after discharge. Three of the latter deaths occurred 1.5 to 6 months after MI, and 4 occurred 6 to 24 months after MI. All deaths were judged cardiac in nature: 3 inhospital deaths were related to sudden pump failure; 4 occurred after the onset of cardiogenic shock. Two posthospital deaths were sudden; 3 occurred after documented reinfarction; and 2 were related to pump failure after coronary bypass surgery. The 56 surviving patients were followed up 6 to 30 months (mean 14) after MI.

**TABLE I Clinical Characteristics of Patients**

| | Group A (ST↓) (n = 47) | Group B (No ST↓) (n = 23) |
|---|---|---|
| Age (yr): Mean and range | 60 (35–78) | 59 (45–72) |
| Interval (h) from chest pain to admission | 3.4 (1–12) | 3.4 (1–10) |
| Interval (h) from chest pain to study | 11 (2–48) | 11 (2–18) |
| Killip II | 8 | 0 |
| CXR findings | 6 | 0 |
| Peak creatine kinase (mean ± SD) | 1,856 ± 1,133 | 1,135 ± 705* |
| Deaths | 13 | 1 |

* $p < 0.005$.
CXR findings = vascular congestion on initial chest X-ray; SD = standard deviation; ST↓ = initial precordial S-T segment depression of ≥1 mm in at least 2 leads from $V_1$ to $V_4$.

**Data analysis:** The significance of a difference between means was tested by the Student's *t* test. The significance of an association between variables was tested by continuity-corrected chi-square analysis.

To assess the relative influence of each risk factor when considered simultaneously with others, a multivariate analysis using multiple logistic regression was performed (BMD-PLR). Regressions were performed using mortality at 3 weeks, 6 months, and overall mortality as the endpoint. In this analysis, all prognostic variables and their interactions were offered as candidates for the model; the first variable selected was the risk factor with the strongest influence on mortality. Subsequent variables were selected in a stepwise manner if their addition to the model resulted in a significant improvement in the model as assessed by the "improvement in fit" chi-square.[13] This statistic was derived from the log of the ratio of the maximized likelihood functions of the current to candidate model and was considered significant if >3.84 (chi-square for 1 degree of freedom at $\alpha = 0.05$).

## Results

Of 70 patients, 47 had significant precordial S-T segment depression on admission (Group A) and 23 did not (Group B). Clinical characteristics of each group are presented in Table I. The mean times of evaluation from onset of symptoms were similar in the 2 groups. Group A had a higher mean peak creatine kinase level and more patients with clinical and radiographic evidence of congestive heart failure on admission. More deaths occurred in Group A.

**Radionuclide studies:** Group A patients had a mean left ventricular EF of 45 ± 10, significantly lower than the mean EF in Group B patients, 52 ± 7, $p < 0.01$ (Table II). Of 46 Group A patients, 9 had a severely depressed left ventricular EF (<40%), compared with only 1 of the 22 Group B patients. In the past, we noted a good correlation between left ventricular EF and creatine kinase-MB infarct size.[12] Therefore, the greater degree of left ventricular dysfunction in Group A patients suggested the presence of larger MIs. The possibility of "distant" regional wall motion abnormalities contributing to global dysfunction remained.

**TABLE II Radionuclide Characteristics**

| | Group A (ST↓) | Group B (No ST↓) |
|---|---|---|
| Left ventricular EF | 45 ± 10 | 52 ± 7† |
| Anteroseptal REF | 54 ± 13 | 56 ± 12* |
| Inferoposterior REF | 40 ± 14 | 52 ± 13‡ |
| Defect index | 21 ± 7 | 16 ± 6‡ |
| Anteroseptal defects | 17/47 (36%) | 5/23 (22%)* |
| Anteroseptal redistribution | 8/31 (26%) | 4/11 (36%)* |

* p = NS.
† p <0.01.
‡ p <0.005.
Values are expressed as mean ± standard deviation.
Defect index = thallium-201 defect index; REF = regional ejection fraction; ST↓ = initial precordial S-T segment depression of ≥1 mm in at least 2 leads from $V_1$ to $V_4$.

**TABLE III Univariate Analysis: 6-Month Mortality**

| Risk Factor | Sensitivity n | Sensitivity % | Specificity n | Specificity % | Predictive Value n | Predictive Value % | $\chi^2$ |
|---|---|---|---|---|---|---|---|
| Killip II | 6/10 | 60 | 58/60 | 97 | 6/8 | 75 | 21.88 |
| LVEF | 6/10 | 60 | 56/60 | 95 | 6/10 | 60 | 15.79 |
| CXR findings | 4/10 | 40 | 56/60 | 95 | 4/6 | 67 | 10.40 |
| Defect index | 4/10 | 40 | 55/60 | 92 | 4/9 | 44 | 5.10 |
| ST↓ | 10/10 | 100 | 23/60 | 38 | 10/47 | 21 | 4.10 |
| CK | 8/10 | 80 | 22/60 | 37 | 8/46 | 17 | 0.45 |

CK = peak creatine kinase >1,000 IU/liter; CXR findings = vascular congestion on chest X-ray; Defect index = thallium-201 defect index >27.0; LVEF = left ventricular ejection fraction <40%; ST↓ = initial precordial S-T segment depressions of ≥1 mm in at least 2 leads from $V_1$ to $V_4$.

Using regional EF analysis, we assessed possible differences in regional wall motion abnormalities between the 2 groups. Group A patients had a mean inferoposterior EF of 40 ± 14, which was significantly lower than that in Group B patients whose mean inferoposterior EF was 52 ± 13, p <0.005. This result indicated greater wall motion abnormalities in the region of infarction in Group A patients. In contrast, there was no significant difference in mean anteroseptal regional EF between Group A and Group B patients, 54 ± 13 versus 56 ± 12, p = NS. Therefore, increased wall motion abnormalities in the region of MI, rather than wall motion abnormalities distant to the site of infarction, appeared to account for the greater LV dysfunction in Group A patients.

Group A patients had a larger mean thallium-201 perfusion defect index than did patients in Group B, 21 ± 7 versus 16 ± 6, p <0.005 (Table II), which also suggests the presence of larger infarcts in Group A patients. Using the presence of thallium-201 defects or thallium-201 redistribution abnormalities in anterior or septal segments as evidence of ischemia, we found no association between precordial S-T segment depression and anterior ischemia. Of 46 patients in Group A, 17 had thallium-201 defects in segments distant to the infarct as compared with 5 of 22 patients in Group B (p = NS). Of the 42 patients with resting thallium-201 redistribution studies, 8 of 31 Group A patients had distant thallium-201 redistribution abnormalities as compared with 4 of 11 patients in Group B (p = NS). Thus, as suggested by the results of the wall motion studies, Group A patients had larger contiguous areas of infarction or ischemia, but no increase in abnormalities in the septum or anterior wall distant to the site of MI.

**Risk factor analysis:** The presence of precordial S-T segment depression in this patient population appeared to be a marker for larger MIs. Other variables reflecting infarct size and left ventricular dysfunction have previously been demonstrated to be important prognostic risk factors in acute MI.[5,14–16] To evaluate the relative prognostic importance of precordial S-T segment depression, this risk factor was compared with other clinical, enzymatic, and radionuclide variables including Killip classification, presence of pulmonary vascular redistribution or interstitial edema on initial chest X-ray, peak creatine kinase, initial left ventricular EF, and thallium defect size.

**Univariate analysis:** The sensitivity, specificity, and predictive value for overall mortality was computed for each risk factor from 2 × 2 contingency tables. The predictive value of a risk factor was equivalent to the proportion of patients with the risk factor whose mortality was correctly predicted. Sensitivity was equivalent to the proportion of patient deaths in which the risk factor was present and specificity was equivalent to the proportion of survivors in which the risk factor was absent. In the analysis presented, 6 month mortality was the end-point used. Analysis of inhospital and overall mortality revealed similar findings.

Univariate analysis indicated that routine clinical methods of risk assessment had the highest predictive values for 6 month mortality. The presence of mild to moderate congestive failure on physical examination (Killip II classification) had a predictive value of 75% for this endpoint and the presence of vascular congestion on chest X-ray had a predictive value of 67% (Table III). In comparison, the presence of precordial S-T segment depression was a poor prognostic factor with a predictive value of 21%. Although this risk factor was present in 100% of the patients that did not survive 6 months, it was also present in over 60% of the patients that did survive that period, indicating a high false-positive rate. Both radionuclide EF and thallium-201 defect size were significant prognostic descriptors on univariate analysis. The EF appeared to be more sensitive and specific. The predictive value of a depressed EF of <40% for 6-month mortality was 60%. Peak creatine kinase level was not significantly associated with mortality because right ventricular infarction and right ventricular contribution to creatine kinase were present in many patients.

**Multivariate analysis:** To evaluate their relative influences on mortality, the prognostic risk factors were then submitted to multivariate analysis using a stepwise logistic regression. With this technique, the variable with the greatest independent influence in predicting mortality is selected first; other variables with significant prognostic influence are then added to the model

**TABLE IV Stepwise Logistic Regression Analysis**

| | Significant Risk Factors (In Order of Selection) | Regression Coefficients* (b) | Standard Error of b [S(b)] | b/S(b)† |
|---|---|---|---|---|
| In-hospital mortality | LVEF | 1.255 | 0.501 | 2.504 |
| | Killip II | 1.252 | 0.513 | 2.438 |
| 6-month mortality | LVEF | 1.446 | 0.615 | 2.351 |
| | Killip II | 1.445 | 0.640 | 2.259 |
| | CXR findings | 1.883 | 0.832 | 2.263 |
| Mortality at last follow-up | Killip II | 1.159 | 0.421 | 2.751 |
| | LVEF | 0.746 | 0.386 | 1.933 |

CXR findings = vascular congestion on chest X-ray; LVEF = left ventricular ejection fraction <40%.
* Based on the multiple logistic function $p = 1/\{1 + e^{-(a + b_1X_1 + b_2X_2 + \ldots b_nX_n)}\}$ where p = probability of death, $b_i$ = partial regression coefficients associated with risk factors $X_i$.
† b/s(b) >1.96 tests the hypothesis $H_A: b \neq o$ at $\alpha < 0.05$.

in a stepwise fashion until no further significant improvement in the prediction of mortality occurs. In-hospital, 6-month, and overall mortality were investigated.

In agreement with univariate analysis, the most important risk factors appeared to be Killip class II, a depressed initial EF of <40%, and findings of pulmonary congestion on initial chest X-ray (Table IV). The EF was selected as the most important risk factor in predicting in-hospital and 6-month mortality. Although this risk factor was also selected for mortality at last follow-up, the associated regression coefficient was of borderline significance. Killip II classification was a significant independent risk factor for all 3 end-points and the most important risk factor in the analysis of overall mortality. The presence of vascular redistribution or interstitial edema on initial chest X-ray improved the prediction of mortality at 6 months. The presence of precordial S-T segment depression was not selected as a significant independent risk factor at any of the 3 time intervals investigated.

## Discussion

The importance of noninfarcted but potentially ischemic areas in acute MI has recently been recognized. Patients who experience postinfarction angina with "distant" ischemic changes on electrocardiogram appear to be at high risk[17]; the presence of S-T segment depression on post-MI stress testing also appears to be a marker for increased risk.[18] Precordial S-T segment depression is frequently noted initially in acute inferior MI. These changes may be due to anterior subendocardial ischemia or a reciprocal phenomenon reflecting posterolateral injury. Previous electrocardiographic and autopsy correlations have demonstrated the presence of posterolateral infarction in patients with these electrocardiographic changes.[19,20] Recently, Shah et al[2] noted an association between precordial S-T segment depression and anteroseptal wall motion abnormalities. They proposed that anterior ischemia could account for the greater left ventricular dysfunction and higher morbidity and mortality seen in these patients. However, the presence of anteroseptal wall motion abnormalities has not been a universal finding. Goldberg et al[3] studied a similar group of patients and found this electrocardiographic phenomenon to be associated only with increased posterolateral hypokinesis. The interpretation of wall motion abnormalities in acute MI is subject to several problems.[21] Methods used to judge the presence and degree of hypokinesia on technetium-99m ventriculograms vary widely from center to center. Although exercise-induced wall motion abnormalities demonstrate high sensitivity and specificity in detecting coronary artery disease,[22] these changes may not be as sensitive or as specific in the context of resting studies performed during acute MI.

Because of the foregoing problems, we attempted to evaluate the presence of anterior wall ischemia in patients with acute inferior wall infarction and precordial S-T segment depression using 2 independent modalities: early quantitative thallium-201 perfusion scintigraphy and technetium-99m radionuclide ventriculography. No significant differences were found between Group A and Group B patients when we examined anteroseptal wall motion, the presence or absence of anteroseptal thallium-201 perfusion defects, or thallium-201 redistribution abnormalities. We did find that Group A patients had larger inferoposterior perfusion defects, lower global EFs, and greater posterior wall hypokinesis. These results suggest that a greater extent of posterolateral infarction rather than anterior ischemia is the cause of precordial S-T segment depression in this setting.

We then compared precordial S-T segment depression to other risk factors reflecting infarct size and left ventricular dysfunction. Our univariate analysis indicated that although mortality was higher in Group A patients, the specificity and predictive value of precordial S-T segment depression for mortality were poor. On multivariate analysis, risk factors such as Killip class, chest X-ray findings, and radionuclide EF were found to have a greater influence on prognosis. Indeed, when these factors were considered, the presence of S-T segment depression did not add prognostic information.

*Conclusion:* The presence of precordial S-T segment depression in acute inferior MI is related to the extent and location of the underlying infarction. These changes do not indicate a separate ischemic process and do not have an independent influence on post-MI prognosis.

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## References


1. **Shah PK, Pichler M, Berman DS, Singh BN, Swan HJC.** Left ventricular ejection fraction determined by radionuclide ventriculography in early stages of first transmural myocardial infarction. Am J Cardiol 1980;45:542–546.
2. **Shah PK, Pichler M, Berman DS, Maddahi J, Peter T, Singh BN, Swan HJC.** Noninvasive identification of a high risk subset of patients with acute inferior myocardial infarction. Am J Cardiol 1980;46:915–921.
3. **Goldberg HL, Borer JS, Jacobstein J, Klugher J, Scheidt S, Alonso DR.** Anterior S-T segment depression in acute inferior myocardial infarction: indicator of posterolateral infarction. Am J Cardiol 1981;48:1009–1015.
4. **Wyatt HL, Forrester JS, daLuz PL, Diamond GA, Chagrasulis R, Swan HJC.** Functional abnormalities in nonoccluded regions of myocardium after experimental coronary occlusion. Am J Cardiol 1976;37:336–372.
5. **Killip T, Kimbal JT.** Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients. Am J Cardiol 1967;20:457–464.
6. **Rosalki SB.** An improved procedure for serum creatine phosphokinase determination. J Lab Clin Med 1967;69:696–705.
7. **Goris ML, Daspit SG, McLaughlin P, Kriss JP.** Interpolative background subtraction. J Nucl Med 1976;17:744–747.
8. **Ong L, Dworkin P, Breen W, Padmanabhan V, Reiser P, Morrison J.** Prediction of multivessel disease after first myocardial infarction with resting thallium-201 redistribution (abstr). Clin Res 1982;30:210A.
9. **Pavel DG, Zimmer AM, Patterson VN.** In vivo labeling of red blood cells with $^{99m}$Tc: a new approach to blood pool visualization. J Nucl Med 1976;18:305–308.
10. **Green MV, Ostrow HG, Douglas MA, Myers RW, Scott RN, Bailey JJ, Johnston GS.** High temporal resolution ECG-gated scintigraphic angiocardiography. J Nucl Med 1974;16:95–98.
11. **Maddox DE, Wynne J, Uren R, Parker JA, Idoine J, Siegel LC, Neill JM, Cohn PE, Holman BL.** Regional ejection fraction: a quantitative radionuclide index of regional left ventricular performance. Circulation 1979;59:1001–1009.
12. **Morrison J, Coromilas J, Munsey D, Robbins M, Zema M, Chiaramida S, Reiser P, Scherr L.** Correlation of radionuclide estimates of myocardial infarction size and release of creatine kinase-MB in man. Circulation 1980;62:277–287.
13. **Lee ET.** Statistical Methods for Survival Data Analysis. Bellmont, CA: Lifetime Learning Publications, 1980:358.
14. **Sobel BE, Bresnahan GF, Shell WE, Yoder RD.** Estimation of infarct size in man and its relation to prognosis. Circulation 1972;46:640–648.
15. **Rigo P, Murray M, Strauss HW, Taylor D, Kelly D, Weisfeldt M, Pitt B.** Left ventricular function in acute myocardial infarction evaluated by gated scintiphotography. Circulation 1974;50:678–684.
16. **Silverman KJ, Becker LC, Bulkley BH, Burow RD, Mellits ED, Kallman CH, Weisfeldt ML.** Value of early thallium-201 scintigraphy for predicting mortality in patients with acute myocardial infarction. Circulation 1980;61:996–1003.
17. **Schuster EH, Bulkley BH.** Early post-infarction angina: ischemia at a distance and ischemia in the infarct zone. N Engl J Med 1981;305:1101–1105.
18. **Theroux P, Waters DD, Halphen C, Debaisieux J, Mizgala H.** Prognostic value of exercise testing soon after myocardial infarction. N Engl J Med 1979;301:341–345.
19. **Meyers GB, Klein HA, Hiratzka T.** VI. Correlation of electrocardiographic and pathological findings in posterolateral infarction. Am Heart J 1949;38:837–862.
20. **Levine HD, Phillips E.** An appraisal of the newer electrocardiography: correlations in one hundred and fifty consecutive cases. N Engl J Med 1951;245:833–842.
21. **Faisetti HL, Marcus ML, Kerber RE, Skorton DJ.** Quantification of myocardial ischemia and infarction by left ventricular imaging. Circulation 1981;63:747–751.
22. **Borer JS, Kent KM, Bacharach SL, Green MV, Rosing DR, Seides SF, Epstein SE, Johnston GS.** Sensitivity, specificity and predictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease. Circulation 1979;60:572–580.


I believe that man will not merely endure: he will prevail. He is immortal, not because he alone among creatures has an inexhaustible voice, but because he has a soul, a spirit capable of compassion and sacrifice and endurance.

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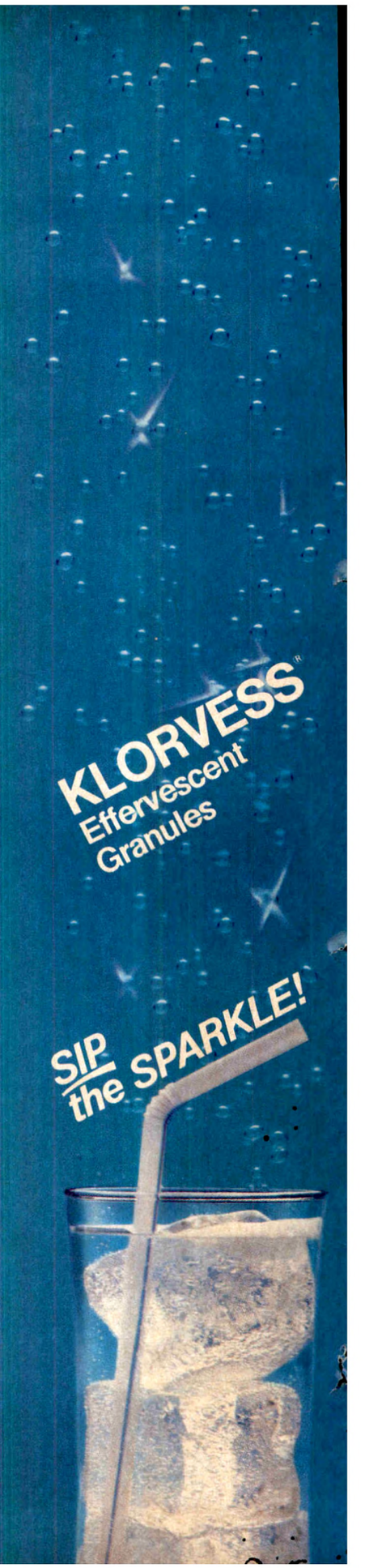
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## Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

*Brief summary of prescribing information*

**DESCRIPTION:** *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

*Klorvess (potassium chloride) 10% Liquid:* Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

**INDICATIONS:** For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

**CONTRAINDICATIONS:** Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

**PRECAUTIONS:** In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

**ADVERSE REACTIONS:** Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

**DOSAGE AND ADMINISTRATION:** *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

*Klorvess (potassium chloride) 10% Liquid:* Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

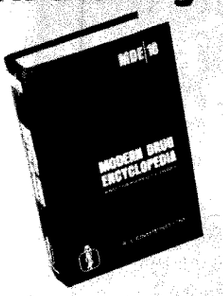
**OVERDOSAGE:** Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

**HOW SUPPLIED:** *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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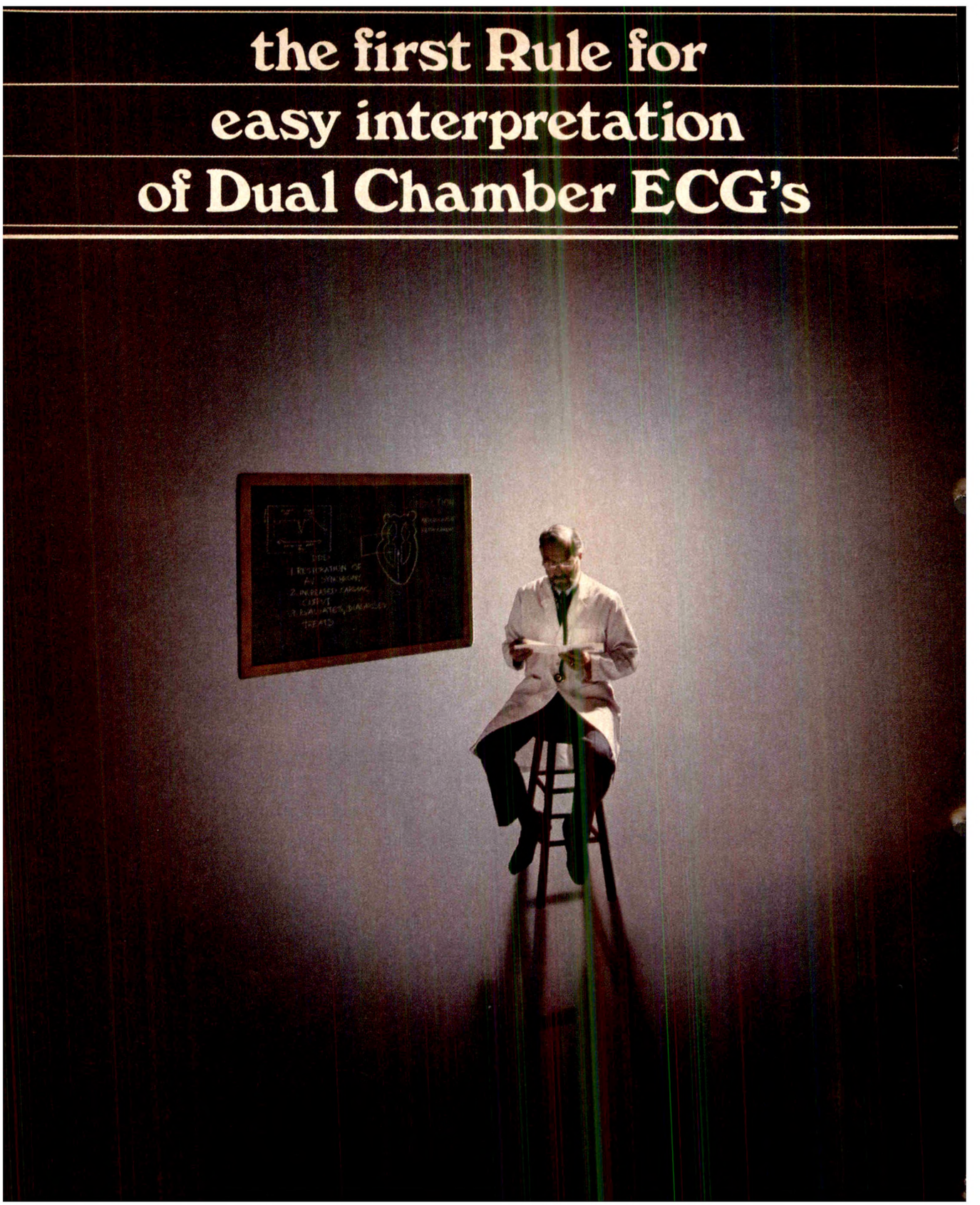
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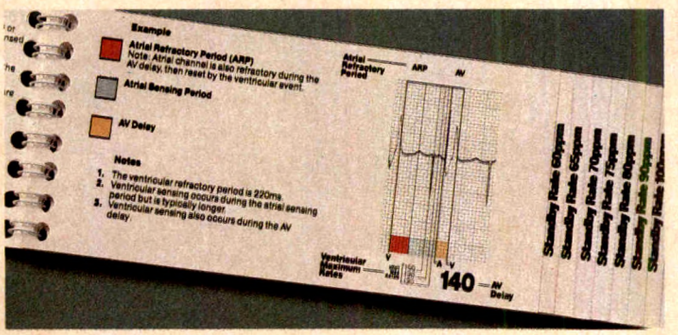
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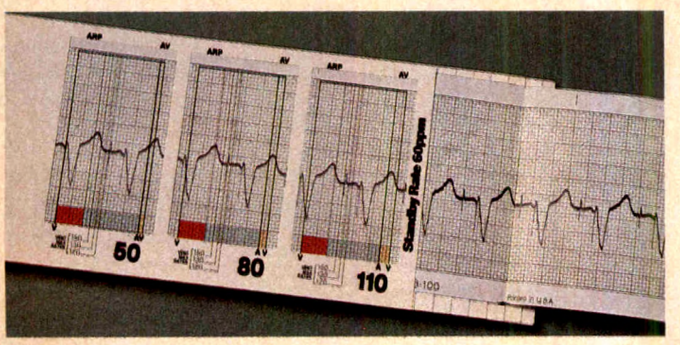
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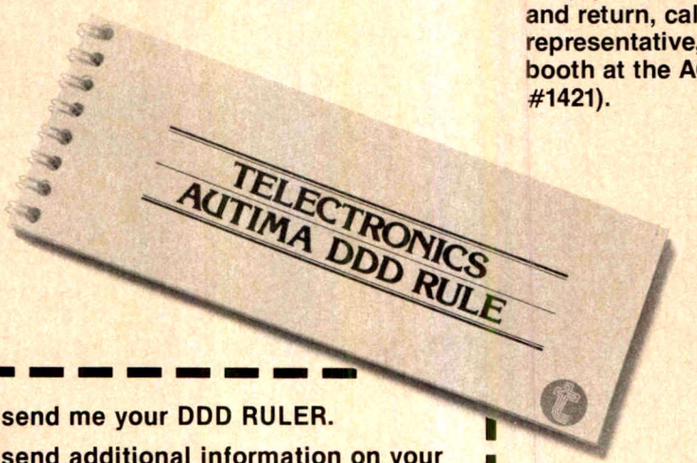
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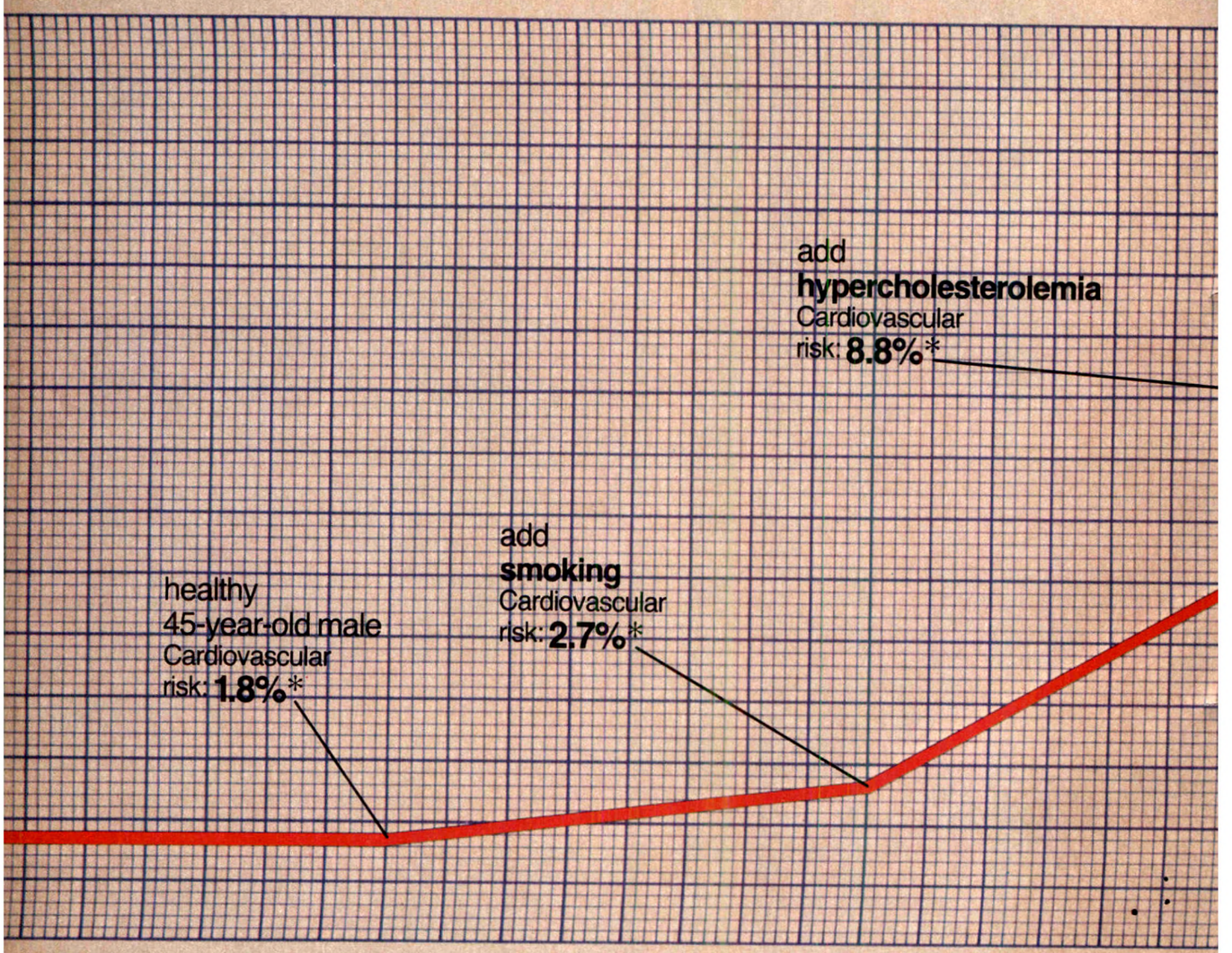
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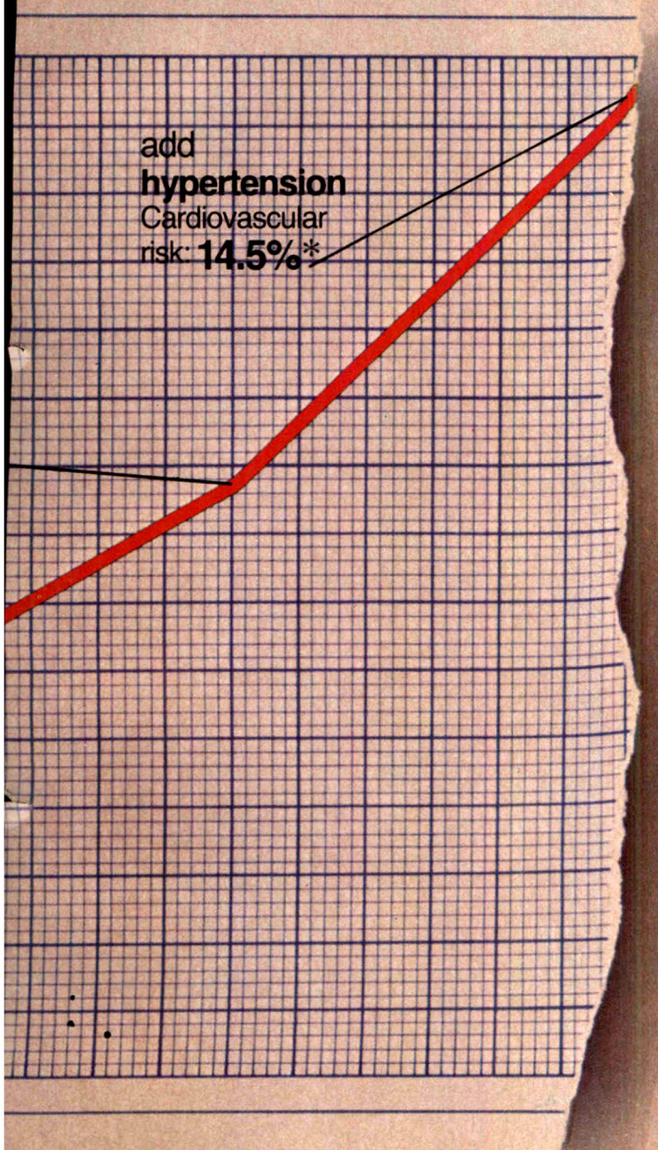



Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

# Consider the Risks




▪ When selecting antihypertensive therapy, clinical consideration should be given to the effects of the specific drug on coronary risk factors. Blood pressure control should be achieved without adversely affecting blood lipids.

## Minipress Effectively Controls Hypertension Without Adverse Effect on Blood Lipids†

▪ Minipress effectively treats hypertension. Patients have benefited from the effectiveness of Minipress in over 5 years of clinical use in this country.[1-5]

▪ Minipress has been shown not to have an adverse effect on blood lipids, according to The Oslo Study and other reports.[6-9] Because Minipress lowers high blood pressure and does not produce lipid changes which are potentially atherogenic, it provides your patient with a net reduction in risk.

†Minipress is not indicated for the treatment of hyperlipidemia.

*Please see Minipress brief summary on following page.*

# Minipress®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

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# Minipress® (prazosin HCl) Capsules 1mg, 2mg, 5mg

## B.I.D. Dosage Convenience

**BRIEF SUMMARY**

**MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use***

**INDICATIONS:** MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

**WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.**

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

***Usage in Pregnancy:*** Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

***Usage in Children:*** No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

**ADVERSE REACTIONS:** The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

**DOSAGE AND ADMINISTRATION:** The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

***Initial Dose:*** 1 mg two or three times a day. (See Warnings.)

***Maintenance Dose:*** Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

***Use With Other Drugs:*** When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

**HOW SUPPLIED:** MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

*More detailed information available on request.*


**References:** 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet:* 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.

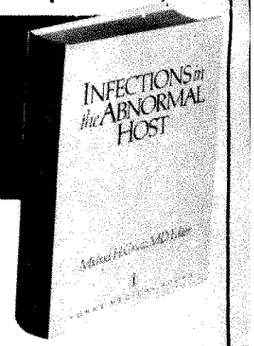

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# Radionuclide-Determined Changes in Pulmonary Blood Volume and Thallium Lung Uptake in Patients With Coronary Artery Disease

RICHARD A. WILSON, MD, ROBERT D. OKADA, MD, CHARLES A. BOUCHER, MD, H. WILLIAM STRAUSS, MD, and GERALD M. POHOST, MD

**Exercise-induced increases in radionuclide-determined pulmonary blood volume (PBV) and thallium lung uptake have been described in patients with coronary artery disease (CAD) and have been shown to correlate with transient exercise-induced left ventricular dysfunction. To compare these 2 techniques in the same patients, 74 patients (59 with and 15 without significant CAD) underwent supine bicycle exercise twice on the same day—first for thallium myocardial and lung imaging and then for technetium-99m gated blood pool imaging for the PBV ratio determination. Thallium activity of lung and myocardium was determined to calculate thallium lung/heart ratio. Relative changes in PBV from rest to exercise were expressed as a ratio of pulmonary counts (exercise/rest). Previously reported normal ranges for thallium lung/heart ratio and PBV ratio were used. The PBV ratio and thallium lung/heart ratio were abnormal in 71 and 36%, respectively, of patients with CAD ($p < 0.01$). Both ratios were normal in all patients without CAD. Although the resting ejection fractions did not differ significantly in patients with normal versus those with abnormal PBV ratios or thallium lung/heart ratios, abnormal PBV ratios and thallium lung/heart ratios were associated with an exercise-induced decrease in ejection fraction. Propranolol use was significantly higher in patients with abnormal than in those with normal thallium lung/heart ratios ($p < 0.01$). No significant difference in propranolol use was present in patients with abnormal or normal PBV ratios. In conclusion: (1) the prevalence of an abnormal thallium lung/heart ratio is less than that of the PBV ratio in patients with CAD; (2) both tests are normal in normal control subjects; (3) propranolol does not cause abnormal results in normal control subjects; however, propranolol may influence lung thallium uptake in patients with CAD; and (4) when both tests are abnormal, there is a high likelihood of multivessel disease.**

Exercise-induced changes in pulmonary blood volume (PBV) have been noninvasively determined in patients using multigated blood pool imaging by previous work from this laboratory.[1] Most patients with coronary artery disease (CAD) had an increase in PBV during supine exercise. No such changes were found in patients without CAD and in patients with disease confined to the right coronary artery. The increase in PBV was found to be due to transient exercise-induced left ventricular dysfunction.[2]

Other studies have described increased thallium lung activity on the initial postexercise thallium images in some patients with CAD.[3–5] A study by Boucher et al[3] showed that increased thallium lung activity reflected transient elevations in the pulmonary capillary wedge pressure during exercise and suggested that transient left ventricular failure caused increased thallium lung uptake. Thus, 2 noninvasive radionuclide techniques are now available for the detection of transient left ventricular failure during exercise in patients with CAD. This study compares these 2 techniques in the same patient population. The purposes were to determine (1) the additive prevalence of either or both abnormal ratios in patients with CAD, and (2) the significance of both ratios being abnormal or normal.

From the Cardiac Unit, Massachusetts General Hospital, Boston, Massachusetts. This study was supported in part by Grant HL-21751, HL-07416, and HL-12322 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received August 6, 1982; revised manuscript received December 3, 1982, accepted December 6, 1982.

Address for reprints: Robert D. Okada, MD, Cardiac Unit, Massachusetts General Hospital, Boston, Massachusetts 02114.

## Methods

**Patient population:** We prospectively studied 74 patients (60 men and 14 women) who were referred for evaluation of chest pain syndromes. The mean age was 51 ± 10 (standard deviation) years (range 28 to 75). Patients with congestive heart failure, recent myocardial infarction, unstable angina, or physical disability limiting exercise were excluded. None

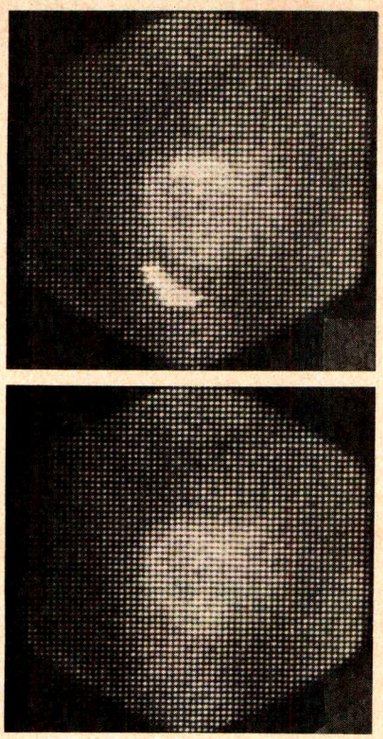


**FIGURE 1.** Representative thallium-201 images of a patient with CAD and increased lung uptake in the anterior projection immediately after maximal supine stress testing. The **bottom image** demonstrates the regions of interest used for the calculation of the lung-to-heart ratio. The patient had significant 3-vessel CAD. The thallium lung-to-heart ratio was 0.78.

of the patients were New York Heart Association functional class III or IV.

**Thallium stress imaging:** Patients were exercised supine in the fasting state on a table equipped with a bicycle ergometer (Cardiac Stress Systems, Engineering Dynamics, Lowell, Massachusetts). Electrocardiographic lead II was monitored continuously during exercise, and leads II, III, aVF, and $V_5$ were monitored at 2- to 3-minute intervals during exercise. Arm cuff blood pressure was recorded every minute. The exercise work load was initiated at 150 kpm/min and increased by 150 kpm/min every 2 minutes until chest pain, dyspnea, leg fatigue, or S-T segment depression ≥2 mm by electrocardiography developed. Thirty seconds before the anticipated termination of exercise, 1.5 mCi of thallous chloride-201 (New England Nuclear, North Billerica, Massachusetts) was injected by way of an indwelling venous catheter. Thallium imaging was performed with the patient in the supine position using an Ohio Nuclear series 120 gamma camera (Ohio Nuclear, Solon, Ohio) equipped with a low energy all-purpose collimator, employing a 30% energy window centered around the 60 to 80 keV mercury x-ray peak of thallium. Imaging was begun immediately after the cessation of exercise. Initial images were collected in a 128 × 128 byte mode matrix format in the anterior and 50° left anterior oblique projections for 6 minutes each. Delayed images were collected at 2 to 3 hours after exercise in the same projections for 6 minutes each. Approximately 200,000 counts were collected per image. Images were collected using a portable cardiac computer system (MUGA-CART, Medical Data Systems, Ann Arbor, Michigan). Field uniformity of the camera was checked and corrected each day using a Cobalt-57 disc source for flood images.

**Exercise gated blood pool imaging:** After the delayed thallium images were obtained, rest and exercise gated blood pool imaging were performed. Three milligrams of stannous pyrophosphate (Pyrolite, New England Nuclear, North Billerica, Massachusetts), followed 30 minutes later by 20 mCi of technetium-99m–labeled pertechnetate, were given intravenously for in vivo labeling of red blood cells. The scintillation camera was repeaked at 140 keV with a 25% window and initial rest studies were performed with the patient in the supine position. Images were recorded in the anterior projection and in the left anterior oblique projection which displayed the ventricular septum most homogeneously (approximately 50° left anterior oblique). Since the technetium-99m photon flux was calculated to be 130 times greater than the thallium photon flux in the technetium energy window, the imaging effects of the previously administered thallium were minimal. The cardiac cycle was divided into 28 equal segments. At least 200,000 counts were collected in each of the 28 frames at rest. Depending on heart rate, imaging time ranged from 5 to 10 minutes. Patients then exercised again to the same endpoints as in the first study. Multigated blood pool images were taken in the 50° left anterior oblique position for 3 minutes during peak exercise. The mean number of counts/frame was 150,000 ± 29,000 (standard deviation) for blood pool images obtained during exercise.

**Lung thallium-201 analysis:** The anterior thallium studies were condensed from a 128 × 128 byte mode matrix to a 64 × 64 word mode matrix and displayed on a cathode ray tube for quantitative analysis. Two independent observers identified a region of interest over 1 of the 3 segments of myocardium in the anterior view (anterolateral, apical, or inferior) with the highest count density and a region of interest over the left upper lung field (Fig. 1). A printout of the counts per picture element for each region of interest was then obtained for the initial thallium images. The mean ± 1 standard deviation total counts in the lung and myocardial regions of interest were 5,152 ± 2,157 and 9,588 ± 4,223, respectively. Lung thallium activity was expressed as a percentage of the maximal myocardial counts for each image (thallium lung/heart ratio). For the purposes of this study, the upper limit of normal for the thallium lung/heart ratio was defined as 2 standard deviations above the mean for a previously reported group of control patients (<0.545).[5]

**Pulmonary blood volume ratio analysis:** The ratio of PBV counts between exercise and rest was determined from the 50° left anterior oblique end-diastolic frame as previously described.[2] The PBV ratio was determined in this projection since this projection is the only one routinely acquired during exercise in most laboratories. Two independent observers determined pulmonary blood volume counts at exercise and rest without knowledge of cardiac catheterization results. The PBV ratio was calculated as the pulmonary counts during exercise divided by counts at rest after correction for differences in acquisition times. Thus, a ratio <1.0 corresponded to a decrease in PBV during exercise, and a ratio >1.0 to an increase in PBV with exercise. The ratios determined by the 2 observers were averaged to produce a single value for each patient. A PBV ratio was considered abnormal if it was ≥1.06, which represents the upper limit of 2 standard deviations above the mean value for a group of previously reported control patients.[1] An example of the regions of interest at rest and exercise used to calculate the PBV ratio is shown in Figure 2.

**Ejection fraction analysis:** The rest multigated blood pool imaging ejection fraction was determined from the left anterior oblique projection utilizing a semiautomatic edge detec-

**TABLE I Percentage of Patients With Abnormal Thallium Lung/Heart Ratios and Pulmonary Blood Volume Ratios in Groups of Patients With and Without Coronary Artery Disease**

| | n | % of Patients With Abnormal Tl L/H | % of Patients With Abnormal PBV |
|---|---|---|---|
| No CAD | 15 | 0 | 0 |
| Single-vessel RCA | 6 | 33 | 17 |
| Single-vessel LAD or CIRC | 15 | 27 | * 73 |
| 2- or 3-Vessel | 38 | 39 | * 79 |
| All CAD | 59 | 36 | * 71 |

CAD = coronary artery disease; CIRC = circumflex coronary artery disease; LAD = left anterior descending coronary artery disease; RCA = right coronary artery disease; Tl L/H = thallium lung/heart ratio.
Brackets indicate statistically significant differences between groups ($p < 0.05$).
* $p < 0.05$.

tion program. A box was positioned to encompass the entire left ventricle at end-diastole. Beginning at the center of the ventricle, the program searched outward in a radial fashion until a matrix point was reached that satisfied 1 of 2 criteria. The first criterion was that the 2-dimensional second derivative be equal to zero. The second criterion was that the number of counts at a matrix point be less than a given threshold value selected by the observer. In this manner, the left ventricular edge was defined for each frame. A background region of interest was selected by the program for a region outside the end-systolic frame. The ejection fraction was calculated as end-diastolic counts minus end-systolic counts divided by end-diastolic count minus background counts.

**Cardiac catheterization and angiography:** All patients underwent left heart catheterization, coronary angiography, and left ventriculography within 1 week of the radionuclide studies. Coronary arteriograms were read by 2 independent observers. Significant stenosis was defined as ≥50% reduction in the intraluminal diameter of a coronary artery in at least 2 projections.

**Statistical analysis:** Comparisons of patient groups with normal or abnormal PBV ratios and thallium lung/heart ratios were made using chi-square analysis or Fisher's exact test. Data for groups of patients were expressed as mean ± standard error of the mean. Comparison between quantitative thallium lung/heart ratios and between PBV ratios and patient groups was made by a one-way analysis of variance and the Newman-Keuls multiple comparison test.

## Results

**Clinical and angiographic findings:** Of the 74 patients, 59 had significant CAD: 21 patients had single-vessel CAD (15 had isolated left anterior descending or circumflex CAD and 6 had isolated right CAD) and 38 patients had multivessel (2- or 3-vessel) CAD. Forty-one patients with and 5 patients without CAD were taking propranolol during the study period. Twenty-eight patients with CAD had a history of previous myocardial infarction.

**Thallium lung/heart ratio analysis:** Table I shows the percentage of patients with abnormal thallium lung/heart ratios in groups of patients with CAD. All 15 patients (100%) with no significant CAD had normal thallium lung/heart ratios using a previously reported

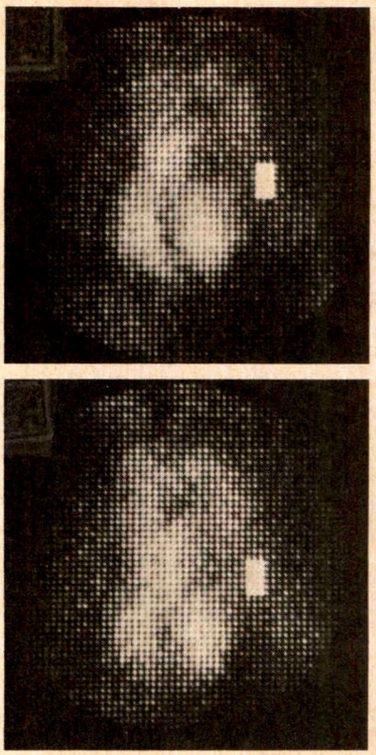


**FIGURE 2.** End-diastolic frames from multigated blood images recorded in the left anterior oblique position at rest (**top**) and peak exercise (**bottom**). Regions of interest are included. The ratio of pulmonary blood volume during exercise compared with that at rest was 1.10 in this patient with CAD. Note that this exercise-induced increase in pulmonary activity is not apparent on visual comparison of the images at exercise and rest.

normal range. Of the 59 patients with significant CAD, 21 (36%) had abnormal thallium lung/heart ratios. The percentage of patients with abnormal thallium lung/heart ratios in the group with no CAD was significantly different from (1) the group with single-vessel left anterior descending or circumflex disease (27%), (2) the group with multivessel disease (39%) ($p < 0.05$), and (3) the group of patients with CAD as a whole (36%) ($p < 0.01$). The prevalence of an abnormal thallium lung/heart ratio was not significantly different in patients with a history of a previous myocardial infarction (39%) and those without such a history (32%).

Figure 3 shows the thallium lung/heart ratios (mean ± standard error of the mean) for groups of patients. There were significant differences between the normal (no CAD) group (0.37 ± 0.02) and (1) the group with CAD as a whole (0.50 ± 0.01) ($p < 0.001$), (2) the group with single-vessel left anterior descending or circumflex disease (0.48 ± 0.03) ($p < 0.01$), and (3) the group with multivessel disease (0.52 ± 0.02) ($p < 0.01$). Although the thallium lung/heart ratio tended to be lower for patients with disease confined to single-vessel right CAD (0.44 ± 0.04) than for those with multivessel disease (0.52 ± 0.02), these differences did not reach statistical significance.

**Pulmonary blood volume ratio analysis:** Table I indicates the percentage of patients with abnormal PBV ratios for each group. All 15 normal subjects (100%) had PBV ratios that were within the previously reported normal range from this laboratory. Of the 59 patients with significant CAD, 42 (71%) had abnormal PBV ratios. The percentage of patients with abnormal PBV ratios with CAD confined to the right coronary artery (17%) was significantly lower than the percentage of patients with abnormal results and either single-vessel left anterior descending or circumflex CAD (73%) or multivessel disease (79%) ($p < 0.05$). The prevalence of an abnormal PBV ratio was not significantly different in patients with a history of a previous myocardial infarction (68%) and those without such a history (74%).

Figure 4 demonstrates the PBV ratio for the different patient groups. There were significant differences in the PBV ratios in normal patients ($0.96 \pm 0.01$) compared with patients with either single-vessel left anterior descending or circumflex disease ($1.15 \pm 0.04$) ($p < 0.01$), or compared with patients with multivessel CAD ($1.13 \pm 0.04$) ($p < 0.05$). Although the PBV ratios for single-vessel right CAD ($1.00 \pm 0.04$) tended to be lower than the PBV ratios for either single-vessel left anterior descending or circumflex disease ($1.15 \pm 0.04$) or for multivessel disease ($1.13 \pm 0.04$), these differences did not reach statistical significance.

**Pulmonary blood volume and thallium lung/heart ratios:** PBV ratios were abnormal in 42 of 59 (71%) while thallium lung/heart ratios were abnormal in 21 of 59 (36%) patients with significant CAD ($p < 0.001$) (Table I). The combined prevalence of either an abnormal PBV or thallium lung/heart ratio (81%) was higher than the prevalence of an abnormal PBV ratio alone (71%) in the patients with CAD. However, the ratios were both normal in all normal controls. PBV ratios were abnormal in 1 of 6 (17%) patients, and thallium lung/heart ratios were abnormal in 2 of 6 patients with single-vessel right CAD. However, PBV ratios in patients with single-vessel left anterior descending or circumflex disease were more likely to be abnormal compared with thallium lung/heart ratios in the same group (11/15 = 73% and 4/15 = 27%, respectively) ($p < 0.05$). Similarly, the PBV ratio was more likely to be abnormal in patients with multivessel disease (30/38 = 79%) compared with the thallium lung/heart ratio (15/38 = 39%) ($p < 0.001$).

Thirteen of 15 CAD patients (87%) with an abnormal PBV and thallium lung/heart ratio, 20 of 33 CAD patients (64%) with either an abnormal PBV or thallium lung/heart ratio, and 5 of 11 CAD patients (45%) with neither an abnormal PBV nor thallium lung/heart ratio had multivessel CAD ($p < 0.05$). Thus, there was a very high likelihood of multivessel disease when both the PBV and thallium lung/heart ratios were abnormal.

**Ejection fraction analysis:** The mean resting left ventricular ejection fraction seen by gated blood pool imaging was $65.0 \pm 2.1\%$ for the patients without CAD and $63.0 \pm 1.5\%$ for all the patients with CAD (difference not significant [NS]). The mean resting ejection fraction for patients with isolated right CAD ($70.5 \pm$

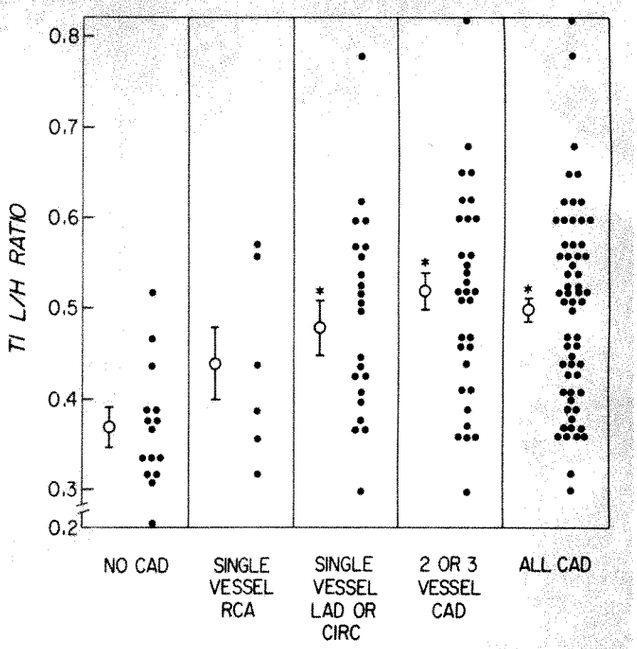



**FIGURE 3.** Pulmonary blood volume (PBV) ratios (exercise PBV/rest PBV) in patients with and without coronary disease (no CAD = no significant CAD; single-vessel LAD or CIRC = single-vessel left anterior descending or circumflex CAD; 2- or 3-vessel CAD = multivessel CAD; all CAD = all patients with significant CAD). * $p < 0.05$ compared with the no CAD group. TI L/H Ratio = thallium lung/heart ratio.

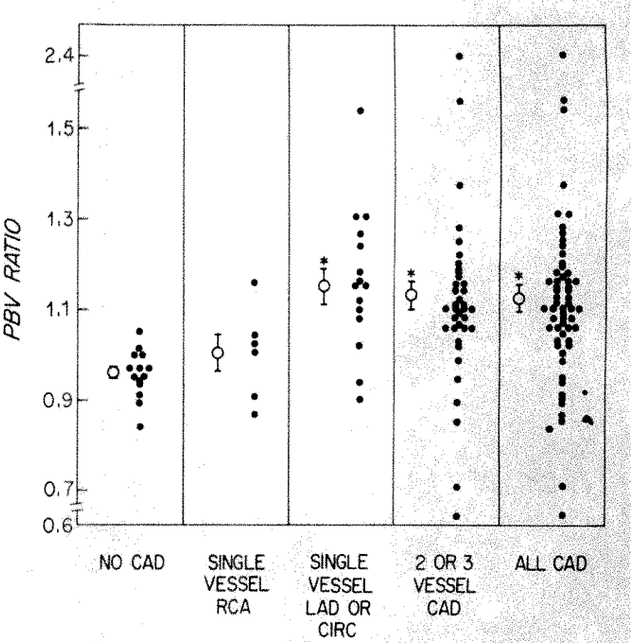



**FIGURE 4.** Thallium lung-to-heart ratios on the immediate postexercise image for patients with and without CAD (no CAD = no significant CAD; single-vessel RCA = significant CAD confined to the right coronary artery; single-vessel LAD or CIRC = significant single-vessel CAD confined to either the left anterior descending or circumflex coronary arteries; 2- or 3-vessel CAD = significant CAD involving 2 or 3 major coronary arteries [RCA, LAD, CIRC]; all CAD = all patients with significant CAD). Values are expressed as mean ± standard error of the mean for each group. * $p < 0.01$ compared with no CAD group.

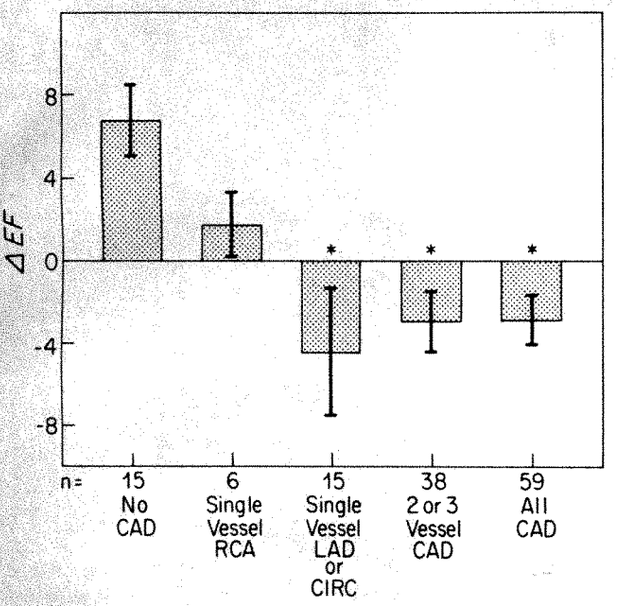



**FIGURE 5.** Change in the ejection fraction from rest to exercise (ΔEF %) (the rest ejection fraction minus exercise ejection fraction) in groups of patients (no CAD = no significant CAD; single-vessel RCA = CAD confined to the right coronary artery; single-vessel LAD or CIRC = CAD confined to the left anterior descending or circumflex coronary arteries; 2- or 3-vessel CAD = multivessel CAD; all CAD = all patients with significant CAD). Values are expressed as mean ± standard error of the mean for each group. * $p < 0.05$ compared with no CAD group.

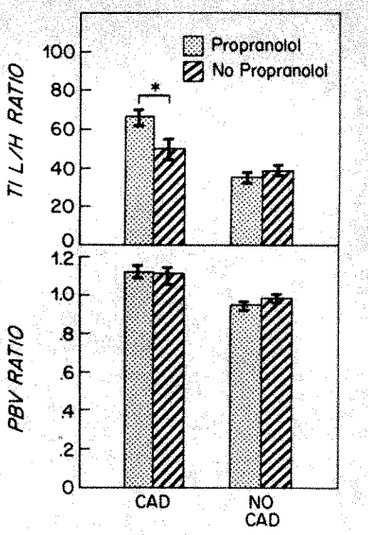



**FIGURE 6.** Effects of propranolol on thallium lung/heart (Tl L/H) and PBV ratios. Patients who were or who were not taking propranolol were grouped according to the presence (CAD) or absence (no CAD) of significant CAD. The thallium lung/heart ratio of patients with CAD who were taking propranolol was significantly higher than the thallium lung/heart ratio of patients not receiving propranolol (* $p < 0.001$), respectively. Values are expressed as mean ± standard error of the mean.

2.2%) was significantly higher than the mean resting ejection fraction for patients with multivessel CAD (61.1 ± 1.8%) ($p < 0.01$) but not isolated left anterior descending or circumflex CAD (64.9 ± 3.7%) (p = NS). However, the change in the ejection fraction from rest to exercise was significantly different in patients with and without CAD (Fig. 5). Patients without CAD and those with single-vessel right CAD had an increase in the ejection fraction with exercise. Patients with either single-vessel left anterior descending or circumflex disease or patients with multivessel disease had a decrease in the ejection fraction with exercise ($p < 0.05$ compared with normal subjects). The resting ejection fraction was not significantly different in the patients with normal or abnormal thallium lung/heart ratios or PBV ratios. However, the change in ejection fraction from rest to exercise was significantly lower in patients with abnormal than in those with normal thallium lung/heart ratios (−4.5 ± 1.8 and +0.6 ± 1.4, respectively) ($p < 0.05$) and in patients with abnormal than in those with normal PBV ratios (−3.4 ± 1.6 and +2.5 ± 1.4, respectively) ($p < 0.01$).

**Effect of propranolol on thallium lung/heart ratios and pulmonary blood volume ratios:** Of the 74 patients, 46 (62%) were taking propranolol at the time of the study. Of these 46, 5 had normal coronary arteries and 41 did not. The thallium lung/heart ratios of the patients taking propranolol were significantly higher than the thallium lung/heart ratios of the patients not taking propranolol (Fig. 6). However, the PBV ratios of patients receiving propranolol were not significantly different from those in patients not taking propranolol. The age, resting ejection fraction, the change in ejection fraction with exercise, and the number of diseased coronary arteries were not significantly different in the patients with CAD taking propranolol and those not receiving propranolol (Table II). However, the percentage of the maximal age-predicted heart rate achieved during exercise was significantly lower in patients taking propranolol than in those not taking propranolol ($p < 0.001$). Of the 21 patients with abnormal thallium lung/heart ratios, 19 (90%) were taking propranolol at the time of the study. This percentage was significantly different from the 51% (27 of 53) of patients with normal thallium lung/heart ratios who were receiving propranolol ($p < 0.01$). However, the percentage of patients with abnormal PBV ratios who were taking propranolol—69% (29 of 42)—was not significantly different from the 53% (17 of 32) of patients with normal PBV ratios who were receiving propranolol.

Of the 15 patients with no significant CAD, 5 were taking propranolol and 10 were not. None of the 15 had abnormal PBV or thallium lung/heart ratios. The thallium lung/heart ratios of the 5 patients receiving propranolol were not significantly different from the 10 patients not taking propranolol (0.36 ± 0.02 and 0.39 ± 0.03, respectively) (Fig. 6). In addition, the PBV ratios of the 5 patients taking propranolol were not significantly different from the 10 patients not taking propranolol (0.95 ± 0.02 and 0.98 ± 0.02, respectively). Age, resting ejection fraction, change in ejection fraction from rest to exercise, and percentage of age-predicted

**TABLE II Findings in Patients With Coronary Artery Disease***

| | Taking Propranolol | Not Taking Propranolol | p Value |
|---|---|---|---|
| n | 42 | 18 | |
| Age | 51.5 ± 1.4 | 54.2 ± 2.6 | NS |
| Resting EF | 63.0 ± 1.7 | 62.9 ± 3.4 | NS |
| ΔEF | −1.9 ± 1.4 | −3.2 ± 2.1 | NS |
| % Max HR | 60.3 ± 1.9 | 72.2 ± 2.7 | = 0.01 |
| Vessels diseased (n) | 1.93 ± 0.13 | 2.00 ± 0.20 | NS |

* Age, resting ejection fraction (EF), change in ejection fraction (ΔEF) in ejection fraction units, the percentage of age-predicted maximal heart rate achieved during exercise (% max HR), and number of diseased vessels in patients with coronary artery disease either taking or not taking propranolol.
Values are expressed as mean ± standard error of the mean.
NS = not significant.

**TABLE III Findings in Patients Without Coronary Artery Disease***

| | Taking Propranolol | Not Taking Propranolol | p Value |
|---|---|---|---|
| n | 5 | 10 | |
| Age | 47.4 ± 5.5 | 48.4 ± 3.5 | NS |
| Resting EF | 62.2 ± 2.1 | 66.4 ± 2.9 | NS |
| ΔEF | 5.4 ± 3.2 | 7.6 ± 2.2 | NS |
| % Max HR | 74.4 ± 4.9 | 73.1 ± 3.4 | NS |

* Age, resting ejection fraction (EF), change in ejection fraction (ΔEF) in ejection fraction units, and the percentage of age-predicted maximal heart rate achieved during exercise (% max HR) in patients without coronary artery disease either taking or not taking propranolol.
Values are expressed as mean ± standard error of the mean.
NS = not significant.

maximal heart rate achieved were not different in normal patients who were taking or who were not taking propranolol (Table III). The percentage of patients with CAD taking propranolol with abnormal thallium lung/heart ratios was significantly higher than the percentage of patients not receiving propranolol with abnormal thallium lung/heart ratios (Table IV). There was no significant difference in the percentage of patients who were and who were not taking propranolol with abnormal PBV ratios.

## Discussion

**Pulmonary blood volume ratio:** The results of this study indicate that increases in radionuclide-determined PBV during exercise in patients with CAD are common, occurring in 71% of patients. Factors that may increase PBV include decreases in myocardial contractility,[6–10] increases in left ventricular diastolic stiffness,[11] and diminished left ventricular relaxation.[12] By increasing left ventricular end-diastolic pressure, these factors may cause an increase in pulmonary venous pressure[8,10,13–18] and volume.[19] Two previous studies, 1 using upright exercise and carbon-11–labeled carbon monoxide inhalation,[20] and the other using supine exercise and an invasive indicator-dilution technique,[21] have shown increases in PBV with exercise in patients with CAD. A more recent study from this laboratory using gated blood pool imaging with technetium-labeled red blood cells also found significant increases in PBV ratio with exercise in patients with CAD.[1]

In the present study, the 6 patients with single-vessel right CAD tended to have a normal PBV ratio (only 1 of 6 patients had an abnormal PBV ratio). It is postulated that this finding is due to exercise-induced right ventricular ischemia which decreases right ventricular function more than left ventricular function, thereby preventing an increase in PBV ratio.[1] In support of this hypothesis is the observation that patients with 2-vessel disease involving the right coronary artery tended to have lower PBV ratios than patients with 2-vessel disease not involving the right coronary artery.[1] Also, patients with right CAD have been shown to have an exercise-induced decrease or no change in the right ventricular ejection fraction while patients without right CAD tend to have increased right ventricular ejection fractions.[22,23] However, abnormal right ventricular performance with exercise may also be related to an abnormal left ventricular response to exercise.[24]

**Thallium lung/heart ratio:** Increased lung thallium activity has been qualitatively[3,4,25,26] observed and quantified[4,5] on initial myocardial images in patients with CAD after treadmill[4,25,26] and supine bicycle exercise.[5] Although the thallium-201 pulmonary extraction fraction is normally 9% on the initial transit through the pulmonary vasculature,[26–30] a previous study has shown that increased lung extraction of thallium occurs in a model of left heart failure in which left atrial pressure or pulmonary transit time or both were increased.[4] Furthermore, Boucher et al[3] have

**TABLE IV Percentages of Patients Taking and Not Taking Propranolol With Abnormal Thallium Lung/Heart (Abn Tl L/H) Ratios and Abnormal Pulmonary Blood Volume (Abn PBV) Ratios**

| | | Taking Propranolol | Not Taking Propranolol | p Value |
|---|---|---|---|---|
| All 74 patients | Abn Tl L/H | 19/46 (41%) | 2/28 (7%) | <0.01 |
| | Abn PBV | 29/46 (63%) | 13/28 (46%) | NS |
| No CAD | Abn Tl L/H | 0/5 | 0/10 | NS |
| | Abn PBV | 0/5 | 0/10 | NS |
| All CAD | Abn Tl L/H | 19/41 (46%) | 2/18 (11%) | <0.01 |
| | Abn PBV | 29/41 (71%) | 13/18 (72%) | NS |

CAD = coronary artery disease; NS = not significant.

shown that increased thallium lung activity occurred in patients with simultaneously measured increases in the pulmonary capillary wedge pressure during exercise. In that study, the mean value of the pulmonary capillary wedge pressure during exercise in the group of patients with increased thallium lung activity was 24 ± 3 mm Hg (mean ± standard deviation). This degree of pressure elevation has been shown to cause transudation of fluid into the pulmonary interstitial space,[21] thus raising the possibility that thallium may also leave the pulmonary intravascular compartment in response to elevated pulmonary capillary wedge pressures. Although direct evidence for the location of thallium uptake in the lungs has not yet been obtained, it has also been noted[3] that the clearance of thallium from the lung within 2 hours is consistent with the known rapid clearance of interstitial lung water.[31] It is unlikely that the increased pulmonary activity is due to blood pool activity since the extraction efficiency of thallium from the blood is 85% on each pass through the circulation and since no activity is seen in the left ventricular cavity. It also appears unlikely that the increases seen in the thallium lung/heart ratio in this and in previous studies[3–5] are due mainly to a decrease in myocardial counts since Bingham[4] found little decrease in absolute myocardial counts used in the denominator of the ratio. It is possible, however, that global ischemia due to severe 3-vessel CAD could result in diminished thallium uptake in all areas of myocardium so that the thallium lung/heart ratio would be elevated.

**Combined pulmonary blood volume and thallium lung/heart ratio results:** In the present study, the PBV ratio was abnormal in 71% of patients with CAD, while the thallium lung/heart ratio was abnormal in 36% of patients with CAD. At least 1 of the 2 ratios was abnormal in 81% of patients with CAD. Both ratios were normal in all of the normal patients without CAD. Thus, the finding of either or both ratios being abnormal is associated with a high likelihood of CAD, whereas the finding of both ratios being normal is associated with a low likelihood of CAD. The current study also demonstrates that when both ratios are abnormal, there is a high likelihood of multivessel disease.

The lower prevalence of abnormal thallium lung/heart ratios in patients with CAD compared with the PBV ratio requires further investigation. Several possible reasons for the different prevalences exist: (1) The PBV ratio detects excess blood volume in the pulmonary vasculature which occurs rapidly with increasing left ventricular end-diastolic pressure. However, the thallium lung/heart ratio may depend on uptake of thallium by the lung which may take longer. (2) The thallium lung/heart ratio uses only the initial postexercise image while the PBV ratio uses rest and exercise images, which tends to cancel out some of the random variables in the determination of the PBV ratio. In addition, the thallium may not have been injected at peak exercise. (3) The thallium lung/heart ratio often uses the anterolateral myocardial wall activity for the denominator of the ratio. If this myocardial region is contaminated by overlying lung activity, thereby making the denominator of the ratio larger, the ratio would tend to be smaller because the lung counts contribute to the myocardial region of interest, thus contributing to a lower prevalence of an abnormal result. (4) Rapid washout of thallium from the lung would also tend to lower the thallium lung/heart ratio if the initial set of images were delayed since the lung thallium content has already decreased. (5) Less stringent upper limits of normal (±2 standard deviations above the mean) may also increase the prevalence of an abnormal thallium lung/heart ratio in patients with CAD; however, this may also be accompanied by an increased incidence of abnormal results in patients without CAD.

Although our results were obtained in patients with coronary artery disease, patients with other diseases affecting the left ventricle would also be expected to demonstrate abnormal PBV and thallium lung/heart ratios. Exercise-induced increases in left ventricular filling pressure would also be expected in patients with volume or pressure overload states, or in patients with decreased left ventricular compliance such as those with cardiomyopathies or constrictive conditions.

**Effect of propranolol on thallium lung/heart ratios and pulmonary blood volume ratios:** Patients taking propranolol at the time of the study were found to have higher thallium lung/heart ratios than patients not receiving propranolol. This difference may be due to patients with more symptoms, more severe disease, or both, being treated with propranolol so that this observation could be explained without invoking a direct causal effect of propranolol on the thallium lung/heart ratio. However, there was no significant difference in the PBV ratio in patients taking or not taking propranolol. Thus it appears that propranolol may affect the thallium lung/heart ratio determination but cause little or no effect on the PBV ratio. The lower heart rate attained during exercise in patients receiving propranolol may have resulted in a lower cardiac output, prolonged pulmonary transit time, and increased contact time of the thallium bolus with the lungs[4] compared with patients with CAD not taking propranolol. Such an increased transit time has been shown to increase lung thallium uptake in experimental models.[4] On the other hand, such an increased transit time would not be expected to change the PBV ratio.

Although propranolol may influence the thallium lung/heart ratio in patients with CAD, it did not appear to influence the thallium lung/heart ratio in patients without significant CAD. However, the small number of normal patients in this study does not allow the exclusion of the possibility that a larger group of normal patients receiving propranolol may show statistically higher thallium lung/heart or PBV ratios (or both) than normal patients not taking propanolol.

*In summary*, in the population studied, abnormal PBV ratios and abnormal thallium lung/heart ratios are quite specific markers of CAD. An abnormal PBV ratio is more prevalent in patients with CAD compared with an abnormal thallium lung/heart ratio. When both ratios are abnormal in the same patient, there is a high likelihood of multivessel CAD. Propranolol may influence the thallium lung/heart ratios in patients with significant CAD.

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## References


1. **Okada RD, Pohost GM, Kirshenbaum HD, Kushner FG, Boucher CA, Block PC, Strauss HW.** Radionuclide-determined change in pulmonary blood volume with exercise. N Engl J Med 1979;301:569–576.
2. **Okada RD, Osbakken MD, Boucher CA, Strauss HW, Block PC, Pohost GM.** Pulmonary blood volume ratio response to exercise: a noninvasive determination of exercise-induced changes in pulmonary capillary wedge pressure. Circulation 1982;65:126–133.
3. **Boucher CB, Zir LM, Beller GA, Okada RD, McKusick KA, Strauss HW, Pohost GM.** Increased lung uptake of thallium-201 during exercise myocardial imaging: clinical, hemodynamic and angiographic implications in patients with coronary artery disease. Am J Cardiol 1980;43:189–196.
4. **Bingham JB, McKusick KA, Strauss HW, Boucher CA, Pohost GM.** The influence of the presence of coronary artery disease on pulmonary uptake of thallium-201. Am J Cardiol 1980;46:821–826.
5. **Kushner FG, Okada RD, Kirshenbaum HD, Boucher CA, Strauss HW, Pohost GM.** Lung thallium-201 uptake after stress testing in patients with coronary artery disease. Circulation 1981;63:341–347.
6. **Katz AM.** Effects of ischemia on the contractile processes of heart muscle. Am J Cardiol 1973;32:456–460.
7. **Tennant R, Wiggers CJ.** The effect of coronary occlusion on myocardial contraction. Am J Physiol 1935;112:351–361.
8. **Dwyer EM Jr.** Left ventricular pressure-volume alteration and regional disorders of contraction during myocardial ischemia induced by atrial pacing. Circulation 1970;42:1111–1122.
9. **Sharma B, Taylor SH:** Localization of left ventricular ischemia in angina pectoris by cineangiography during exercise. Br Heart J 1975;37:963–970.
10. **Pasternac A, Gorlin R, Sonnenblick EH, Haft JI, Kemp HG.** Abnormalities of ventricular motion induced by atrial pacing in coronary artery disease. Circulation 1972;45:1195–1205.
11. **Barry WH, Brookes JZ, Alderman EL, Harrison DC.** Changes in diastolic stiffness and tone of the left ventricle during angina pectoris. Circulation 1974;49:255–263.
12. **McLaurin LP, Rolett EL, Grossman W.** Impaired left ventricular relaxation during pacing-induced ischemia. Am J Cardiol 1973;32:751–756.
13. **Parker JO, Ledwick JR, West RO, Case RB.** Reversible cardiac failure during angina pectoris: hemodynamic effects of atrial pacing in coronary artery disease. Circulation 1969;39:745–755.
14. **Linhart JW, Hildner FJ, Barold SS, Lister JW, Samet P.** Left heart hemodynamics during angina pectoris induced by atrial pacing. Circulation 1969;40:483–492.
15. **Pepine CJ, Wiener L.** Relationship of angina symptoms to lung mechanics during myocardial ischemia. Circulation 1972;46:863–869.
16. **Kazemi H, Parson EF, Valenca LM, Strieder DJ.** Distribution of pulmonary blood flow after myocardial ischemia and infarction. Circulation 1970; 41:1025–1030.
17. **Cannon DS, Harrison DC, Schroeder JS.** Hemodynamic observations in patients with unstable angina pectoris. Am J Cardiol 1974;33:17–22.
18. **McDonough JR, Danielson RA, Wills RE, Vine DL.** Maximal cardiac output during exercise in patients with coronary artery disease. Am J Cardiol 1974;33:23–29.
19. **Dock DS, Kraus WL, McGuire LB, Hyland JW, Haynes FW, Dexter L.** The pulmonary blood volume in man. J Clin Invest 1961;40:317–328.
20. **Nichols AB, Strauss HW, Moore RH, Guiney TE, Cochavi S, Beller GA, Pohost GM.** Acute changes in cardiopulmonary blood volume during upright exercise stress testing in patients with coronary heart disease. Circulation 1979;60:520–530.
21. **Austin SM, Schreiner BF, Shah PM, Yu PN.** Acute effects of increases in pulmonary vascular distending pressure on pulmonary blood volume and pulmonary extravascular fluid volume in man. Circulation 1976;53:356–363.
22. **Maddahi J, Berman D, Matsuoka D, Charuzi Y, Waxman A, Gray R, Swan HJC, Forrester J.** Right ventricular ejection fraction during exercise in coronary artery disease by multiple gated equilibrium scintigraphy (abstr). Circulation 1978;57,58:Suppl II:II-131.
23. **Johnson LL, McCarthy D, Sciacca R, Cabot C, Rudin B, Cannon PJ.** Right ventricular ejection fraction with exercise in patients with coronary artery disease (abstr). Circulation 1978;57,58:Suppl II:II-61.
24. **Berger HJ, Johnston DE, Sands MJ, Gottschalk A, Zaret BL.** First-pass radionuclide assessment of right ventricular performance during exercise in coronary artery disease: relationship to left ventricular reserve and right coronary stenosis (abstr). Circulation 1978;57,58:Suppl II:II-132.
25. **Bingham JB, Strauss HW, McKusick KA, Pohost GM.** Thallium-201 clearance from human myocardium and lungs following injection at stress (abstr). In: World Federation for Nuclear Medicine and Biology, Second International Congress, 1978:51.
26. **Bingham JB, Strauss HW, Pohost GM, McKusick KA.** Mechanisms of lung uptake of thallium-201. Circulation 1978;58:Suppl II:II-62.
27. **Atkins HL, Budinger TF, Lebowitz E, Ansari AN, Greene MW, Fairchild RG, Ellis KJ.** Human distribution and physical imaging properties. J Nucl Med 1977;18:133–140.
28. **Strauss HW, Harrison K, Pitt B.** Thallium-201: noninvasive determination of the regional distribution of cardiac output. J Nucl Med 1977;18:1167–1170.
29. **Llaurado JG, Madden JA, Meade RD, Smith GA.** Distribution of thallium-201 injected into rats following stress, imaging, organ-to-plasma uptake ratios, and myocardial kinetics. J Nucl Med 1978;19:172–177.
30. **Narahara KA, Hamilton GW, Williams DL, Gould KL.** Myocardial imaging with thallium-201: an experimental model for analysis of the true myocardial and background image components. J Nucl Med 1977;18:781–786.
31. **Fishman AP:** Pulmonary edema. The water-exchanging function of the lung. Circulation 1972;46:390–408.

# Sinus Node Coronary Arteries Studied With Angiography

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**Coronary angiograms of 309 consecutive patients undergoing coronary angiography were reviewed to investigate the blood supply to the sinus node area. Blood was supplied from the right coronary artery in 59% of cases, from the left coronary artery in 38%, and from both coronary arteries in 3%. The posterior sinus node artery was demonstrated in 32 patients (27% of the 119 patients with the sinus node artery originating from the left circumflex and 10.5% of all patients).**

Since its original description by Keith and Flack,[1] the sinus node has been known to have a special arterial blood supply. Many postmortem studies have demonstrated that the sinus node artery (SNA), which is the largest atrial coronary branch, originates from the right coronary artery in approximately 60% of hearts and from the left circumflex in the remaining 40%.[2–7] Of 300 human hearts studied at necropsy, Nerantzis and Avgoustakis[7] observed a posterior sinus node artery (which they named "the S-shaped sinus node artery") in 21% of the cases in which the sinus node artery arose from the left circumflex artery. The present angiographic study was undertaken to investigate the blood supply to the sinus node area.

## Methods

We reviewed our hospital records and the coronary arteriograms of 309 consecutive patients who underwent coronary arteriography between April 1980 and December 1981. Of the 309 patients, 205 had coronary heart disease and the remaining 104 had valvular heart disease. There were 232 male and 77 female patients ranging in age from 19 to 70 years (mean 51). Coronary arteriography was performed with either the Sones or Judkins technique in standard projections.

The origin and course of the sinus node artery as demonstrated in postmortem studies was as follows. The right sinus node artery originated from the proximal right coronary artery, passed across the anteromedial wall of the right atrium, and penetrated the atrial septum below the interatrial bundle. The left sinus node artery arose from the proximal portion of the left circumflex and coursed through the anterior ramus of the interatrial muscle bundle and then through the bundle itself. The posterior sinus node artery arose from the left circumflex artery at any point throughout its length, curved gently upward and backward in the region of the left atrium between the atrial appendage and the left superior pulmonary vein, and reached the atrial septum. From the atrial septum each of these types reached the base of the superior vena cava which it encircled as it penetrated the center of the sinus node.[3,8]

## Results

In the 309 patients studied, 261 had a right dominant coronary arterial system (posterior descending artery originating from the right coronary artery), 45 had a left dominant coronary arterial system (posterior descending artery originating from the left circumflex), and 3 had a balanced type with 2 posterior descending arteries, 1 arising from the right coronary artery and 1 from the left circumflex.

The sinus node artery originated from the right coronary artery in 182 patients (59%), the left circumflex

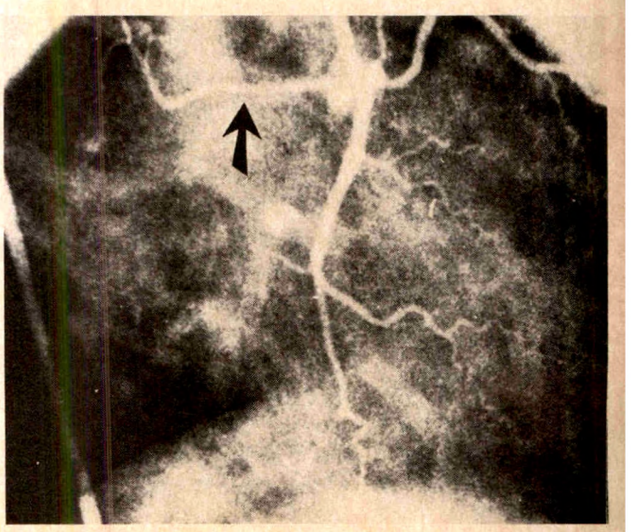


**FIGURE 1.** Right coronary arteriogram in right anterior oblique projection showing the origin of the sinus node artery (**arrow**).

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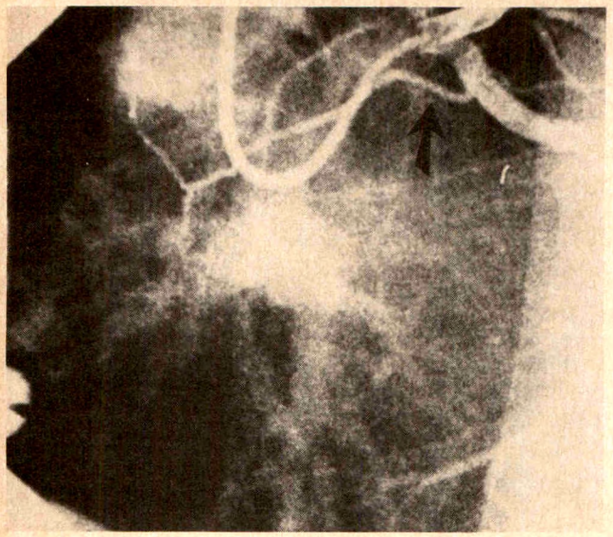


**FIGURE 2.** Left coronary arteriogram in the left anterior oblique projection. The sinus node artery (**arrow**) arises from the proximal portion of the left circumflex artery and courses cephalad along the body of the left atrium, behind the aorta, to the sinoatrial node.

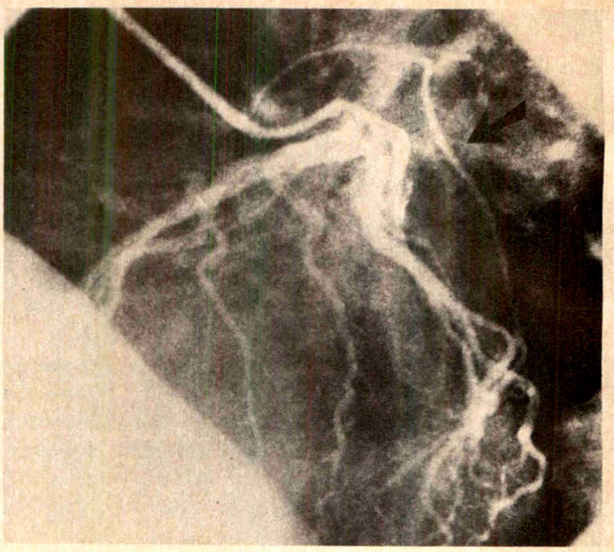


**FIGURE 3.** Left coronary arteriogram in the left anterior oblique projection showing the posterior sinus node artery (**arrow**) arising from the posterolateral part of the left circumflex and passing below the lower left pulmonary vein to the sinoatrial node.

in 119 patients (38%), and both coronary arteries in 8 patients (3%).

The posterior sinus node artery was found in 32 patients (27% of the 119 patients with the sinus node artery originating from the left circumflex and 10.5% of all patients). The posterior sinus node artery constituted the sole arterial blood supply to the sinus node in 26 of the 32 cases, and in the remaining 6 there were 2 sinus node arteries arising from both the right coronary artery and the left circumflex.

The posterior sinus node artery originated from the upper part of a divided left circumflex in 10 cases. It constituted a branch of the left circumflex in 16 cases and in 6 it formed the main continuation of this artery, following in every case the same basic route to the sinus node area.

## Discussion

A detailed knowledge of the atrial circulation and its anatomy is important for a better understanding of cardiac physiology and from a surgical point of view. Fainting, syncope, and cardiac arrhythmias are characteristic clinical features of acute infarcts because of transient ischemia of the sinus node.[9,10] Incisions in the right or left atrial wall during mitral valve surgery, clamping and excision of the right atrial appendage as during closed operation on the mitral valve, or insertion of a decompression catheter into this region may result in damage to the sinus node artery.[8]

The sinus node artery has 3 anatomic variations demonstrating a different origin, course, and relation to the surrounding structures.[8] The right sinus node artery originates from the right coronary artery (Fig. 1), passes across the anteromedial wall of the right atrium, and then surrounds the superior vena cava, giving branches to the sinus node and the near tissues. The left sinus node artery arises from the proximal portion of the left coronary artery (Fig. 2) and courses through the anterior wall of the left atrium to reach the sinus node. The posterior sinus node artery originates from the posterolateral part of the left coronary artery (Fig. 3) and courses over the lateral wall of the left atrium between the atrial appendage and the left superior pulmonary vein ending in the sinus node area. The posterior sinus node artery constitutes a branch of the left circumflex, an upper part of a divided left circumflex artery, or in the minority of cases a main continuation of the left circumflex artery.[7]

## References


1. **Keith A, Flack M.** The form and nature of the muscular connections between the primary divisions of the vertebrate heart. J Anat Physiol 1907;41:172–189.
2. **Gross L.** The Blood Supply to the Heart in Its Anatomical and Clinical Aspects. New York: Paul B Hoeber, 1921:170–173.
3. **James TN, Burch GE.** The atrial coronary arteries in man. Circulation 1958;17:90–98.
4. **James TN.** Anatomy of the human sinus node. Anat Rec 1961;141:109–139.
5. **Romhilt DW, Hackel DB, Estes EH Jr.** Origin of blood supply to sinoauricular and atrioventricular node. Am Heart J 1968;75:279–280.
6. **Kennel AJ, Titus JL.** The vasculature of the human sinus node. Mayo Clin Proc 1972;47:556–566.
7. **Nerantzis C, Avgoustakis D.** An S-shaped atrial artery supplying the sinus node area. Chest 1980;78:274–278.
8. **McAlpine WA.** Heart and Coronary Arteries. New York: Springer-Verlag, 1975:151–159.
9. **James TN.** Myocardial infarction and atrial arrhythmias. Circulation 1961;24:761–776.
10. **James TN.** An etiologic concept concerning the obscure myocardiopathies. Prog Cardiovasc Dis 1964;7:43–64.

# Beneficial Effects of Ibuprofen in Pacing-Induced Myocardial Ischemia

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**Lysosomal membrane instability and platelet activation are both associated with acute myocardial ischemia. The effect of ibuprofen on cathepsin D as a marker of lysosomal membrane "leakiness" and thromboxane $B_2$ as a marker of platelet activation was evaluated in 44 patients with angina pectoris. Samples of blood analyzed for cathepsin D, thromboxane $B_2$, and lactate were withdrawn from the coronary sinus and brachial artery before and after pacing to 140 beats/min for 4 minutes. Myocardial ischemia was assessed by determination of transmyocardial lactate extraction or production. Ibuprofen (800 mg) or placebo was administered orally 2 hours before cardiac catheterization. Patients were classified into 4 groups on the basis of administration of placebo or ibuprofen and the presence or absence of myocardial ischemia as determined by demonstration of lactate extraction or production after atrial pacing.**

**In patients with lactate extraction, no significant efflux of cathepsin D or thromboxane $B_2$ occurred after pacing. In patients with lactate production given placebo, a 64 ± 25% increase in the thromboxane $B_2$ level and a 113 ± 37% increase in cathepsin D activities occurred in the coronary sinus effluent sampled after pacing. In contrast, in patients with comparable coronary artery disease and comparable lactate production who were given ibuprofen, no release of thromboxane $B_2$ ($p = 0.05$ compared with patients given placebo) or cathepsin D ($p < 0.01$ compared with patients given placebo) occurred after pacing-induced ischemia. These findings suggest that ibuprofen stabilizes membranes and prevents platelet-activated release of thromboxane $A_2$ in pacing-induced myocardial ischemia.**

Sampling of coronary venous efflux after atrial pacing has been an effective clinical means of understanding metabolic changes and pathophysiologic mechanisms that accompany myocardial ischemia. We previously demonstrated coronary venous efflux of thromboxane $B_2$, the stable hydrolytic product of thromboxane $A_2$, and of cathepsin D after atrial pacing in patients with significant coronary artery disease.[1,2] These patients had evidence of myocardial ischemia based on concurrent demonstration of lactate production after atrial pacing.

Thromboxane $A_2$, a platelet aggregator and coronary vasoconstrictor, could potentially exacerbate myocardial ischemia by both obstructive and vasoconstrictive mechanisms.[3] Cathepsin D, a lysosomal hydrolase, could also exacerbate myocardial ischemia by its proteolytic effect.[4] Moreover, cathepsin D, a marker of damage to the lysosomal membrane, could reflect the release of additional lysosomal hydrolytic enzymes that may be responsible for propagation of ischemic damage.

Ibuprofen, a nonsteroidal anti-inflammatory agent, has been reported effective in enhancing lysosomal membrane stability and in decreasing release of thromboxane $A_2$ by inhibition of cyclo-oxygenase.[5,6] Ibuprofen has also been demonstrated to limit the extent of ischemic damage in an animal model of acute myocardial ischemia.[7] These effects of ibuprofen are effective in experimental myocardial ischemia but have not yet been assessed in patients with coronary artery disease.

The purpose of this study, therefore, was to evaluate the effect of ibuprofen in patients with coronary artery disease and to assess its effect on the pacing-induced release of cathepsin D and thromboxane $B_2$.

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**TABLE I Clinical and Catheterization Characteristics of Patients**

| | Group | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Patients (n) | 12 | 9 | 10 | 13 |
| Age (yr) | 56.2 ± 1.95 | 52.0 ± 2.40 | 58.9 ± 2.54 | 56.9 ± 2.00 |
| Sex | 4F/8M | 1F/8M | 2F/8M | 5F/8M |
| Previous myocardial infarction | 5 | 6 | 6 | 8 |
| Vessels (n) with >50% obstruction | 1.25 ± 0.33 | 1.67 ± 0.29 | 1.9 ± 0.31 | 2.46 ± 0.183* |
| Left ventricular end-diastolic pressure (mm Hg) | 12.9 ± 1.6 | 16.2 ± 1.8 | 15.1 ± 2.2 | 15.5 ± 1.8 |
| Left ventricular ejection fraction | 75.6 ± 4.0 | 78.4 ± 3.0 | 76.7 ± 4.6 | 74.5 ± 3.5 |
| Lactate extraction | +21.90 ± 4.10 | +20.95 ± 3.42 | −60.35 ± 16.99 | −73.15 ± 13.05 |
| Drug | Placebo | Ibuprofen | Placebo | Ibuprofen |

* $p < 0.05$ compared with Groups I and II.

## Methods

Forty-four patients were included in the current study. These patients had been admitted to Thomas Jefferson University Hospital for cardiac catheterization for evaluation of an anginal syndrome. Coronary artery spasm was not suspected in any patient. Patients with either stable or unstable angina were included in the study, and randomized into placebo or ibuprofen groups. Two hours before catheterization, patients were given either 800 mg of ibuprofen orally, or placebo; they received no other medication before the procedure. All other medications were withheld for 12 hours before catheterization, including beta-adrenergic blocking drugs and nitrates. Before coronary arteriography and ventriculography, atrial pacing was performed. A size 7 Gorlin catheter was advanced from the brachial vein and positioned in the coronary sinus. A size 20 longdwell cannula was inserted into the right brachial artery.

Samples of blood were simultaneously withdrawn from the coronary sinus and brachial artery to be analyzed for lactate, thromboxane $B_2$, and cathepsin D. Samples, withdrawn in a heparinized syringe, were obtained at rest and immediately after atrial pacing. The sample to be analyzed for lactate was immediately transferred into a chilled glass tube containing polyethyleneglycol. The sample to be analyzed for thromboxane $B_2$ and cathepsin D was immediately placed in a chilled 5 ml vacutainer tube (Becton-Dickson) prefilled with 7.5% of EDTA and 100 $\mu$m of sodium meclofenamate. These tubes were placed in an ice bath and handled as described herein.

Atrial pacing was initiated at a rate of 90 beats/min and gradually increased to a rate of 140 beats/min. Pacing was maintained at 140 beats/min for 4 minutes. Although pacing could be continued for 4 minutes in most patients, it was occasionally discontinued early because the patient had severe chest pain. However, in no patient was pacing maintained for less than 2 minutes. After atrial pacing, selective coronary angiography and ventriculography were performed. There were no complications or sequelae consequent to the atrial pacing procedure, and there were no adverse effects related to administration of ibuprofen.

Patients were excluded from this study if there was any history of ingestion or parenteral administration of any steroidal or nonsteroidal anti-inflammatory agent in the previous 7 days. Informed consent was obtained from all patients before inclusion in the study.

Lactate extraction was determined as follows: Lactate extraction = $[(\text{lactate}_{\text{arterial}} - \text{lactate}_{\text{venous}})/\text{lactate}_{\text{arterial}}] \times 100$.

Statistical analysis was performed by a 2-way analysis of variance with log transformation comparing the percent change in values obtained after pacing with the prepacing control values.

Lactate analysis was performed as previously described.[8] Analysis of plasma samples for thromboxane $B_2$ was determined by specific radioimmunoassay as described by Lewy et al.[9] Cathepsin D activity was assessed by the spectrophotometric method of Anson using hemoglobin as substrate at a pH of 3.5.[10] All samples were performed in duplicate to ensure reproducibility.

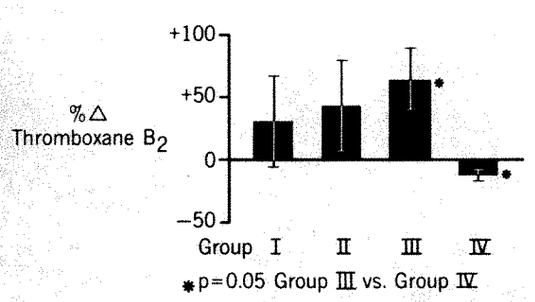



**FIGURE 1.** Percent change in concentrations of thromboxane $B_2$ in venous effluent sampled from the coronary sinus. Thromboxane $B_2$ concentrations immediately after pacing are compared with prepacing values (mean ± standard error of the mean). There is a significant difference between Groups III and IV as determined by a 2-way analysis of variance.

## Results

Patients were classified into 4 groups on the basis of whether they received ibuprofen or placebo as well as on the basis of manifestation of transmyocardial lactate extraction or production after atrial pacing. Groups I and III received placebo whereas Groups II and IV received ibuprofen. Groups I and II demonstrated lactate extraction after atrial pacing, whereas Groups III and IV demonstrated lactate production after pacing. There were 12 patients in Group I, 9 patients in Group II, 10 patients in Group III, and 13 patients in Group IV (Table I).

Clinical characteristics of the 4 groups are listed in Table I. There was no significant difference in age, male/female ratio, or incidence of previous myocardial infarction in the 4 groups. There was no difference in the medical regimen of patients in the 4 groups. Comparable numbers of patients were taking beta-adrenergic blocking drugs and nitrate preparations.

Catheterization variables are also listed in Table I. There was no difference in left ventricular ejection

fraction or left ventricular end-diastolic pressure among the 4 groups. There were no differences in the number of vessels with >50% obstruction in patients in Groups I and II or Groups III and IV. Patients in Group IV had a greater number of vessels with >50% obstruction than both Groups I and II ($p < 0.05$). Group I and II patients had comparable lactate extraction after pacing, suggesting no evidence of myocardial ischemia in the region drained. Groups III and IV patients manifested comparable degrees of lactate production, suggesting severe myocardial ischemia.

In Figure 1, the percent change in thromboxane $B_2$ concentrations in the coronary sinus is demonstrated. Thromboxane $B_2$ concentrations immediately after pacing are compared with the values measured before pacing. In Groups I and II, consisting of patients without significant myocardial ischemia, there was a slight increase in thromboxane $B_2$ concentrations after pacing (31 ± 36% and 43 ± 36%, respectively). However, this was not statistically significant. In contrast, Group III exhibited a 64 ± 25% increase in thromboxane $B_2$ values immediately after atrial pacing. In Group IV patients, who had a comparable degree of myocardial ischemia and coronary vascular disease as Group III patients, there were no significant changes in thromboxane $B_2$ concentrations after pacing (−11 ± 4%). Ibuprofen thus greatly inhibited the pacing-induced release of thromboxane $B_2$ in patients with severe coronary artery disease. ($p = 0.05$, Group III versus Group IV).

Figure 2 summarizes the percent change in cathepsin D activities in the coronary sinus. Cathepsin D activities immediately after pacing are compared with activities measured before pacing. In Groups I and II, no increase in cathepsin D activities was noted (13 ± 14% and 29 ± 9%, respectively). In Group III, a 113 ± 37% increase in cathepsin D values after pacing was observed. This increase in cathepsin D values differed significantly ($p < 0.01$) from the response observed in Group IV patients, who received ibuprofen (−14 ± 15%).

## Discussion

We have demonstrated that atrial pacing in patients with significant myocardial ischemia results in an increase in thromboxane $B_2$ values, confirming our earlier findings.[1] Occasionally in patients without demonstration of significant ischemia, plasma thromboxane $B_2$ concentrations were also elevated after pacing. However, this was not a consistent finding. The source of the thromboxane that is generated after atrial pacing is not clear. Presumably it is generated in and around the atherosclerotic plaque and may be related to the stimulation of platelets and the pacing-induced change in hydraulics of flow in the diseased vessel. Possible alternative sources of circulating thromboxane $B_2$ include the pulmonary artery, the ischemic myocardium itself, or small coronary vessels.[11]

Similarly, circulating cathepsin D activities were elvated in patients with severe myocardial ischemia as had been shown in a previous study.[2] Although no evidence of acute myocardial infarction was noted in our patients, the degree of ischemia that was induced may lead to leakiness of the lysosomal membrane resulting in lysosomal enzyme release. Alternatively, there may have been preexisting lysosomal injury related to the underlying severe coronary disease. The stress of atrial pacing may then have been adequate stimulus to induce the further change in the lysosomal membrane required to enable hydrolase leakage out of the lysosome, similar to hypoxia or ischemia, which are known lysosomal-labilizing stimuli.[12]

A variety of anti-inflammatory agents both steroidal and nonsteroidal may block thromboxane $A_2$ synthesis. Glucocorticoids act by blocking the action of phospholipases that release arachidonic acid and by stimulating the synthesis of a lipase that rapidly clears circulating arachidonic acid.[13,14] The nonsteroidal anti-inflammatory agents act by inhibiting cyclo-oxygenase-mediated conversion of arachidonic acid to prostaglandin endoperoxidases intermediary to the formation of thromboxane $A_2$.[15] Glucocorticoids have been also demonstrated effective in the stabilization of lysosomal membranes.[16] Among the nonsteroidal anti-inflammatory agents indomethacin, meclofenamic acid, and acetylsalicylic acid have been found unable to stabilize lysosomal membranes in acute myocardial ischemia in an experimental model.[17] Ibuprofen, on the other hand has been found effective in stabilizing lysosomal membranes and preserving myocardial integrity in acute myocardial ischemia.[18]

The combination of inhibition of thromboxane $A_2$ and stabilization of lysosomal membranes may be beneficial in the setting of acute myocardial ischemia. Hence this study was performed using the model of pacing-induced myocardial ischemia to assess the inhibitory effects of ibuprofen.

There was no significant increase in cathepsin D or thromboxane $B_2$ in the coronary sinus venous effluent samples in patients with no evidence of myocardial ischemia. In contrast, there was a significant increase in thromboxane $B_2$ and cathepsin D values noted immediately after atrial pacing in Group III patients exhibiting pacing-induced severe myocardial ischemia. In Group IV patients, with comparable coronary artery disease and with comparable myocardial ischemia, release of thromboxane $B_2$ and cathepsin D was inhibited by the administration of ibuprofen.

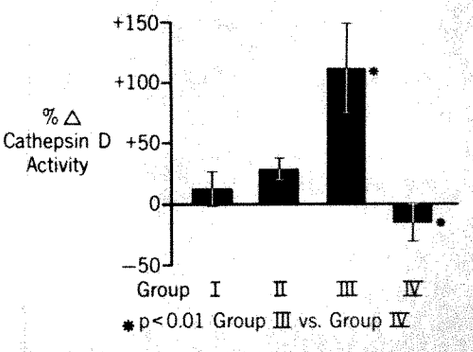



**FIGURE 2.** Percent change in cathepsin D activities in venous effluent sampled from the coronary sinus. Values for cathepsin D activities immediately after pacing are compared with prepacing values (mean ± standard error of the mean). There is a significant difference between Groups III and IV as determined by a 2-way analysis of variance.

Generation and release of thromboxane $B_2$ and lysosomal hydrolases may have deleterious effects in the setting of myocardial ischemia or myocardial infarction. Thromboxane $A_2$ has been demonstrated to be released after experimental myocardial infarction.[19] Inhibition of thromboxane $A_2$ release by a specific thromboxane synthetase inhibitor resulted in a decrease in ischemic damage after coronary artery occlusion in cats.[20] Conversely, administration of a synthetic thromboxane analog resulted in an increase in ischemic damage.[21]

Release of cathepsin D may also be deleterious in the setting of acute myocardial ischemia. Cathepsin D is a marker of lysosomal membrane disruption, and thus lysosomal enzymes other than cathepsin D may be released at the same time. These may induce additional proteolysis and lipolysis, resulting in membrane damage that may exacerbate myocardial edema and lead to further compromise of the coronary microcirculation. Thus, inhibition of both of these phenomena by ibuprofen may be significant. Whether a specific thromboxane synthetase inhibitor, as recently described, would be of more specific benefit with regard to thromboxane inhibition remains to be determined.[22]

Several therapeutic procedures have been studied in patients with acute myocardial infarction and ischemia and have been demonstrated effective experimentally in the reduction of infarct size and limitation of ischemia, including beta-adrenergic blocking agents, hyaluronidase, nitroglycerin, glucocorticoids, cobra venom factor, and intraaortic balloon counter pulsation.[23–28] In addition, recanalization of coronary artery thrombus in acute myocardial infarction has also been demonstrated feasible and holds promise in limitation of infarct size.[29] Ibuprofen, by virtue of the mechanisms described in this study, should be added to the list of agents that may be effective in the limitation of infarct size in patients. Such an effect has been demonstrated in an animal model.[7] In addition, ibuprofen may also complement other established therapy after coronary artery thrombolysis by limiting the extent of myocardial ischemic damage and by stabilizing platelets with the subsequent inhibition of thromboxane $A_2$ generation.

## References


1. **Wiener L, Lefer AM, Walinsky P, Dragotta D, Spath MA.** Relationship of cathepsin D release to myocardial lactate production in patients with acute myocardial ischemia. In: Mason DT, Neri-Serneri GG, Oliver MS, eds. Florence International Meetings on Myocardial Infarction. New York: Excerpta Medica, 1979:494–505.
2. **Lewy RI, Wiener L, Walinsky P, Lefer AM, Silver MJ, Smith JB.** Thromboxane release during pacing-induced angina pectoris: possible vasoconstrictor influence on the coronary vasculature. Circulation 1980;61: 1165–1171.
3. **Hamberg M, Svensson J, Samuelsson B.** Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. Proc Natl Acad Sci USA 1975;72:2994–2998.
4. **Ricciutti MA.** Lysosomes and myocardial cellular injury. Am J Cardiol 1972;30:498–502.
5. **Kantor TG.** Ibuprofen. Ann Intern Med 1979;91:877–882.
6. **Phillips MKL, Muirden KD.** An effect of ibuprofen and prednisone on lysosomes. J Pharm Pharmacol 1972;24:653–654.
7. **Lefer AM, Polansky EW.** Beneficial effects of ibuprofen and acute myocardial ischemia. Cardiology 1979;64:265–279.
8. **Wiener L, Walinsky P, Kasparian H, Duca P, Gottlieb RS, Hanckel F, Templeton JY, Brest AN.** Therapeutic implications of myocardial lactate metabolism in patients considered for emergency myocardial revascularization. J Thorac Cardiovasc Surg 1978;75:612–620.
9. **Lewy RI, Wiener L, Smith JB, Walinsky P, Silver MJ, Sala J.** Comparison of plasma concentrations of thromboxane $B_2$ in Prinzmetal's variant angina and classical angina pectoris. Clin Cardiol 1979;2:404–406.
10. **Anson ML.** Estimation of cathepsin with hemoglobin and the partial purification of cathepsin. J Gen Physiol 1936;20:565–574.
11. **Ingerman-Wojenski C, Silver MJ, Smith JB, Macarak E.** Bovine endotheleal cells in culture produce thromboxane as well as prostacyclin. J Clin Invest 1981;67:1292–1296.
12. **Ferguson WW, Glenn TM, Lefer AM.** Mechanisms of production of circulatory shock factors in isolated perfused pancreas. Am J Physiol 1972; 222:450–457.
13. **Hong SL, Levine L.** Inhibition of arachidonic acid release from cells as the biochemical action of anti-inflammatory corticosteroids. Proc Natl Acad Sci USA 1976;73:1730–1735.
14. **Araki H, Peck RC, Lefer AM, Smith JB.** Mechanism of protection against arachidonate induced death by glucocorticoid. Prostaglandins 1981;21: 387–399.
15. **Vane JR.** The mode of action of aspirin-like drugs. Agents Actions 1978; 8:430–431.
16. **Weissmann G.** The effects of steroids and drugs on lysosomes. In: Dingle JT, Fell HB, eds. Lysosomes in Biology and Pathology. Part I. Amsterdam: North-Holland, 1969:276–298.
17. **Ogletree ML, Lefer AM.** Influence of non-steroidal anti-inflammatory agents on myocardial ischemia. J Pharmacol Exp Ther 1976;197:582–593.
18. **Lefer AM, Crossley K.** Mechanisms of the optimal protective effects of ibuprofen in acute myocardial ischemia. Adv Shock Res 1980;3:133–141.
19. **Sakai K, Ito T, Ogawa, Enomoto I, Kai I, Satake T.** Increased levels of prostaglandins and thromboxane after acute coronary occlusion (abstr). Circulation 1980;62:Suppl III:III-241.
20. **Schror K, Smith III EF, Bickerton M, Smith JB, Nicolaou KC, Magolda R, Lefer AM.** Preservation of ischemic myocardium by pinane thromboxane $A_2$. Am J Physiol 1980;238:H87–H92.
21. **Smith EF, Lefer AM, Aharony D, Smith JB, Magolda RL, Claremon D, Nicolaou KC.** Carbocyclic thromboxane $A_2$: aggrevation of myocardial ischemia by a new synthetic thromboxane $A_2$ analog. Prostaglandins 1981;21:443–456.
22. **Tyler HM, Saxton CA, Parry MJ.** Administration to man of UK-37, 248-01, a selective inhibitor of thromboxane synthetase. Lancet 1981;1:629–632.
23. **Morris PT, Clarke ED.** Reduction of enzyme levels by propranolol after acute myocardial infarction. Circulation 1978;57:1091–1095.
24. **Maroko PR, Libby P, Bloor CM, Sobel BE, Braunwald E.** Reduction by hyaluronidase of myocardial necrosis following coronary artery occlusion. Circulation 1972;46:430–437.
25. **Awan NA, Amsterdam EZ, Vera Z, DeMaria AN, Miller RR, Mason DT.** Reduction of ischemic injury by sublingual nitroglycerin in patients with acute myocardial infarction. Circulation 1976;54:761–765.
26. **Libby P, Maroko PR, Sobel BE, Bloor CM, Covell JW, Braunwald E.** Reduction in infarct size following experimental coronary occlusion by hydrocortisone treatment. Clin Res 1972;20:207.
27. **Maroko PR, Carpenter CB, Chiariello M, Fishbein MC, Radvany P, Knostman JD, Hale SL.** Reduction of cobra venom factor of myocardial necrosis following coronary artery occlusion. J Clin Invest 1978;61: 661–670.
28. **Maroko PR, Bernstein EF, Libby P, Delaria GA, Covell JW, Ross J Jr, Braunwald E.** Effects of intra-aortic balloon counterpulsation on the severity of myocardial ischemia injury following acute coronary occlusion. Circulation 1972;45:1150–1159.
29. **Ganz W, Buchbinder N, Marcus H, Mondkar A, Maddahi J, Charuzi Y, O'Connor L, Shell W, Fishbein MC, Kass R, Miyamoto A, Swan HJC.** Intracoronary thrombolysis in evolving myocardial infarction. Am Heart J 1981;101:4–13.

# Improved Exercise Ventilatory Responses After Training in Coronary Heart Disease During Long-Term Beta-Adrenergic Blockade

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**Exercise ventilatory responses of 7 men with well-documented myocardial infarction receiving long-term beta-adrenergic blockade were studied before and after 4 months of endurance training. Observations were obtained during graded levels of upright treadmill exercise continued until 85% of the predetermined symptom-limited heart rate (working heart frequency limit). This submaximal testing procedure revealed a significant slowing of the heart rate ($p < 0.005$) together with an increased oxygen pulse ($p < 0.05$) after training, for what was previously a maximal work load for the working heart frequency limit. In addition, all patients achieved an increased exercise duration and work load, accompanied by significant increases in maximal oxygen uptake ($p < 0.01$), oxygen pulse ($p < 0.025$), and respiratory exchange ratio, for their working heart frequency limit after exercise conditioning. These results show that prolonged physical training results in physiologic adaptations to cardiac rehabilitation in the presence of long-term beta-adrenergic blockade.**

Exercise training is a recommended mode of therapy for suitable patients after myocardial infarction. Endurance conditioning may produce a number of physiologic adaptations of demonstrable or potential benefit in these patients.[1] The major improvements are thought to result from peripheral alterations brought about by the repetitive use of skeletal muscles at an exercise intensity above a threshold level of metabolic activity.[2]

A recent study based on respiratory exchange data expressed doubts about the capability of patients with coronary heart disease who are receiving long-term beta-adrenergic blockade to attain this desired metabolic level during training.[3] At the same time, data on the ability of such patients to achieve a significant training effect are both scarce and conflicting in nature. Two studies demonstrated prolonged maximal symptom-free exercise duration after training in the presence of beta-adrenergic blockade,[4,5] whereas 1 report showed no benefits from conditioning.[6] None of these studies included direct measurement of exercise ventilatory responses in the experimental design, a factor necessary for unequivocal evidence of an improved aerobic capacity. Accordingly, this investigation was undertaken to examine the ventilatory adjustments to exercise that accompany gains in fitness when patients with a well-documented myocardial infarction (MI) receiving long-term beta-adrenergic blockade undertake 4 months of physical conditioning.

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## Methods

Seven ambulatory male survivors of a well-documented acute MI involved in a cardiac rehabilitation exercise program were selected for study. Six patients were receiving a nonselective beta-blocking agent, and 1 patient a $beta_1$-selective blocking drug, as part of their medication in the following daily doses: 160 mg of propranolol hydrochloride in 4 patients, 160 mg of sotalol hydrochloride in 1 patient, 20 mg of timolol maleate in 1 patient, and 50 mg of atenolol in 1 patient. These doses remained unchanged throughout the investigation. Physical characteristics pertaining to the patients include age 50 ± 8 years (mean ± standard deviation), height 180 ± 5 cm, and weight 84.4 ± 10.1 kg. The interval between MI and enrollment in the exercise program ranged from 3 months to 2 years.

Before the study all patients underwent a symptom-limited stress test in the presence of their usual cardioactive medications with use of the modified Bruce protocol and electrocardiographic monitoring by means of a Marquette computer-assisted system. The heart frequency limit to be used during subsequent testing and conditioning, the working heart

**TABLE I Effect of Training on Performance at Work Load for Which Initial Test Was Terminated (Altitude 1,400 Meters)**

| | Before Training* | After Training* | Percent Difference | p† |
|---|---|---|---|---|
| HR (beats/min) | 103.9 ± 15.8 | 90.6 ± 14.5 | −12.8 | <0.005 |
| Oxygen pulse (ml/beat) | 14.6 ± 3.4 | 16.5 ± 3.5 | +13.1 | <0.05 |
| $\dot{V}_E$ (liters/min) | 39.8 ± 13.2 | 38.6 ± 11.6 | −3 | NS |
| $\dot{V}O_2$ (ml/min) | 1,542.1 ± 513.3 | 1,506.3 ± 520.2 | −2.3 | NS |
| $\dot{V}O_2$ (ml/kg/min) | 18.1 ± 4.7 | 18.1 ± 4.5 | 0 | NS |
| $\dot{V}CO_2$ (ml/min) | 1,259.3 ± 470.7 | 1,244.3 ± 480.9 | −1.2 | NS |

* Mean value ± standard deviation.
† Significance of difference calculated by paired $t$ test.
HR = heart rate; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}_E$ = minute ventilation; $\dot{V}O_2$ = oxygen uptake.

frequency limit, was calculated as follows: Working heart frequency limit = 85/100 × symptom-limited heart rate.

For at least 2 hours before the determination of maximal oxygen uptake for each patient's working heart frequency limit, termed *working maximal oxygen uptake*, all patients avoided meals and stimulants such as tea, coffee, cola beverages, and cigarettes. In addition to their previous treadmill experience, patients were given a familiarization trial. Measurement of working maximal oxygen uptake was performed with a Morgan exercise test system using progressive work loads on a Quinton (model 18-60) clinical research treadmill. After a 20-minute rest in the seated position, patients commenced walking at a treadmill speed of 2.5 km/hour with a gradient of 2°. The speed was increased by 0.5 km/hour every 3 minutes in order to permit a gradual increase in heart rate, until the working heart frequency limit was reached. Analyses of oxygen and carbon dioxide levels were performed every minute during exercise with a Morgan m/262D oxygen analyzer and a Morgan (model 801) carbon dioxide analyzer, both of which had been calibrated before each test with tanked calibrated gas. Heart rate and electrocardiogram were monitored continuously on an oscilloscope using the bipolar chest lead $CM_5$. In addition, a standard 12-lead electrocardiogram was recorded together with the blood pressure on completion of each work load. Blood pressure was measured with the auscultatory method and was therefore not used as an experimental variable because of possible inaccuracy of this technique during ambulation. The final work load for which the heart frequency was equal to or below the working heart frequency limit was used for data collection.

Measurement of working maximal oxygen uptake was repeated using an identical protocol after 4 months of exercise training comprising 3 sessions per week each of 90 minutes' duration. These supervised classes consisted of a 20-minute warm-up of muscular and flexibility exercises followed by an aerobic exercise such as walking, jogging, or cycling, and ending with a cool-down period. All patients were encouraged to train at an exercise intensity that would bring the heart rate as close as possible to the working heart frequency limit without exceeding it. Patients commenced with a "low-dose" individualized exercise prescription that was gradually increased as their cardiorespiratory and musculoskeletal systems adapted to the exercise.

Significances of differences were analyzed by means of the paired $t$ test.

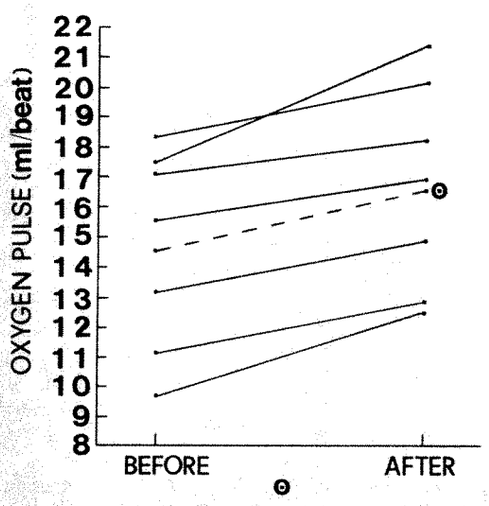



**FIGURE 1.** Oxygen pulse for work load which was initially the maximal for the working heart frequency limit, before and after 4 months endurance training in 7 patients receiving long-term beta-adrenergic blockade after myocardial infarction. **Black circles,** 13.1% increase, $p < 0.05$ versus before training.

## Results

Table I lists the mean values of paired comparisons of experimental variables for the work load which was initially the maximal work load for the patients' working heart frequency limit. The data demonstrate a 12.8% ($p < 0.005$) reduction in heart rate after training. The prescribed training had no effect on oxygen uptake at this level. However, relating oxygen uptake to heart rate, oxygen pulse was increased by 13.1% ($p < 0.05$) (Fig. 1).

All patients attained a markedly increased absolute treadmill duration for their working heart frequency limit after training. Exercise conditioning resulted in significant increases in working maximal oxygen uptake (26%, $p < 0.01$) (Fig. 2), oxygen pulse (24.1%, $p < 0.025$), minute ventilation (32.2%, $p < 0.01$), carbon dioxide output (30.3%, $p < 0.025$), and respiratory exchange ratio. The heart rate used for data collection in the initial test was 103.9 ± 15.8 beats/min, as compared with 103.6 ± 15.5 beats/min in the second test (the working heart frequency limit was 104 ± 14.8 beats/min). The means and standard deviations are found in Table II.

The aforementioned results were accompanied by major improvements in training times and distances during the course of study. No complications arose during training or testing.

**TABLE II Effect of Training on Maximal Performance for Working Heart Frequency Limit**

| | Before Training* | After Training* | Percent Difference | p† |
|---|---|---|---|---|
| Oxygen pulse (ml/beat) | 14.6 ± 3.4 | 18.2 ± 3.3 | +24.1 | <0.025 |
| $\dot{V}_E$ (liters/min) | 39.8 ± 13.2 | 52.6 ± 15.2 | +32.2 | <0.01 |
| $W\dot{V}O_2$ max (ml/min) | 1,542.1 ± 513.3 | 1,909.7 ± 598.7 | +23.8 | <0.01 |
| $W\dot{V}O_2$ max (ml/kg/min) | 18.1 ± 4.7 | 22.8 ± 5.3 | +26 | <0.01 |
| $\dot{V}CO_2$ (ml/min) | 1,259.3 ± 470.7 | 1,641.0 ± 517.8 | +30.3 | <0.025 |
| R | 0.80 ± 0.07 | 0.86 ± 0.03 | +7.5 | <0.05 |
| Exercise test duration (min) | 17.7 ± 7.2 | 26 ± 5.4 | +46.9 | <0.005 |

* Mean value ± standard deviation.
† Significance of difference calculated by paired *t* test.
R = respiratory exchange ratio; $W\dot{V}O_2$ max = working maximal oxygen uptake; other abbreviations as in Table I.

## Discussion

Propranolol, a nonselective beta-blocking agent, has been associated with reduced lactate and carbon dioxide production during exercise in normal subjects as well as in patients with coronary heart disease.[3,7] After the ingestion of 40 mg of propranolol, patients with coronary heart disease in 1 study were unable to reach a respiratory exchange ratio >0.85, the level of metabolic activity believed necessary to create a peripheral training effect.[3] Inhibition of glucose metabolism related to beta-adrenergic blockade was a suggested mechanism for this decreased respiratory exchange ratio. In our trial, all patients derived a significant training effect despite an initial mean respiratory exchange ratio of 0.80 ± 0.07 for their working heart frequency limit. An explanation for this is provided in the finding by Twentyman et al[8] of a propranolol-induced decreased carbon dioxide output early in exercise, followed by an increased output at a later stage involving a greater work load. They suggest that reduced muscle perfusion due to decreased cardiac output together with a possible direct effect of propranolol on the muscle blood supply[9] results in increased anaerobic metabolism and a delayed rate of carbon dioxide removal from the exercising muscles, thereby lowering measured carbon dioxide output during early exercise. Elevated local metabolite concentrations override the effects of beta-adrenergic blockade on the muscle blood supply later in exercise, causing an increased blood flow facilitating carbon dioxide removal. Under these conditions the respiratory exchange ratio is obviously a poor indicator of the muscular metabolic activity at a given time. In agreement with this explanation, after 4 months of training our patients were able to achieve an increased exercise duration and maximal treadmill speed for their working heart frequency limit, thereby reaching a mean elevated respiratory exchange ratio of 0.86 ± 0.03 ($p < 0.05$). Similar increases in the physical working capacity in patients with coronary heart disease after training during long-term therapy with beta-adrenergic blockade were noted by Obma[4] and Pratt[5] and their co-workers. Malmborg's[6] finding of no such improved exercise ability is most likely the result of an inadequate training stimulus.

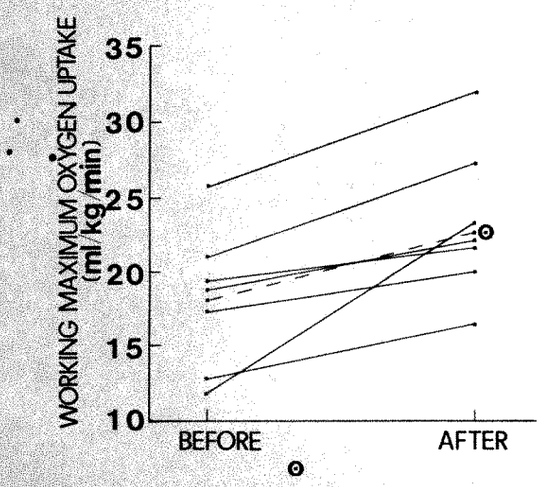



**FIGURE 2.** Working maximal oxygen uptake before and after 4 months endurance training in 7 patients receiving long-term beta-adrenergic blockade after myocardial infarction. **Black circles,** 26% increase, $p < 0.01$ versus before training.

The reasoning behind a heart rate exercise prescription is that myocardial work reflects oxygen consumption, which in turn is proportional to the heart rate. This is true under most circumstances of everyday life, the major exceptions being isometric and arm work. Patients participating in the cardiac rehabilitation program at our center are advised never to exceed their working heart frequency limit, whether it be in training or any of a multitude of life-style activities. The individual's working maximal oxygen uptake reflects his or her maximal "safe" permissible energy expenditure, thus limiting the variety of recreational as well as occupational pursuits. An increased working maximal oxygen uptake widens this choice and thus improves the quality of life, the major goal of cardiac rehabilitation in our opinion. If a heart rate prescription is employed, it becomes unnecessary to determine oxygen uptake using maximal testing. Respiratory data collected at the level of maximal exercise have to be interpreted with caution in patients with coronary heart disease because this maximal oxygen uptake is symptom-limited and therefore does not have the same physiologic meaning as a true maximal oxygen uptake measured in a normal person. In addition, working maximal oxygen uptake

is a submaximal measurement and can therefore be used to assess aerobic performance on a regular basis with a high level of safety in patients with coronary heart disease. With this technique we demonstrated a 12.8% ($p < 0.005$) decrease in heart rate after training, for what was initially the maximal work load for the working heart frequency limit. This slowing of the heart rate was accompanied by a 13.1% ($p < 0.05$) increase in oxygen pulse. The heart rate response to submaximal exercise may be lower after exercise training due either to an improved external mechanical work efficiency,[10] (in which case the oxygen consumption–heart rate relation [that is, oxygen pulse] remains unchanged), or to an enhanced capacity for oxygen transport and utilization (resulting in an increased oxygen pulse). Oxygen pulse is representative of the volume of oxygen consumed by the tissues with each heart beat, and can be shown, with use of the Fick principle, to equal stroke volume times arteriovenous oxygen difference. Increases in both variables account for the increased oxygen pulse during submaximal exercise in normal persons with physical training,[11] whereas an increased arteriovenous oxygen difference is believed to be the major factor in patients with coronary heart disease.[12] Beta-adrenergic blockade itself results in an increased arteriovenous oxygen difference,[13] but although its mechanism of action is to reduce venous oxygen content by increasing peripheral oxygen extraction, exercise training in addition to this effect causes an increased arterial oxygen content,[12] and may thereby further widen an already increased arteriovenous oxygen difference in patients with coronary heart disease receiving long-term beta-adrenergic blockade. Although arteriovenous oxygen difference was not directly measured in our study, the increased oxygen pulse during submaximal exercise most likely reflects an exercise conditioning induced increase in arteriovenous oxygen difference, despite the presence of long-term beta-adrenergic blockade. Whatever the mechanism, this increased oxygen pulse provides unequivocal evidence of a significant physiologic training effect in patients with coronary heart disease receiving long-term beta-blocking agents while participating in a cardiac rehabilitation exercise program.

After 4 months of endurance conditioning patients in our study increased their working maximal oxygen uptake by 26%, providing further evidence that a cardiac rehabilitation exercise program is not contraindicated by the use of beta-blocking drugs. This improvement in working maximal oxygen uptake is in fact similar to the increases "maximal oxygen uptake" noted in previous studies of coronary patients not receiving beta-blockade.[12,14]

Exercise conditioning-related improvements in redistribution of peripheral blood flow, oxygen transport capacity, and skeletal muscle oxygen extraction and utilization, are the likely mechanisms of this increased aerobic capacity.

**Implications:** This study has documented an unequivocal physiologic adaptation to endurance training in 7 patients receiving long-term beta-adrenergic blocking agents after myocardial infarction. The small patient sample used together with the lack of a control group do not detract from our findings which suggest that appropriately selected patients with coronary heart disease may derive the full benefits from a suitable cardiac rehabilitation exercise program in the presence of long-term beta-blockade. Whether it may in fact be preferable for such patients to receive beta-adrenergic blockade has still to be demonstrated.

## References


1. **Clausen JP.** Circulatory adjustments to dynamic exercise and effect of physical training in normal subjects and in patients with coronary artery disease. Prog Cardiovasc Dis 1976;18:459–494.
2. **Amsterdam EA, Laslett LJ, Dressendorfer RH, Mason DT.** Exercise training in coronary heart disease: is there a cardiac effect? Am Heart J 1981; 101:870–873.
3. **Hossack KF, Bruce RA, Kusumi F.** Altered exercise ventilatory responses by apparent propranolol-diminished glucose metabolism: implications concerning impaired physical training benefit in coronary patients. Am Heart J 1981;102:378–382.
4. **Obma RT, Wilson PK, Goebel ME, Campbell DE.** Effect of a conditioning program in patients taking propranolol for angina pectoris. Cardiology 1979;64:365–371.
5. **Pratt CM, Welton DE, Squires WG, Kirby TE, Hartung GH, Miller RR.** Demonstration of training effect during chronic beta-adrenergic blockade in patients with coronary artery disease. Circulation 1981;64:1125–1129.
6. **Malmborg R, Isaccson S, Kallivroussis G.** The effect of beta blockade and/or physical training in patients with angina pectoris. Curr Ther Res 1974;16:171–183.
7. **Anderson SD, Bye PT, Perry CP, Hamor GP, Theobald G, Nyberg G.** Limitation of work performance in normal adult males in the presence of beta-adrenergic blockade. Aust NZ J Med 1979;9:515–520.
8. **Twentyman OP, Disley A, Gribbin HR, Alberti KGGM, Tattersfield AE.** Effect of beta-adrenergic blockade on respiratory and metabolic responses to exercise. J Appl Physiol 1981;51:788–793.
9. **Brick I, Glover WE, Hutchison KJ, Roddie IC.** Effects of propranolol on peripheral vessels in man. Am J Cardiol 1966;18:329–333.
10. **Dressendorfer RH, Smith JL, Amsterdam EA, Mason DT.** Reduction of submaximal exercise myocardial oxygen demand post-walk training program in coronary patients due to improved physical work efficiency. Am Heart J 1982;103:358–362.
11. **Hanson JS, Tabakin BS, Levy AM, Nedda W.** Long-term physical training and cardiovascular dynamics in middle-aged men. Circulation 1968;38: 783–799.
12. **Detry J-MR, Rousseau M, Vandenbroucke G, Kusumi MS, Brasseur LA, Bruce RA.** Increased arteriovenous oxygen difference after physical training in coronary heart disease. Circulation 1971;44:109–118.
13. **Reybrouck T, Amery A, Bill L.** Haemodynamic response to graded exercise after chronic beta-adrenergic blockade. J Appl Physiol 1977;42:133–135.
14. **Ben Ari E, Kellerman JJ, Lapitod C.** Effect of prolonged intensive training on cardiorespiratory response in patients with angina pectoris. Br Heart J 1978;40:1143–1148.

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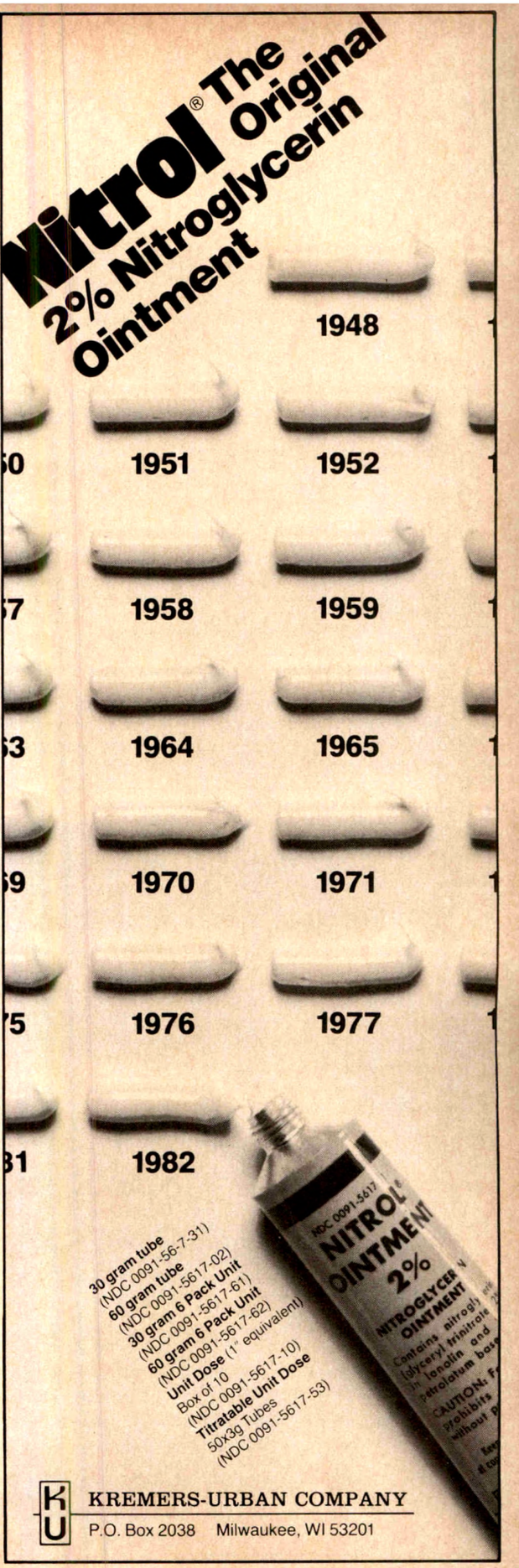
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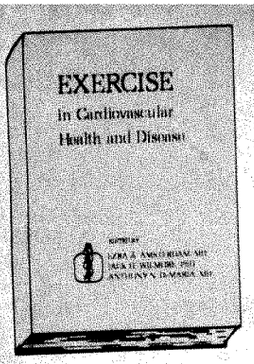
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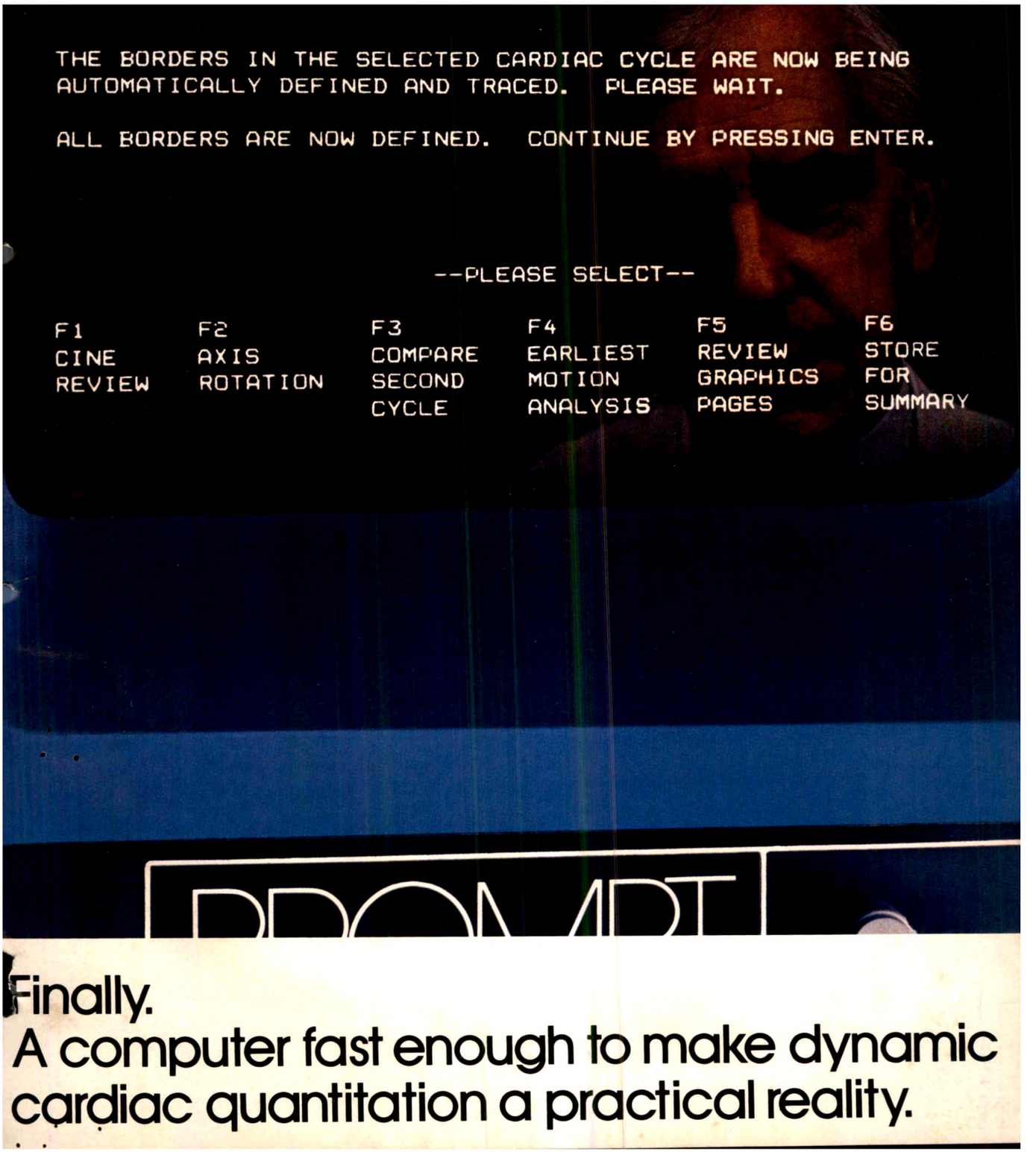
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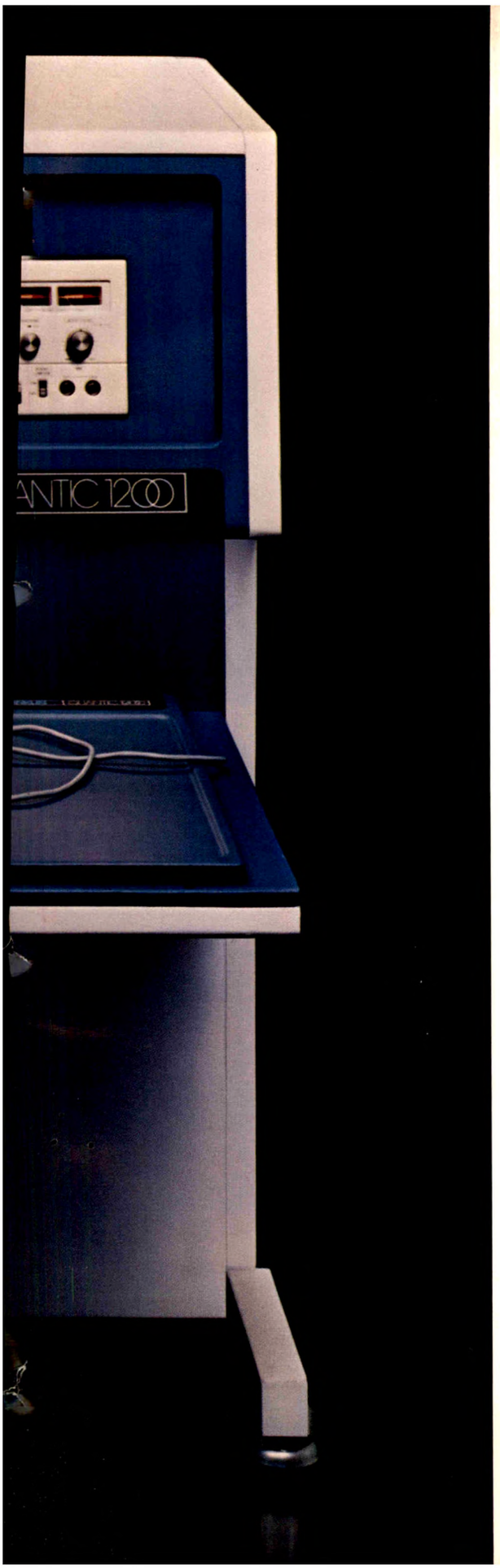
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# Disopyramide: Evaluation of Electrophysiologic Effects and Clinical Efficacy in Patients With Sustained Ventricular Tachycardia or Ventricular Fibrillation

BRUCE B. LERMAN, MD, HARVEY L. WAXMAN, MD, ALFRED E. BUXTON, MD, and MARK E. JOSEPHSON, MD

**The efficacy of disopyramide in the management of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) was evaluated in 50 patients by programmed ventricular stimulation: 38 patients had coronary artery disease (16 with left ventricular aneurysm), 8 had other cardiac diseases, and 4 had no apparent heart disease. Disopyramide was administered orally for 72 hours (dosage 400 to 1,600 mg/day), resulting in a plasma level of 3.6 ± 1.2 μg/ml (mean ± standard deviation [SD]). Disopyramide prevented induction of sustained ventricular tachyarrhythmias in 17 patients (34%) and failed to prevent induction in 33 patients (66%). Plasma levels were not significantly different regardless of response to disopyramide. The VT cycle length in patients responding to disopyramide was shorter than in nonresponding patients (225 ± 51 ms versus 281 ± 70 ms, p = 0.005). Disopyramide increased VT cycle length in those patients in whom it was ineffective (failed to prevent induction) from 281 ± 70 ms to 347 ± 64 ms (p <0.001). Ventricular refractory periods, QRS, and QTc durations significantly increased after disopyramide administration.**

**Of the 17 patients in whom tachyarrhythmias were noninducible on disopyramide, 11 were discharged on disopyramide and followed up for 19 ± 9 months; 9 of them remained free of VT. Heart failure developed in 2 of these patients. One other patient in whom disopyramide was ineffective had irreversible heart failure and died.**

**It is concluded that disopyramide (1) prevents induction of ventricular tachyarrhythmias in one third of patients studied and remains clinically effective in approximately 80%, (2) is more frequently effective in rapid tachycardias, (3) prolongs the VT cycle length when ineffective, and (4) may produce marked hemodynamic embarrassment in patients with significant left ventricular dysfunction.**

Disopyramide phosphate is a type I antiarrhythmic agent approved for use in the United States for treatment of ventricular arrhythmias in 1978. Nevertheless, previous investigations have failed to systematically analyze the ability of disopyramide to suppress inducible ventricular tachycardia (VT) and characterize its utility in a large group of patients with sustained ventricular tachycardia or ventricular fibrillation (VF).

Programmed ventricular stimulation is both sensitive and specific for the detection of clinical VT.[1-3] Response to conventional antiarrhythmic drugs during programmed ventricular stimulation has been shown to predict clinical response.[2-4] This report relates the immediate and long-term experience with disopyramide evaluated by programmed ventricular stimulation in 50 patients with sustained VT, VF, or both.

## Methods

**Patients:** Disopyramide was administered and electrophysiologic studies were performed in 50 patients with sustained ventricular arrhythmias between January 1977 and January 1982. There were 41 men and 9 women. Their average age was 54 years with a range of 28 to 73. Thirty-eight patients had coronary artery disease, including 29 with a history of a myocardial infarction, 16 of whom had a left ventricular aneurysm. Other cardiac diseases included cardiomyopathy in

From the Clinical Electrophysiology Laboratory, Hospital of the University of Pennsylvania, Cardiovascular Section, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. This study was supported in part by National Institutional Training Grant HL07346, by Research Service Award HL07201, by Research Career Development Award HL00361, and by Grant HL24278 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; and by grants from the American Heart Association, Southeastern Pennsylvania Chapter, Philadelphia, Pennsylvania. Manuscript received May 27, 1982; revised manuscript received November 17, 1982, accepted November 18, 1982.

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2, nonobstructive asymmetric septal hypertrophy in 1, mitral valve prolapse in 3, status postaortic valve replacement for aortic stenosis in 1, and status postrepair of tetralogy of Fallot in 1. Four patients had no clinical evidence of organic heart disease and had normal results on echocardiographic, radionuclide, or coronary arteriographic studies.

Forty-four patients were studied for evaluation of sustained VT and 6 for cardiac arrest whose first documented arrhythmia was VF. The number of clinical episodes of VT or VF before study ranged from 1 to >100. One to 5 (2.2 ± 1) conventional antiarrhythmic drugs had been tried empirically before electrophysiologic evaluation. No patient had an acute myocardial infarction within 4 weeks of study.

**Electrophysiologic study:** All studies were performed with the patient in the nonsedated, postabsorptive state after informed consent had been obtained. During the initial study, all antiarrhythmic drugs were discontinued for at least 5 half-lives before evaluation. Usually, 3 quadripolar and 1 tripolar catheter were inserted either percutaneously or by way of cutdown and advanced under fluoroscopic guidance into the high right atrium, coronary sinus, right ventricular apex-outflow tract, and atrioventricular junction for recording of the His bundle. The distal pair of quadripolar electrodes were used for stimulation and the proximal pair for recording the local atrial or ventricular electrogram. Intracardiac recordings were filtered at 30 to 500 Hz and simultaneously displayed with 3 electrocardiographic leads on a multichannel oscilloscope (Electronics for Medicine VR-16, White Plains, New York). The data were stored on magnetic tape (Honeywell model 5600) and later retrieved on photographic paper at speeds of 100 to 200 mm/s for illustrative purposes. Real-time recordings were made with an ink jet recorder (Siemens Elema Mingograph). Programmed ventricular stimulation was performed with a specially designed programmable stimulator and isolated constant current source (Bloom Associates Ltd, Narberth, Pennsylvania). Stimuli were delivered as rectangular pulses, 1 ms in duration at twice diastolic threshold.

The stimulation protocol consisted of single, double, and, in most cases, triple premature ventricular stimuli introduced during sinus rhythm at ventricular paced cycle lengths of 600 and 400 ms, and rapid ventricular pacing (≥5 seconds at cycle lengths of 350 to 250 ms) as previously described.[1-4] Stimulation was performed initially at the right ventricular apex and if the tachycardia was not induced, stimulation at the right ventricular outflow tract was employed. Left ventricular stimulation was not required in any patient in this study. After the induction of VT, programmed ventricular stimulation or rapid ventricular pacing was used for termination. If VT tachycardia degenerated into VF either spontaneously or as a result of pacing or ensuing loss of consciousness, direct-current cardioversion was employed.

After control study demonstrating reproducible initiation of ventricular tachyarrhythmia, disopyramide was adminis-

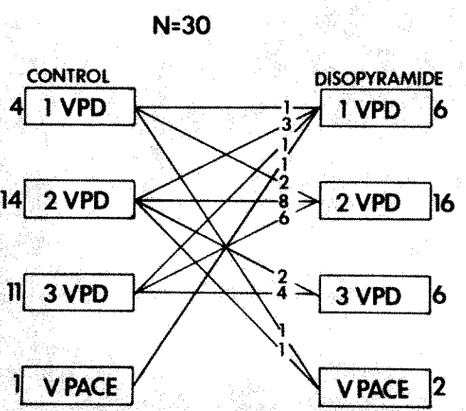



**FIGURE 1.** Mode of induction during the control study and after disopyramide administration. No difference in the induction mode as a result of disopyramide is demonstrated. VPD = ventricular premature depolarization; VPACE = ventricular pacing.

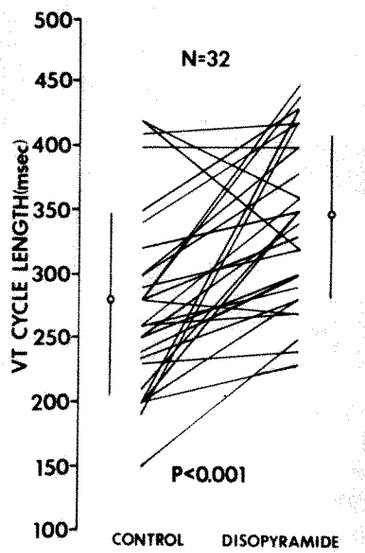



**FIGURE 2.** Effect of disopyramide on ventricular tachycardia (VT) cycle length. The mean VT cycle increased from 281 ms to 347 ms. (Note: 3 patients had identical control and postdisopyramide VT cycle lengths—320 ms and 350 ms, respectively—while 2 patients had similar control cycle lengths of 340 ms and postdisopyramide values of 420 ms.)

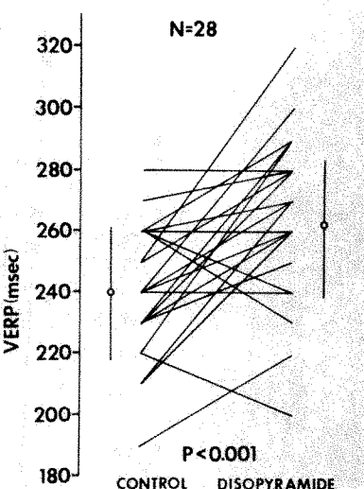



**FIGURE 3.** Effect of disopyramide on the ventricular effective refractory period (VERP). The mean ventricular effective refractory period increased from 240 to 264 ms. (Note: 4 patients had identical control and postdisopyramide ventricular effective refractory periods—240 and 270 ms. Three other pairs of patients also had identical values—190 to 220 ms, 280 to 280 ms, and 240 to 240 ms before and after disopyramide.)

tered orally at an initial dose of 100 to 200 mg every 6 hours for 72 hours. Programmed stimulation was then repeated at twice diastolic threshold using a quadripolar catheter placed in the right ventricular apex-right ventricular outflow tract. If the initial dose of disopyramide failed to prevent tachycardia induction, the dose of disopyramide was increased and the patient restudied after a new steady state level was achieved. No patient received any other antiarrhythmic agent during this period, with the exception of digoxin or propranolol for treatment of angina pectoris. The highest dose of disopyramide tested was 400 mg every 6 hours. Plasma levels of disopyramide were obtained immediately after the programmed ventricular stimulation protocol or shortly after the initiation of VT or VF.

In addition to mode of induction and cycle length of induced tachycardia, the effects of disopyramide on the ventricular effective refractory period, QRS duration, and QTc interval (Bazett's formula) were determined (the latter 2 were measured from the surface electrocardiogram).

**Statistical methods:** Statistical analysis was performed using the paired and unpaired $t$ test. Data are expressed as mean ± standard deviation.

**Definitions:** (*1*) *Sustained ventricular tachycardia:* Ventricular tachycardia that lasted at least 30 seconds either clinically or during induction with programmed ventricular stimulation, or required termination by programmed ventricular stimulation or cardioversion sooner because of hemodynamic deterioration. (*2*) *Effective response (disopyramide):* Prevention of sustained VT induced by programmed ventricular stimulation. (*3*) *Clinical effectiveness:* Absence of clinical or monitored sustained VT or VF during the follow-up period.

## Results

**Induction:** VT was induced in all 50 patients during the control study. In most patients tachyarrhythmias were induced with either double (26) or triple premature stimuli (13). Sixteen patients required direct-current cardioversion to terminate the arrhythmia, while programmed ventricular stimulation was successful in the remainder. Disopyramide prevented induction of sustained VT in 17 of 50 patients (34%). Eleven of these 17 patients had nonsustained VT (≥6 complexes) induced, none of which lasted more than 8 seconds. Six patients had <6 complexes induced. Three patients in whom the initial dose of disopyramide failed to prevent induction of sustained tachycardia had an effective response at a higher dose. Disopyramide did not significantly alter the mode of induction in those patients in whom it was ineffective (Fig. 1).

**Cycle length:** The cycle length of induced VT was 265 ± 70 ms. Disopyramide significantly increased the cycle length of VT in those patients in whom it was ineffective, from 281 ± 70 ms to 347 ± 64 ms ($p < 0.001$). In 3 patients, however, it decreased the VT cycle length by 20 to 30 ms (Fig. 2). The shorter the VT cycle length during the control study, the more frequently disopyramide prevented induction of VT: 225 ± 51 ms versus 281 ± 70, $p = 0.005$.

**Refractory periods:** Disopyramide increased the right ventricular effective refractory period from 240 ± 23 ms to 264 ± 27 ms, $p < 0.001$ (Fig. 3); however, in 4 patients a decrease was noted. There was no difference in the ventricular effective refractory period between those who were inducible with disopyramide and those who were not: 266 ± 33 ms versus 263 ± 23 ms, $p > 0.10$.

**QRS width:** The QRS interval after disopyramide increased from 104 ± 22 ms to 111 ± 22 ms, $p < 0.002$ (Fig. 4). There was no statistical difference in QRS duration between inducible and noninducible patients; 113 ± 7 ms versus 106 ± 6 ms, $p > 0.10$.

**QTc interval:** The QTc increased from 422 ± 48 ms to 461 ± 60 ms ($p < 0.001$) after disopyramide. There was no difference between patients with inducible and noninducible tachycardias: 480 ± 60 ms versus 450 ± 60 ms, $p = 0.11$ (Fig. 5).

**Plasma levels:** Disopyramide plasma levels were measured in 25 patients during programmed ventricular stimulation. The mean level was 3.6 ± 1.2 μg/ml. There was no significant difference between those in whom disopyramide prevented induction of ventricular tachyarrhythmias (10 patients) and in those 15 patients in whom it did not (3.7 ± 1.4 μg/ml versus 3.5 ± 1.1 μg/ml, $p > 0.10$).

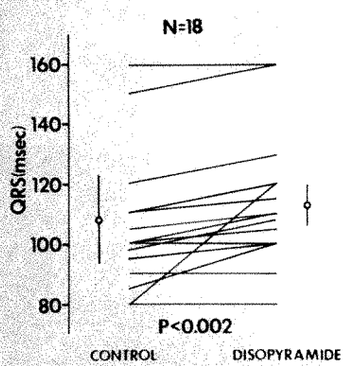



**FIGURE 4.** Effect of disopyramide on the QRS interval. The mean QRS increased from 104 to 111 ms. (Note: 3 pairs of patients had identical control and postdisopyramide QRS intervals—105 to 110 ms, 95 to 110 ms, and 80 to 80 ms, respectively.)

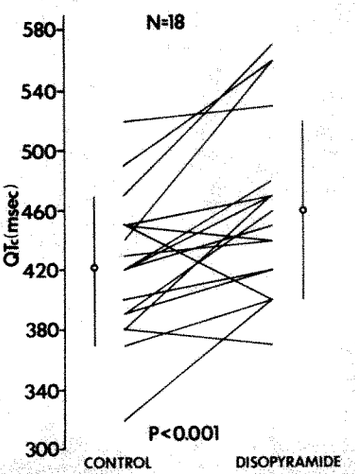



**FIGURE 5.** Effect of disopyramide on the QTc interval. The mean QTc interval increased from 422 ms during the control study to 460 ms after disopyramide administration.

**Adverse reactions:** Adverse effects associated with disopyramide administration developed in 10 of 50 (20%) patients. One patient with angiographic evidence of a left ventricular aneurysm was studied while taking disopyramide at a dosage of 200 mg every 6 hours, which was well-tolerated. VT was induced during programmed ventricular stimulation and the oral dose was increased to 300 mg every 6 hours. After the third dose, irreversible heart failure and electromechanical dissociation developed in the patient. There were 4 instances of dry mouth, 3 of urinary hesitancy, and 2 of blurred vision within 48 hours of receiving the drug. These symptoms decreased with a lower dose. In each case, the patient was discharged with this lower dose as long as an effective response to the drug at this dose was demonstrated during programmed ventricular stimulation.

**Long-term follow-up (Table I):** Eleven of 17 patients in whom disopyramide prevented induction of VT were discharged with the drug as their only antiarrhythmic agent. The remaining 6 patients were treated with other agents alone or in combination with disopyramide because (1) adverse effects required reducing the dosage below that shown effective, or (2) similar efficacy was demonstrated with another drug with less myocardial depressant effects than disopyramide. Amiodarone was added to disopyramide in 1 patient (Case 17) because rapid nonsustained polymorphic VT (<8 seconds) was induced while the patient was receiving disopyramide alone. This was considered an unsatisfactory response. The follow-up period for the 11 patients has been 19 ± 9 months. The maintenance dose of disopyramide ranged from 0.6 to 1.2 g/day (0.81 ± 0.24 g).

*Arrhythmias:* Nine of 11 patients remain free of VT. VT recurred in 2 patients. One patient (Case 9) had a recurrence of VT 6 weeks after starting disopyramide. Endocardial mapping, ventricular aneurysmectomy, and endocardial resection were subsequently performed. The other patient (Case 10) had VT 25 months after initiation of therapy (3 and 8 ventricular complexes were respectively induced in each patient during their initial disopyramide study). Another patient (Case 8) had an episode of VT complicated by a fatal anterior wall myocardial infarction 6 months after starting disopyramide. He was free of VT during the period preceding infarction.

Four patients were treated with disopyramide in combination with other antiarrhythmic agents. In Patient 12, VT was noninducible with disopyramide or with the combination of quinidine and propranolol. However, the development of blurred vision, urinary hesitancy, and diarrhea necessitated decreasing the effective dose of disopyramide and quinidine. VT was not induced when a lower dose of both drugs in combination was tested. Patient 12 has remained arrhythmia-free for 30 months with a regimen of disopyramide, quinidine, and propranolol. Another patient (Case 17) was discharged receiving the combination of disopyramide and amiodarone which prevented induction of sustained VT. The patient has been arrhythmia-free for 3 months. In another patient, disopyramide alone slowed the VT cycle length from 260 to 290 ms. Mexiletine, separately, increased the cycle length to 315 ms and the combination of both drugs at their original doses resulted in induction of 16 seconds of VT with a cycle length of 420 ms. This patient has not had an episode of VT during the 14-month follow-up period. The final patient had VT with a cycle length of 200 ms induced while taking disopyramide. Aprindine (not tested independently) in combination with disopyramide resulted in inducible VT at a cycle length of 440 ms. He was discharged receiving both drugs and died 1 month later of recurrent VT.

*Adverse effects:* Two patients died of intractable congestive heart failure at 13 and 25 months after disopyramide administration (Cases 1 and 10, Table I). Both had ejection fractions <40% and previous histories of congestive heart failure. The discharge maintenance doses were 200 and 300 mg, respectively, on a 6-hour regimen.

Minor adverse effects including dry mouth, blurred vision, or urinary hesitancy have either been tolerated or improved with time.

## Discussion

Electrophysiologic effects of disopyramide are similar to those of procainamide and quinidine. In man, it lengthens the atrial effective refractory period, decreases the effective refractory period of the atrioventricular node, and increases the relative refractory period of the His-Purkinje system.[5] In isolated canine Purkinje fibers, disopyramide diminishes $\dot{V}_{max}$, membrane responsiveness, spontaneous phase 4 depolarization, and maximal diastolic potential; it increases action potential duration.[6-8]

**Response to programmed ventricular stimulation:** Disopyramide prevented induction of VT in one third of patients studied. Programmed stimulation predicted long-term success in over 80% of patients discharged taking the drug. This is similar to the positive predictive value of programmed stimulation using other type I agents.[2-4]

Our data are consistent with findings from previous studies that examined the electrophysiologic efficacy of disopyramide in a similar patient population.[9-12] A 30 to 50% success rate has been reported using doses from 600 to 1,400 mg/day. These studies, however, have been limited by both the number of patients evaluated and the incomplete follow-up data provided.

The effect of disopyramide on the QRS interval, QTc interval, or ventricular effective refractory period did not distinguish between effective or ineffective responders. Interestingly, the faster the VT cycle length in the control study, the more likely an effective response was achieved. This observation has been noted by other investigators evaluating mexiletine.[13]

**Effect of disopyramide on VT cycle length:** Disopyramide significantly increased the cycle length of the tachycardia. This has important clinical implications. It suggests that even though the drug may fail to prevent reinduction of VT, it may result in a hemodynamically stable, and, therefore, better tolerated tachycardia.

**Electrocardiographic effects:** Disopyramide lengthened the QTc interval by a small but statistically significant amount. No marked prolongation associated

**TABLE I Disopyramide: Noninducibility With Programmed Ventricular Stimulation**

| Case | Age (yr) & Sex | Cardiac Diagnosis | Ejection Fraction | Episodes (n) of VT/VF Before PVS | Drugs (n) Before PVS | Serum Level of D During PVS (μg/ml) | Maintenance Dose of D/24 h (g) | Duration of Follow-Up (mo) | Recurrence of VT | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 69M | S/P MI | 30% | 1 | 2 | . . . | 0.8 | 13 | No | CHF; died |
| 2 | 47F | MVP | . . . | 2 | 2 | 1.7 | 1 | 13 | No | Dry mouth |
| 3 | 60M | S/P MI | . . . | Numerous | NA | . . . | 1.2 | 24 | No | None |
| 4 | 42M | S/P MI | 30% | 2 | 4 | 3.5 | 0.6 | 28 | No | None |
| 5 | 32M | None | 84% | 3 | 3 | . . . | 0.6 | 25 | No | None |
| 6 | 43M | CAD, LV aneurysm | . . . | 1 | 2 | 4.5 | 0.6 | 22 | No | Blurred vision, dry mouth |
| 7 | 68F | None | 78% | 1 | 2 | . . . | 0.6 | 30 | No | Dry mouth |
| 8* | 54M | CAD | . . . | 3 | 3 | 6.3 | 0.9 | 6 | No | None |
| 9 | 62M | CAD, LV aneurysm | . . . | 2 | 3 | 3.7 | 0.8 | 1.5 | Yes | None |
| 10 | 54M | S/P MI | 37% | 1 | 2 | . . . | 1.2 | 25 | Yes | CHF, died |
| 11 | 31M | Normal | 64% | 1 | 2 | 2.0 | 0.6 | 19 | No | None |
| 12 | 35F | MVP | . . . | 5 | 2 | 5.3 | D, Q, PROP | 30 | No | Blurred vision, urinary hesitancy |
| 13 | 62M | S/P MI | . . . | 2 | 2 | 2.8 | Q | . . . | . . . | None |
| 14 | 50M | CAD, LV aneurysm | 26% | Numerous | 1 | 3.7 | P | . . . | . . . | None |
| 15 | 73F | CAD | . . . | 1 | 1 | . . . | M | . . . | . . . | None |
| 16 | 50M | CAD, LV aneurysm | 38% | Numerous | 5 | . . . | P | . . . | . . . | None |
| 17† | 44M | AS, S/P AVR | . . . | 1 | 3 | 3.6 | D,A | 3 | No | None |

* Patient had a fatal myocardial infarction accompanied by VT 6 months after discharge.
† Patient had 26 beats of polymorphic VT with a cycle length of <200 ms induced with programmed ventricular stimulation while taking disopyramide alone.
A = amiodarone; AS = aortic stenosis; AVR = aortic valve replacement; CAD = coronary artery disease; D = disopyramide; LV = left ventricle; M = mexiletine; MI = myocardial infarction; MVP = mitral valve prolapse; NA = not available; P = procainamide; PROP = propranolol; PVS = programmed ventricular stimulation; Q = quinidine; S/P = status post; VT = ventricular tachycardia.

with torsade de pointes was observed. Disopyramide-related torsade de pointes, VT, and VF have been described in association with prolonged QRS and QT intervals or QT intervals alone.[14–17] Disopyramide levels were markedly elevated in the 2 cases in which they were reported, 7.2 μg/ml (dose 100 mg orally every 6 hours) and 7.5 μg/ml (dose 600 mg orally every 6 hours). Congestive heart failure and renal or hepatic insufficiency may predispose the patient to elevated plasma levels.

While a statistically significant increase in QRS duration was also observed, no significant degree of heart block was noted. A recent study using intravenous disopyramide in patients with bundle branch block demonstrated that although mean infranodal conduction time increased 18%, from 67 ± 35 ms to 79 ± 41 ms ($p < 0.001$), no spontaneous second- or third-degree atrioventricular block occurred. Mean peak serum levels were 5.1 ± 2.2 μg/ml.[18]

**Adverse effects:** Anticholinergic symptoms are the most common adverse effects associated with disopyramide administration. In our study, urinary hesitancy, dry mouth, and blurred vision usually occurred within 48 hours of receiving the drug; however, these symptoms were usually mild and resolved with time or with a reduction in dose. In no case was discontinuation of the drug necessary. Other associated symptoms such as nausea, vomiting, and headache were not present in our study.

A major concern with disopyramide is its effect on left ventricular function. Cathcart-Rake et al[19] recently reported that although doses of 800 mg/day of disopyramide caused a slight decrease in left ventricular ejection fraction as evaluated by M-mode echocardiography in normal volunteers, this did not result in development of clinically significant symptoms. However, a preliminary report by Desai et al[20] demonstrated electromechanical dissociation with disopyramide in 6 patients with congestive heart failure and renal insufficiency. Plasma levels, when available, were elevated. All patients had significant lengthening of the QTc interval at least 24 hours before death. Postmortem examination eliminated other potential causes for electromechanical dissociation. We saw 1 death due to electromechanical dissociation. Two patients receiving long-term disopyramide had worsening of congestive heart failure. Podrid et al[21] reported that in patients with a history of congestive heart failure, disopyramide may precipitate recurrence of failure in 50% while resolution usually occurs with discontinuation of the drug. Most instances of failure occurred within 3 weeks of initiating treatment. There was no significant difference in either dose or plasma levels in patients with and without congestive heart failure in their series.

**Conclusions:** Disopyramide prevented induction of sustained VT in one third of patients studied and remained effective therapy in 80% of patients treated chronically. Though minor adverse effects developed in 20% of patients receiving disopyramide, the major factor limiting its use was myocardial depression. This occurred only in those patients with preexisting ventricular dysfunction.

## References


1. **VandePol CJ, Farshidi A, Spielman SR, Greenspan AM, Horowitz LN, Josephson ME.** Incidence and clinical significance of induced ventricular tachycardia. Am J Cardiol 1980;45:725–731.
2. **Mason JW, Winkle RA.** Electrode-catheter arrhythmia induction in the selection and assessment of antiarrhythmic drug therapy for recurrent ventricular tachycardia. Circulation 1978;58:971–985.
3. **Ruskin JN, Garan H.** Chronic electrophysiologic testing in patients with recurrent sustained ventricular tachycardia (abstr). Am J Cardiol 1979; 43:400.
4. **Horowitz LN, Josephson ME, Farshidi A, Spielman SR, Michelson EL, Greenspan AM.** Recurrent sustained ventricular tachycardia. 3. Role of the electrophysiologic study in selection of antiarrhythmic regimens. Circulation 1978;58:986–997.
5. **Josephson ME, Caracta AR, Lau SH, Gallagher JJ, Damato AN.** Electrophysiological evaluation of disopyramide in man. Am Heart J 1973;86: 771–776.
6. **Danilo P, Rosen MR.** Cardiac effects of disopyramide. Am Heart J 1976; 92:532–536.
7. **Kus T, Sasyniuk TI.** Electrophysiological action of disopyramide phosphate on canine ventricular muscle and Purkinje fibers. Circ Res 1975;37: 844–854.
8. **Danilo P, Hordof AM, Rosen MR.** Effects of disopyramide on electrophysiologic properties of canine cardiac Purkinje fibers. J Pharmacol Exp Ther 1977;201:701–710.
9. **Breithardt G, Seipel L, Abendroth R.** Comparative cross-over study of the effects of disopyramide and mexiletine on stimulus-induced ventricular tachycardia (abstr). Circulation 1980;62:Suppl III:III-53.
10. **Swiryn S, Wyndham C, Bauernfeind R, Dhingra R, Rosen K.** Prediction of response to Class I antiarrhythmic drugs during chronic electrophysiologic study of ventricular tachycardia (abstr). Circulation 1980;62:Suppl III:III-85.
11. **Benditt DG, Pritchett ELC, Wallace AG, Gallagher JJ.** Recurrent ventricular tachycardia in man: evaluation of disopyramide therapy by intracardiac electrical stimulation. Eur J Cardiol 1979;9:255–276.
12. **Denes P, Wu D, Wyndham C, Dhingra R, Bauernfeind R, Swiryn S, Rosen KM.** Chronic long-term electrophysiologic study of paroxysmal ventricular tachycardia. Chest 1980;77:478–487.
13. **DiMarco JP, Garan H, Ruskin JN.** Mexiletine for refractory-ventricular arrhythmias: results using serial electrophysiologic testing. Am J Cardiol 1981;47:131–138.
14. **Lo KS, Gantz KB, Stetson PL, Lucchesi BR, Pitt B.** Disopyramide-induced ventricular tachycardia. Arch Intern Med 1980;140:413–414.
15. **Meltzer RS, Robert E, McMorrow M, Martin RP.** Atypical ventricular tachycardia as a manifestation of disopyramide toxicity. Am J Cardiol 1978;42:1049–1053.
16. **Nicholson WJ, Martin CE, Gracey JG, Knoch HR.** Disopyramide-induced ventricular fibrillation. Am J Cardiol 1979;43:1053–1055.
17. **Tzivoni D, Keren A, Stern S, Cottlieb S.** Disopyramide-induced Torsade de pointes. Arch Intern Med 1981;141:946–947.
18. **Desai JM, Scheinman M, Peters RS, O'Yang J.** Electrophysiological effects of disopyramide in patients with bundle branch block. Circulation 1979; 59:215–225.
19. **Cathcart-Rake WF, Coker JE, Atkins FL, Huffman DH, Hassanein KM, Shen DD, Azarnoff DL.** The effect of concurrent oral administration of propranolol and disopyramide on cardiac function in healthy men. Circulation 1980;61:938–945.
20. **Desai J, Hirschfeld D, Peters R, Scheinman M, Gonzalez R.** Electromechanical dissociation associated with disopyramide (abstr). Circulation 1978;57,58:Suppl II:II-178.
21. **Podrid PJ, Schoeneberger A, Lown B.** Congestive heart failure caused by oral disopyramide. N Engl J Med 1980;302:614–617.

# Effects of Oral Digoxin on Ventricular Ectopy and Its Relation to Left Ventricular Function

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**The ventricular antiarrhythmic properties of oral digoxin were examined in 13 patients with chronic ventricular ectopy using serial 24-hour electrocardiographic monitoring. Mean premature ventricular complex frequency (per 1,000 normal beats) decreased from 56 ± 47 during the placebo period to 40 ± 27 ($p$ = not significant [NS]) and 25 ± 17 ($p < 0.05$) during daily administration of digoxin, 0.25 and 0.375 mg. Digoxin had no significant effect on the qualitative occurrence of complex ventricular arrhythmia patterns (multiformity, bigeminy, couplets, ventricular tachycardia). Radionuclide left ventricular (LV) ejection fraction was measured during the placebo period. Seven patients had normal (ejection fraction >50%) and 6 abnormal global LV performance. In the normal group, the mean premature ventricular complex frequency decreased from 69 ± 58 to 20 ± 18 ($p < 0.05$) and the mean couplet frequency decreased from 0.59 ± 0.85 to 0.07 ± 0.06 ($p < 0.04$) during the placebo and 0.375 mg digoxin dosing periods, respectively. In contrast, no significant changes in either variable occurred after digoxin in subjects with depressed LV function. This study indicates that oral digoxin is moderately effective in suppressing premature ventricular complexes, and that its effects are greatest in patients with normal overall LV performance.**

The digitalis glycosides exert a variety of direct and indirect effects on myocardial cells[1–3] and are widely utilized for their inotropic and atrial antiarrhythmic properties. These agents have not, however, been generally used in the treatment of ventricular arrhythmias and, indeed, in toxic doses, are often implicated in their production.[4] In 1977, Lown et al[5] reported that intravenous administration of the digitalis-like agent acetylstrophanthidin was effective in suppressing ventricular ectopy in approximately one half of patients studied over a monitoring period of several hours.[5] That study has stimulated considerable interest in the ventricular antiarrhythmic properties of cardiac glycosides.

The present study was undertaken to determine the effects of digoxin—the most commonly used oral digitalis preparation—on the occurrence of ventricular ectopy. Long-term ambulatory electrocardiographic monitoring was used to provide a statistically adequate sampling of arrhythmia frequencies, in view of recent studies documenting the wide spontaneous variation which may occur in the frequency of premature ventricular complexes.[6,7] In addition, global left ventricular (LV) function was assessed with radionuclide angiocardiography and related to antiarrhythmic drug response.

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## Methods

**Patient population:** Seventeen ambulatory outpatient men participated in the study. Subjects were selected on the basis of a random 24-hour ambulatory electrocardiographic recording demonstrating a mean premature ventricular complex frequency ≥10/1,000 normal beats. Patients in whom a history of life-threatening arrhythmia precluded temporary discontinuation of antiarrhythmic drug therapy or in whom ventricular tachycardia was noted on random Holter monitoring were excluded. Also excluded were patients with a serum creatinine level ≥1.5 mg/100 ml. In 4 subjects, the mean premature ventricular complex frequency decreased spontaneously during the placebo period (see section on Protocol) to values <2/1,000 normal beats. These patients were not included in final data analysis.

Thirteen patients aged 45 to 66 years (mean 57) completed the protocol and are the subject of data analysis. Six had definite coronary artery disease, documented by prior myocardial infarction or coronary arteriography; 1 additional patient with a classic anginal syndrome was presumed to have coronary disease. The remaining 7 patients had systemic hypertension; 1 of these also had aortic valvular stenosis. Two patients had a history of congestive heart failure; neither was in clinical heart failure at the time of study. Five patients had symptoms potentially referable to arrhythmias; 1 had palpitations and dizziness, 2 palpitations alone, and 2 dizziness alone.

**Protocol:** A single-blind placebo-controlled study design was utilized. At the initial study visit, antiarrhythmic medications were withdrawn and subjects began receiving a placebo tablet (identical in appearance to Lanoxin®, 0.25 mg) once daily. At the end of a 1-week dosing period, a 24-hour ambulatory electrocardiogram was recorded. In addition, resting left ventricular ejection fraction (LVEF) was determined using first-pass quantitative radionuclide angiocardiography. Subjects were then given oral digoxin (Lanoxin), 0.25 mg daily for a 1-week period, at the end of which ambulatory monitoring was repeated. If no signs or symptoms of digitalis intoxication were noted, the digoxin dose was increased to 0.375 mg daily and a final 24-hour electrocardiogram recorded at the end of a 1-week dosing period. (One patient in whom sinus bradycardia developed during the 0.25 mg dosing period did not receive the higher dose.) Pill counts were used to verify compliance.

**Arrhythmia detection and quantification:** Ambulatory electrocardiograms were recorded on 2-channel Avionics Model 425 Electrocorders using a bipolar $V_5$ and $V_5R$ lead system. Electrocardiographic recordings were analyzed using the YALECG research minicomputer system.[8] Currently configured on a Data General Eclipse S/130 processor, the YALECG algorithm is based on a width-sensitive peak detector for location of QRS complexes and a dual width correlation matching algorithm for waveform comparison. The system is operator-interactive and a series of on-line validity checks is used to ensure optimal program function.

The accuracy of this system in detecting premature ventricular complexes has been validated previously.[8] In a study of 20 1-hour electrocardiographic recording segments, system output was compared with a beat-by-beat hand count of the electrocardiogram. These recording segments, which were different from those used during algorithm development, contained 100,771 normal beats and 9,070 premature ventricular complexes. The true-positive rate for detection of premature ventricular complexes (sensitivity) was found to be 99.2%, the true-negative rate (specificity) 99.9%, and the false-positive rate 0.20%.

Mean heart rate and the total frequency of premature ventricular complexes (expressed per 1,000 normal beats) were determined for each electrocardiogram. The occurrence of 2 consecutive premature ventricular depolarizations was defined as a couplet, and couplet frequencies (per 1,000 normal beats) were also determined. The time of occurrence and QRS morphologic sequence of complex arrhythmic events—couplets, bigeminy, and ventricular tachycardia (defined as ≥3 consecutive premature ventricular complexes occurring at a rate of ≥100/min)—were recorded in a computer-generated remark file.

**Radionuclide angiography:** Patients were studied while they were supine in the anterior position using a computerized multicrystal scintillation camera (Baird-Atomic System-77, Bedford, Massachusetts). An 18 gauge 1.5 inch catheter was placed in an antecubital vein and high-specific activity technetium-99m pertechnetate (10 to 15 mCi) injected. LVEF was determined from first-pass quantitative radionuclide angiocardiograms using standard techniques previously reported from this laboratory.[9,10]

Left ventricular end-diastolic volume (LVEDV) was measured using planimetry of the end-diastolic images obtained.[11] LVEDV measured in this manner correlates well with that

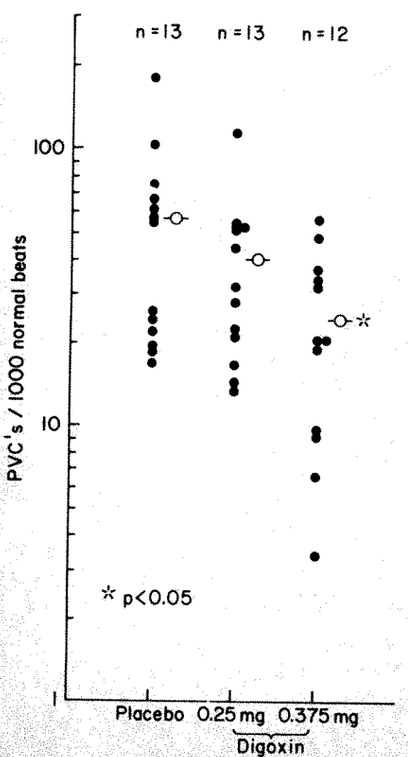



**FIGURE 1.** Effect of digoxin on the mean frequency of premature ventricular complexes (PVC's) in 13 patients.

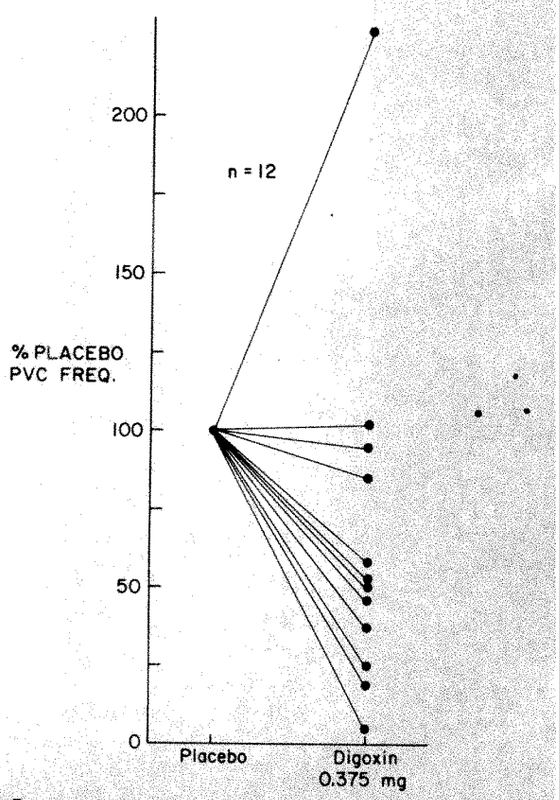



**FIGURE 2.** Percent change in the mean frequency of premature ventricular complexes (PVC FREQ.) during administration of digoxin, 0.375 mg daily.

measured by contrast angiography, and, in our laboratory, a correlation coefficient (r = 0.87) was noted in a group of 25 patients studied by both techniques. End-systolic volume (ESV) was calculated using the following formula: ESV = EDV − EDV·LVEF.

**Statistical methods:** Data are expressed as mean values ± standard deviation. Comparisons of mean heart rates and $\log_{10}$ of premature ventricular complex and couplet frequencies were made by paired (2-tailed) $t$ test. When multiple $t$ tests were performed on a data set, p values were corrected by multiplying the calculated p value by the number of tests performed, as suggested by Glantz.[12] Comparisons of the incidence of complex arrhythmia patterns were performed by the chi-square method. A p value <0.05 was considered significant.

## Results

**Electrocardiography:** Digoxin administration resulted in a modest decrease in the average heart rate. The mean heart rate declined from 84.4 ± 14.5 beats/min during the placebo period to 79.4 ± 12.4 beats/min (p <0.06) and 80.2 ± 11.5 beats/min (p <0.04) during the digoxin 0.25 mg and 0.375 mg dosage periods, respectively. The P-R interval increased from a placebo mean value of 0.164 ± 0.03 second to 0.177 ± 0.03 second (p <0.02) during the low-dose and 0.181 ± 0.04 second (p <0.002) during the high-dose digoxin treatment period. A decrease in the rate-corrected[13] Q-T interval was observed from 0.447 ± 0.05 second (placebo) to 0.429 ± 0.06 (digoxin 0.25 mg) and 0.426 ± 0.06 (digoxin 0.375 mg). These changes in the Q-$T_c$ interval did not reach statistical significance.

**Ventricular arrhythmias:** For the group as a whole, mean premature ventricular complex frequency (per 1,000 normal beats) decreased from 56.1 ± 46.6 during the placebo period to 40.0 ± 27.2 (p = NS), and 24.8 ± 17 (p <0.05) during administration of digoxin, 0.25 and 0.375 mg, respectively (Fig. 1). Changes in premature ventricular complex frequency in individual patients are depicted in Figure 2. Two subjects showed an increase and 10 of 12 (83%) a decrease in mean premature ventricular complex frequency. However, only 3 of 12 (25%) demonstrated ≥75% ectopic suppression.

The effect of digoxin on ventricular couplet frequency was also examined. Mean couplet frequency (per 1,000 normal beats) decreased from 1.13 ± 1.9 during placebo to 0.84 ± 1.5 (p = NS) and 0.36 ± 0.59 during the low- and high-dose digoxin periods. The observed reduction in couplet frequency at the 0.375 mg dose closely approached statistical significance (t = 2.5520, p <0.06).

Digoxin appeared to have little effect on the qualitative occurrence of complex ventricular ectopic patterns (Table I). During the placebo period, multiformity was present in 12 of 13 (93%) patients, bigeminy in 13 of 13 (100%), couplets in 13 of 13 (100%), and ventricular tachycardia in 2 of 13 (15%). There was no significant change in the incidence of these arrhythmia patterns during either of the digoxin dose periods.

**Left ventricular function and ventricular arrhythmia:** Resting LVEF during the placebo period ranged from 40 to 69% and averaged 51.4%. Seven patients had normal and 6 demonstrated depressed overall LV performance (ejection fraction <50%). In patients with a normal ejection fraction, end-diastolic volume averaged 144 ± 13 ml and end-systolic volume 58 ± 12 ml. Patients with an abnormal ejection fraction had significantly higher mean values for both end-diastolic volume (226 ± 44 ml, p <0.005) and end-systolic volume (131 ± 25 ml, p <0.001).

**TABLE I Effect of Digoxin on Complex Ventricular Ectopic Patterns (n = 13)**

| | Placebo | Digoxin, 0.25 mg | Digoxin, 0.375 mg |
|---|---|---|---|
| Multiformity | 12/13 (93%) | 12/13 (93%)* | 9/12 (75%)* |
| Bigeminy | 13/13 (100%) | 13/13 (100%)* | 12/12 (100%)* |
| Couplets | 13/13 (100%) | 13/13 (100%)* | 11/12 (92%)* |
| Ventricular tachycardia | 2/13 (15%) | 2/13 (15%)* | 1/12 (9%)* |

* p = NS, compared with placebo.

The effect of digoxin on premature ventricular complex frequency in these 2 subgroups is shown in Figure 3. In patients with a normal ejection fraction, the mean frequency decreased from 69.3 ± 57.9 during placebo to 20.4 ± 17.8 during the digoxin 0.375 mg dosing period (p <0.05). A significant reduction in couplet frequency was also observed, with mean values decreasing from 0.59 ± 0.85 to 0.07 ± 0.06 (p <0.04). All patients exhibiting ≥75% premature ventricular complex suppression were in the subgroup with normal LV function.

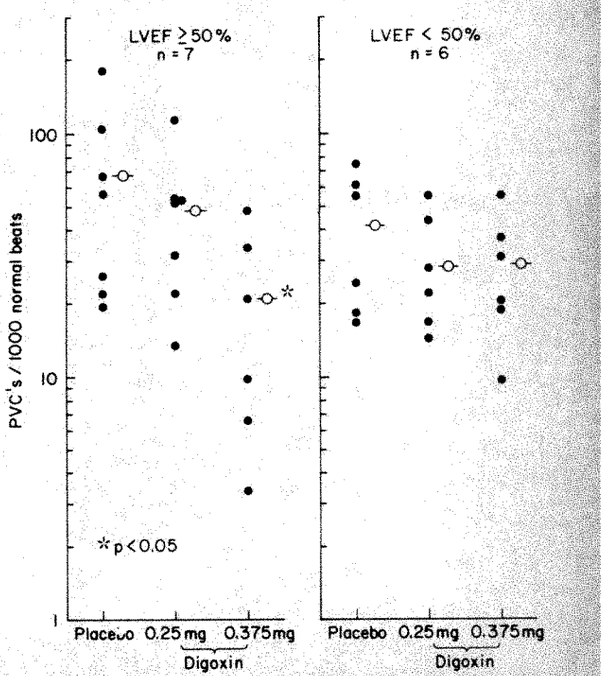



**FIGURE 3.** Effect of digoxin on the mean frequency of premature ventricular complexes (PVC's) in patients with normal (≥50%) and abnormal (≥50%) left ventricular ejection fraction (LVEF).

In the subset of patients with depressed LV function, however, no significant changes occurred either in mean premature ventricular complex or couplet frequencies after digoxin administration. Mean values for premature complex frequency were 42.0 ± 29.9 during placebo and 29.2 ± 16.5 during digoxin 0.375 mg (p = NS). Mean couplet frequency values were 0.71 ± 0.90 and 0.65 ± 0.76 (p = NS), respectively, during the same 2 dosing periods.

**Toxicity:** No study patient exhibited signs or symptoms of digitalis toxicity. One subject did show a 127% increase in premature ventricular complex frequency and had short runs of ventricular tachycardia while receiving digoxin. Whether these changes were an expression of digitalis toxicity or merely an example of spontaneous arrhythmia frequency variation is uncertain.

## Discussion

Given their propensity, at toxic doses, for producing serious and even fatal ventricular rhythm disturbances, the digitalis glycosides have not received extensive evaluation in the treatment of ventricular dysrhythmias. The notion that they may be useful in this context is not, however, new. Scherf[14] reported in 1960 that "the various digitalis glycosides abolish most atrial and ventricular extrasystoles, provided they are not caused by digitalis." Blumberg et al[15] reported that oral digitalis preparations reduced premature ventricular complex frequency by >90% in 12 of 16 patients with frequent ventricular ectopy but without other evidence of organic heart disease. More recently, Lown et al[5] performed short-term acetylstrophanthidin tolerance testing in a group of 143 patients, and reported that 46% demonstrated >50% ventricular ectopic suppression after intravenous drug administration. Furthermore, in this subgroup of "responders" it was observed that repetitive ectopic beats (couplets and ventricular tachycardia) were abolished in all but 1 of the patients exhibiting them during the control period.

The present study demonstrates that oral digoxin also possesses significant activity against ventricular ectopy, but indicates that the extent of this activity is somewhat limited. At a daily digoxin maintenance dose of 0.375 mg, total premature ventricular complex frequency decreased 56%, and there appeared to be a concurrent reduction in couplet frequency. In contrast to Blumberg's study, however, complete or near-complete premature complex suppression was rarely seen and, unlike in Lown's study, there was little observed reduction in maximal arrhythmia grade.

The apparent discrepancy between these results and those of earlier studies probably reflects differences in study design. In Blumberg's study (available only in abstract form), patients were apparently recruited on the basis of a single 10-hour electrocardiographic recording demonstrating a premature ventricular complex frequency ≥30/1,000 QRS complexes. Several studies have now documented that significant spontaneous variation regularly occurs in premature ventricular complex frequencies in many individuals.[6,7,16] The selection of subjects on the basis of a random electrocardiographic recording exhibiting a high premature complex frequency will therefore tend to result in the inclusion of many individuals at the "high tide" of their ectopic frequency pattern, while excluding patients at a low point in their ectopic occurrence. The danger of this type of recruitment process is that the results of any study in which ectopic beat frequency is used as an end point will be biased in the direction of demonstrating the efficacy of the particular treatment modality in question. In the current study, patients were chosen initially on the basis of an average premature ventricular complex frequency of >10/1,000 normal beats. Four of these original 17 patients demonstrated a >90% *spontaneous* reduction in premature complex frequency during the placebo period. Use of a placebo-controlled study design allows such patients to be recognized and excluded from data analysis and avoids exaggerating treatment efficacy.

In Lown's study, the finding that repetitive beat formation was almost completely abolished in the "responder" subset may also in part be a function of study design. It has been observed that the reproducibility of couplet occurrence over short monitoring periods is often poor[7,17] and that couplet detection is directly related to monitoring duration.[18,19] It is possible that the observation periods used in Lown's study (several hours or less) may not have been sufficient to document continued couplet occurrence. In the present study, couplet frequency could be shown to decline after drug administration, but complete abolition of repetitive beat formation was observed in only 1 subject. This probably reflects the longer (24-hour) electrocardiographic monitoring periods used in the present study.

It is of interest that digoxin was found more effective in suppressing premature ventricular complexes in patients with normal, compared to abnormal, baseline LV function. While this finding could prove to be due to small sample size, it more likely represents one aspect of the complex pathophysiologic interrelationship between ventricular arrhythmias and abnormalities of ventricular function. In patients surviving acute myocardial infarction, for example, several studies have shown that the prognostic implications of recorded ventricular arrhythmias are more adverse in the presence of significant LV dysfunction.[20,21] It is possible that ventricular arrhythmias in the setting of myocardial structural abnormalities severe enough to compromise overall LV function will prove more resistant to any attempts at pharmacologic suppression. Further study is needed to clarify this issue.

Recent experimental evidence suggests that the ventricular antiarrhythmic properties of the digitalis glycosides are mediated by way of the autonomic nervous system. It is now well-established that the effects of digitalis on the central nervous system are complex, dose-related, and probably responsible for many of the manifestations of digitalis toxicity.[3] At toxic doses, digitalis augments sympathetic neural input to the heart; this increased sympathetic activity has been correlated with the development of malignant ventricular dysrhythmias.[22] In studies performed on the anesthetized cat, Evans and Gillis[23] reported that

subtoxic doses of ouabain *decrease* sympathetic activity and prevent the development of arrhythmias produced by hypothalamic stimulation. Gillis and Quest[3] postulated that this reduction in efferent sympathetic activity, which appears to be reflexly mediated, may account for the antiarrhythmic effects of digitalis on the ventricle. Digitalis drugs also augment vagal tone and other investigators[5] have suggested that the antiarrhythmic effects of vagal stimulation[24–26] may be important in explaining the effects of these agents in suppressing ventricular arrhythmias.

Hemodynamic mechanisms may also be postulated in explaining the ventricular antiarrhythmic properties of digoxin. Previous authors have speculated that digitalis drugs might reduce ventricular arrhythmias in patients with congestive heart failure by increasing contractility, reducing LV size and wall stretch, and improving myocardial oxygen supply/demand ratio.[4] Although approximately half of our patients had depressed resting LV function at the time of study, none had clinical congestive heart failure. Furthermore, the patients found most responsive to digoxin were those with normal LV function. In this circumstance, digitalis would be expected to actually increase myocardial oxygen demand.[27,28] It thus seems unlikely that hemodynamic changes are the primary mechanism responsible for reducing ventricular ectopy in the present study.

**Conclusion:** This study indicates that oral digoxin is a moderately effective agent for suppressing premature ventricular complexes. Its inability to effectively treat the complex ventricular arrhythmias (multiformity, bigeminy, couplets, and ventricular tachycardia) which have been shown in some patient populations to be harbingers of sudden death[20,29–32] is disturbing, and may limit the utility of this class of drugs as ventricular antiarrhythmic agents. Further studies, such as those designed to evaluate the effect of digoxin on ventricular tachycardia inducibility in the electrophysiology laboratory, may be of particular value in determining the place of the digitalis glycosides in the armamentarium of ventricular antiarrhythmic agents.

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## References

1. **Smith TW, Haber E.** Digitalis. Part 1. N Engl J Med 1973;289:945–952.
2. **Smith TW, Haber E.** Digitalis. Part 2. N Engl J Med 1973;289:1010–1015.
3. **Gillis RA, Quest JA.** The role of the nervous system in the cardiovascular effects of digitalis. Pharmacol Rev 1980;31:19–97.
4. **Rosen MR, Wit AL, Hoffman BF.** Electrophysiology and pharmacology of cardiac arrhythmias IV: cardiac antiarrhythmic and toxic effects of digitalis. Am Heart J 1975;89:391–399.
5. **Lown B, Graboys TB, Podrid PJ, Cohen BH, Stockman MB, Gaughan CE.** Effect of a digitalis drug on ventricular premature beats. N Engl J Med 1977;296:301–306.
6. **Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Dunkman WB.** Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 1978;58:408–414.
7. **Winkle RA.** Antiarrhythmic drug effect mimicked by spontaneous variability in ventricular ectopy. Circulation 1978;57:1116–1121.
8. **Gradman AH, Lewis JW.** YALECG: a new system for computer analysis of ambulatory electrocardiograms. In: Ripley KL, Ostrow HG, eds. Computers in Cardiology. Long Beach, CA: IEEE, 1978:211–214.
9. **Marshall RC, Berger HJ, Costin JC, Freeman GS, Wolberg J, Cohen LS, Gottschalk A, Zaret BL.** Assessment of cardiac performance with quantitative radionuclide angiography: sequential left ventricular ejection fraction, normalized left ventricular ejection rate and regional wall motion. Circulation 1977;56:820–829.
10. **Marshall RC, Berger HJ, Reduto L, Gottschalk A, Zaret BL.** Variability in sequential measures of left ventricular performance assessed by radionuclide angiocardiography. Am J Cardiol 1978;41:531–536.
11. **Jones RH, McEwan P, Newman GE, Port S, Rerych SK, Scholz PM, Upton MT, Peter CA, Austin EH, Leong K, Gibbons RJ, Cobb FR, Coleman RE, Sabiston DC.** Accuracy of diagnosis of coronary artery disease by radionuclide measurement of left ventricular function during rest and exercise. Circulation 1981;64:586–601.
12. **Glantz SA.** Biostatistics: how to detect, correct and prevent errors in the medical literature. Circulation 1980;61:1–7.
13. **Bazett HC.** An analysis of the time relations of electrocardiograms. Heart 1920;7:353–370.
14. **Scherf D.** The mechanism and treatment of extrasystoles. Prog Cardiovasc Dis 1960;2:370–390.
15. **Blumberg JM, Hayes JG, Stevens M, Sullivan G, Killip T.** Digitalis in treatment of ventricular extrasystoles in the otherwise normal heart (abstr). Circulation 1973;37,38:Suppl IV:IV-18.
16. **Winkle RA, Gradman AH, Fitzgerald JW.** Antiarrhythmic drug effect assessed from ventricular arrhythmia reduction in the ambulatory electrocardiogram and treadmill test: comparison of propranolol, procainamide and quinidine. Am J Cardiol 1978;42:473–480.
17. **Michelson EL, Morganroth J.** Spontaneous variability of complex ventricular arrhythmias detected by long-term electrocardiographic recording. Circulation 1980;61:690–695.
18. **Gradman AH, Harbison MA, Lewis JW.** Variability of repetitive arrhythmia formation in patients with chronic ventricular arrhythmia. Am J Cardiol 1981;48:438–442.
19. **Thanavaro S, Kleiger RE, Heib BR, Krone RJ, DeMello VR, Oliver GC.** Effect of electrocardiographic recording duration on ventricular dysrhythmia detection after myocardial infarction. Circulation 1980;62:262–265.
20. **Schulze RA Jr, Strauss HW, Pitt B.** Sudden death in the year following myocardial infarction: relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction. Am J Med 1977;62:192–199.
21. **Borer JS, Rosing DR, Miller RH, Stark RM, Kent KM, Bacharach SL, Green MV, Lake CR, Cohen H, Holmes D, Donohue D, Baker W, Epstein SE.** Natural history of left ventricular function during 1 year after acute myocardial infarction: comparison with clinical, electrocardiographic and biochemical determinations. Am J Cardiol 1980;46:1–12.
22. **Gillis RA, Raines A, Sohn YJ, Levitt B, Standaert FG.** Neuroexcitatory effects of digitalis and their role in the development of cardiac arrhythmias. J Pharmacol Exp Ther 1972;183:154–168.
23. **Evans ED, Gillis RA.** Effect of ouabain and its interaction with diphenylhydantoin on cardiac arrhythmias induced by hypothalamic stimulation. J Pharmacol Exp Ther 1975;195:577–586.
24. **Kent KM, Smith ER, Redwood DR, Epstein SE.** Electrical stability of acutely ischemic myocardium—influences of heart rate and vagal stimulation. Circulation 1973;47:291–298.
25. **Kolman BS, Verrier RL, Lown B.** The effect of vagus nerve stimulation upon vulnerability of the canine ventricle—role of sympathetic-parasympathetic interactions. Circulation 1975;52:578–585.
26. **Weiss T, Lattin GM, Engelman K.** Vagally mediated suppression of premature ventricular contractions in man. Am Heart J 1975;89:700–707.
27. **Covell JW, Braunwald E, Ross J Jr, Sonnenblick EH.** Studies on digitalis XVI. Effects on myocardial oxygen consumption. J Clin Invest 1966;45:1535–1542.
28. **DeMots H, Rahimtoola SH, Kremkau EL, Bennett W, Mahler D.** Effects of ouabain on myocardial oxygen supply and demand in patients with chronic coronary artery disease. A hemodynamic, volumetric, and metabolic study in patients without heart failure. J Clin Invest 1976;58:312–319.
29. **Kotler MN, Tabatznik B, Mower MM, Tominaga S.** Prognostic significance of ventricular ectopic beats with respect to sudden death in the late post-infarction period. Circulation 1973;47:959–966.
30. **Vismara LA, Amsterdam EW, Mason DT.** Relationship of ventricular arrhythmias in the late phase of acute myocardial infarction to sudden death after hospital discharge. Am J Med 1975;59:6–12.
31. **Ruberman W, Weinblatt E, Goldberg JD, Frank CW, Shapiro S.** Ventricular premature beats and mortality after myocardial infarction. N Engl J Med 1977;297:750–757.
32. **Bigger JT Jr, Weld FM, Rolnitzky LM.** Prevalence, characteristics and significance of ventricular tachycardia (three or more complexes) detected with ambulatory electrocardiographic recording in the late hospital phase of acute myocardial infarction. Am J Cardiol 1981;48:815–823.

# Cardiac Electrophysiologic Effects of Flecainide Acetate For Paroxysmal Reentrant Junctional Tachycardias

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**Intravenous flecainide acetate was administered to 33 patients undergoing routine electrophysiologic study: 18 patients had a direct accessory atrioventricular (AV) pathway and 15 patients had functional longitudinal A-H dissocciation (dual A-H pathways). Flecainide was given to 14 patients during sustained AV reentrant tachycardia and to 9 patients during sustained intra-AV nodal reentrant tachycardia.**

**AV reentrant tachycardia was successfully terminated in 12 of 14 patients. Tachycardia termination was due to retrograde accessory pathway block in 11 patients and AV nodal block in 1. During flecainide administration, tachycardia cycle lengths increased (327 ± 55 to 426 ± 84 ms) principally because of retrograde conduction delay in the accessory pathway (127 ± 34 to 197 ± 67 ms). After flecainide administration, tachycardia reinitiation was not possible in 6 patients. In all 18 patients with accessory AV pathway conduction, flecainide significantly increased both anterograde and retrograde accessory pathway effective refractory periods, with anterograde accessory pathway block in 3 patients and retrograde accessory pathway block in 8.**

**Intra-AV nodal reentrant tachycardia was successfully terminated in 8 of 9 patients. Tachycardia termination was due to retrograde "fast" A-H pathway block in 7 patients and anterograde "slow" A-H pathway block in 1 patient. During flecainide administration, tachycardia cycle lengths increased (326 ± 50 to 433 ± 64 ms) due to both anterograde, A-H and H-V (AV 242 ± 97 to 343 ± 75 ms), and retrograde, earliest ventricular to earliest atrial (51 ± 14 to 70 ± 23 ms) conduction delay. After flecainide administration, reinitiation of intra-AV nodal reentrant tachycardia was not possible in 4 patients. In all 15 patients with dual A-H pathways, flecainide selectively prolonged the retrograde effective refractory period of the fast A-H pathway, having little effect on anterograde fast A-H pathway refractoriness or on anterograde and retrograde slow A-H pathway refractoriness. Anterograde fast A-H pathway block occurred in 1 patient and retrograde fast A-H pathway block occurred in 6 patients. No serious adverse effects were encountered during the study.**

**Flecainide acetate is an effective agent for the acute termination of both orthodromic AV and intra-AV nodal reentrant tachycardias. This antiarrhythmic action appears to be mediated through a predominant effect on either accessory AV pathway or retrograde fast A-H pathway refractoriness.**

Flecainide acetate (Riker Laboratories, St. Paul, Minnesota) is a membrane-stabilizing antiarrhythmic agent[1] with proven efficacy in the termination of some experimentally induced arrhythmias.[2–4] Favorable pharmacokinetic properties[5,6] and preliminary clinical studies demonstrating its effectiveness against a wide spectrum of arrhythmias[7–9] indicate that flecainide may be a valuable addition to presently available antiarrhythmic agents. Recent electrophysiologic studies have shown that flecainide prolongs all cardiac conduction intervals with particularly marked effects on His-Purkinje and ventricular myocardial conduction.[10] On the basis of its pronounced effect on cardiac conduction but its relatively minor effect on the duration of repolarization, flecainide has been described as a class IC antiarrhythmic drug.[11] Although flecainide appears to have little effect on refractoriness of normal cardiac tissue, it significantly prolongs the refractoriness of accessory

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pathways.[10] This drug may therefore be particularly valuable in the management of reentrant tachycardias which utilize such tissues. The present study was undertaken to investigate this antiarrhythmic potential.

## Methods

**Patient group:** In 33 consecutive patients (18 male and 15 female) aged 22 to 73 years (mean 40) electrophysiologic studies were performed for the investigation of recurrent paroxysmal "junctional" tachycardias. Eighteen patients had a direct accessory atrioventricular (AV) pathway, 15 of whom had provocable AV reentrant (orthodromic) tachycardia utilizing the accessory pathway as the retrograde limb of the tachycardia circuit. Accessory pathway conduction was bidirectional, with ventricular preexcitation during sinus rhythm (Wolff-Parkinson-White syndrome) in 9 patients and retrograde only (electrophysiologically concealed AV accessory pathway conduction) in the remaining 9 patients. The other 15 patients had functional longitudinal A-H dissociation; 9 of these had inducible intra-AV nodal reentrant tachycardia.[12-16]

**Electrophysiologic study:** All patients were studied after absorption in nonsedated state after giving informed written consent. All antiarrhythmic drugs were discontinued at least 3 drug elimination half-lives before electrophysiologic study.

Under local anesthesia (10 to 15 ml of 1% lidocaine) and by means of fluoroscopic guidance, 4 pacing electrodes were introduced into the heart. By way of the left subclavian vein, the tip of a hexapolar electrode was positioned at the right ventricular apex. The 2 distal poles were used for right ventricular pacing and 2 of the 4 proximal poles were selected to obtain the best possible bipolar recording from the lateral wall of the right atrium. A quadripolar electrode was introduced from the same subclavian vein and positioned in the coronary sinus for both stimulating and recording. Two bipolar electrodes were introduced by way of a femoral vein. One electrode was advanced into the high right atrium for pacing and the other electrode was positioned against the septal leaflet of the tricuspid valve to record distinct low right atrial, His bundle, and proximal right ventricular electrograms. Intracardiac signals were filtered between 50 and 500 Hz and recorded on a 16-channel Mingograf inkjet recorder (Siemens-Elema, Stockholm, Sweden) simultaneously with surface electrocardiographic leads I, aVF, $V_1$, and $V_6$. Paper speeds of 100 and 250 mm/s were used. Intracardiac stimulation was achieved with a Devices-type 4279 "programmable" stimulator (Digitimer, Welwyn, Hertfordshire, England) using pulse amplitudes at twice diastolic threshold and pulse durations of 1.5 to 2.5 ms.

Intracardiac conduction intervals were measured during sustained AV reentrant tachycardia (14 patients) and sustained intra-AV nodal reentrant tachycardia (9 patients). Refractory periods of accessory AV (18 patients) and dual A-H pathways (15 patients) were determined during basic atrial and ventricular pacing using the extrastimulus technique.[17,18]

Tachycardia initiation windows were determined in each patient during basic atrial or ventricular pacing followed by the introduction of a single atrial or ventricular extrastimulus, respectively. The tachycardia initiation window is defined as the difference, in milliseconds, between the longest and shortest atrial or ventricular extrastimulus coupling intervals which result in the initiation of 2 or more beats of reentrant tachycardia.

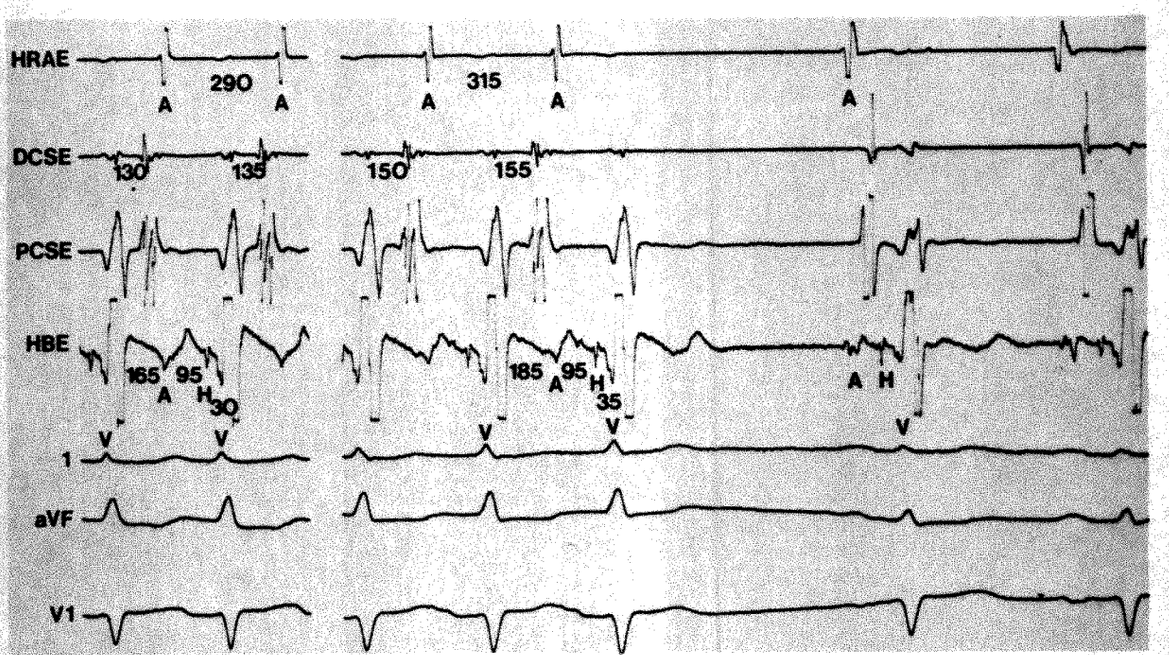



**FIGURE 1.** In this patient with a left free wall accessory AV pathway, tachycardia termination occurred 45 seconds after flecainide administration began, that is, after 14 mg of a total dose of 88 mg had been given. Tachycardia termination resulted from retrograde block in the accessory pathway, the last electrical event in tachycardia being ventricular depolarization. Before termination, the tachycardia cycle length increased from 290 to 315 ms due to delay in ventricular to atrial conduction. A small increase in the HV interval was also observed. A = intracardiac atrial electrogram; DCSE = distal coronary sinus electrogram; H = intracardiac His bundle deflection; HBE = His bundle electrogram; HRAE = high right atrial electrogram; PCSE = proximal coronary sinus electrogram; L1, aVF, $V_1$, and $V_6$ = surface electrocardiographic leads; V = ventricular depolarization. All measurements in milliseconds.

All measurements were made to the nearest 5 ms. For comparison, identical basic atrial and ventricular cycle lengths were used before and after flecainide administration. Conduction intervals and refractory periods were determined as previously described.[10]

**Flecainide administration:** After baseline electrophysiologic evaluation, a dose of flecainide acetate (2 mg/kg of body weight) was administered intravenously over 5 minutes. Flecainide was given during reentrant tachycardia to 23 patients (14 with AV reentrant tachycardia and 9 with intra-AV nodal reentrant tachycardia) in whom tachycardia had been initiated and sustained for at least 10 minutes before injection. Flecainide was given to the remaining 10 patients during sinus rhythm. The complete dose of flecainide was administered whether termination of tachycardia occurred or not. Electrophysiologic assessment after drug administration began 15 minutes after commencing drug infusion and was completed within 45 minutes of drug administration. Before beginning electrophysiologic evaluation after drug administration, pacing thresholds were readjusted to twice diastolic threshold.

Flecainide acetate doses in all 33 patients ranged from 88 to 175 mg (mean 134).

**Statistics:** Statistical data were analyzed using Student's 2-tailed $t$ test for paired data.

## Results

**Orthodromic AV reentrant tachycardia (Tables I and II):** Flecainide acetate successfully terminated AV reentrant tachycardia in 12 patients an average of 3 minutes (range 45 seconds to 8 minutes) after beginning administration. Tachycardia termination was due to block in the retrograde limb of the tachycardia circuit in 11 patients and block in the anterograde (A-H) limb in the remaining patient. A typical example of tachycardia termination is illustrated in Figure 1.

After starting flecainide administration, tachycardia cycle lengths increased in all patients (Fig. 2) due principally to an increase in retrograde conduction time (Table I). Anterograde conduction intervals during

**TABLE I Tachycardias**

| | AV Reentry | | Intra-AV Nodal Reentry | |
|---|---|---|---|---|
| | Before | After | Before | After |
| Cycle length | 327 ± 55 | 426 ± 84* | 326 ± 50 | 433 ± 64* |
| AV time | 174 ± 51 | 190 ± 46 | 242 ± 97 | 343 ± 75* |
| A-H time | 133 ± 48 | 133 ± 49 | 197 ± 96 | 267 ± 87† |
| H-V time | 41 ± 9 | 51 ± 17* | 45 ± 11 | 60 ± 11‡ |
| V-A time | 127 ± 34 | 197 ± 67* | 51 ± 14 | 70 ± 23† |
| Initiation of tachycardia | 14 patients | 9 patients | 9 patients | 5 patients |
| Initiation window (atrial) | 61 ± 16 | 26 ± 11† | 46 ± 13 | 20 ± 9 |

All measurements are in milliseconds (mean ± 1 standard deviation).
Before = before flecainide administration; after = 15 minutes after flecainide administration or immediately before tachycardia termination; V-A = shortest ventricular to atrial.
* $p < 0.001$.
† $p < 0.05$.
‡ $p < 0.01$.

**TABLE II Accessory AV Pathways**

| | AVERP | | VAERP | | Tachycardia Initiation | | Tachycardia Terminated by Flecainide |
|---|---|---|---|---|---|---|---|
| Case | Before | After | Before | After | Before | After | |
| 1 | 220 | 265 | <220 | <230 | AVRT | AVRT | + |
| 2 | <230 | 290 | 260 | 260 | AVRT | AVRT | + |
| 3 | 240 | 700 | <230 | <240 | AVRT | AVRT | 0 |
| 4 | 250 | 300 | 275 | 290 | AVRT | AVRT | + |
| 5 | 255 | 270 | <235 | <260 | AVRT | AVRT | + |
| 6 | <265 | 265 | 220 | 280 | AVRT | AVRT | 0 |
| 7 | 300 | >600 | 280 | 315 | AVRT | 0 | ... |
| 8 | 440 | >600 | 320 | >600 | AVRT | 0 | + |
| 9 | 480 | >600 | 330 | >600 | AVRT | 0 | + |
| 10 | Concealed | | <250 | >600 | AVRT | 0 | + |
| 11 | Concealed | | 260 | <240 | AVRT | AVRT | + |
| 12 | Concealed | | 275 | 475 | AVRT | AVRT | + |
| 13 | Concealed | | 295 | 310 | AVRT | AVRT | + |
| 14 | Concealed | | 300 | >600 | AVRT | 0 | + |
| 15 | Concealed | | 320 | >600 | 0 | 0 | ... |
| 16 | Concealed | | 350 | >600 | AVRT | 0 | + |
| 17 | Concealed | | 350 | >600 | 0 | 0 | ... |
| 18 | Concealed | | 390 | >600 | 0 | 0 | ... |

AVERP = anterograde effective refractory period; VAERP = retrograde effective refractory period; AVRT = orthodromic AV reentrant tachycardia; Before = before flecainide administration; After = after flecainide administration.
All measurements in milliseconds.

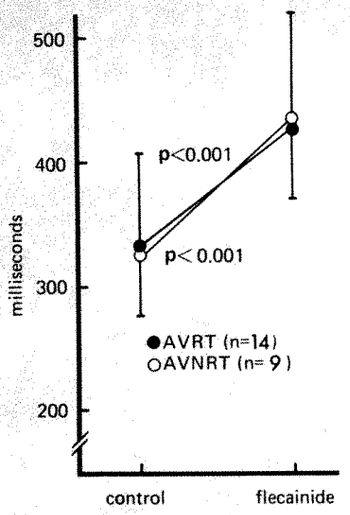



**FIGURE 2.** Comparison of tachycardia cycle lengths before flecainide administration and immediately before tachycardia termination. AVNRT = intra-AV nodal reentrant tachycardia; AVRT = orthodromic AV reentrant tachycardia.

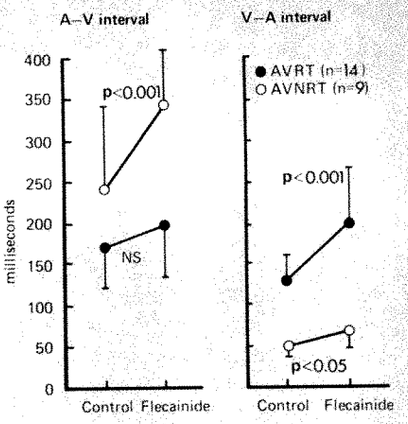



**FIGURE 3.** Comparison of anterograde and retrograde conduction intervals during reentrant "junctional" tachycardia before flecainide administration and immediately before tachycardia termination. A-V interval = A-H + H-V conduction times; V-A interval = earliest ventricular to earliest atrial conduction time.

tachycardia increased only slightly, due almost entirely to increased H-V conduction time (Fig. 3).

Tachycardia was reinitiated in 9 patients (6 with overt preexcitation and 3 with concealed accessory pathway conduction) during the course of the electrophysiologic assessment after drug infusion. A single atrial extrastimulus was able to initiate reentrant tachycardia in 15 patients during the control study but sustained tachycardia was possible in only 14. In these 15 patients this tachycardia initiation window was significantly reduced and in 6 patients was completely abolished by flecainide infusion. A single ventricular extrastimulus initiated tachycardia in only 3 of the 18 patients before flecainide administration. No orthodromic AV reentrant tachycardia initiation windows to a single ventricular extrastimulus were present after flecainide. However 1 patient (Table I, Case 6) had antidromic AV reentrant tachycardia during ventricular extrastimulation after flecainide. In this patient, ventricular extrastimuli with coupling intervals shorter than the retrograde effective refractory period of the accessory pathway (280 ms) conducted retrogradely through the AV node and then anterogradely through the accessory pathway, resulting in antidromic reentrant tachycardia at a cycle length of 370 ms.

Flecainide administration resulted in anterograde accessory pathway block in 3 patients, all of whom had long refractory periods during the control study (300, 440, and 480 ms). In the remaining 6 patients with overt

**TABLE III Dual A-H Pathways**

| | Fast A-H Pathway | | | | Slow A-H Pathway | | | | Tachycardia Initiation | | Tachycardia Terminated by Flecainide |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | AVERP | | VAERP | | AVERP | | VAERP | | | | |
| Case | Before | After | Before | After | Before | After | Before | After | Before | After | |
| 1 | <245 | 260 | <260 | 400 | ... | <220 | ... | <250 | AVNRT | AVNRT | 0 |
| 2 | 250 | 260 | <225 | 260 | <210 | <225 | ... | <240 | AVNRT | 0 | + |
| 3 | 275 | 360 | 320 | 450 | <220 | <255 | <220 | <260 | AVNRT | AVNRT | + |
| 4 | 300 | 360 | 300 | 440 | 280 | 315 | ... | 285 | AVNRT | AVNRT | + |
| 5 | 340 | 440 | <280 | 390 | 230 | 230 | ... | 320 | AVNRT | AVNRT | + |
| 6 | 360 | 400 | <280 | >600 | 280 | 295 | ... | 460 | AVNRT | 0 | + |
| 7 | 365 | 355 | 280 | 280 | 345 | 335 | <270 | <250 | AVNRT | AVNRT | + |
| 8 | 370 | 320 | <215 | >600 | <205 | <225 | ... | >600 | AVNRT | 0 | + |
| 9 | 380 | 385 | 320 | >600 | 275 | <285 | <250 | >600 | AVNRT | 0 | + |
| 10 | 290 | >600 | 280 | >600 | <280 | <295 | <260 | <260 | 0 | 0 | ... |
| 11 | 325 | 325 | 280 | 370 | <250 | <240 | 225 | 300 | 0 | 0 | ... |
| 12 | 360 | 340 | <205 | 360 | <260 | <260 | ... | 320 | 0 | 0 | ... |
| 13 | 380 | 320 | >600 | >600 | 325 | 260 | >600 | >600 | 0 | 0 | ... |
| 14 | 400 | 390 | 510 | >600 | 230 | 260 | 410 | >600 | 0 | 0 | ... |
| 15 | 440 | 360 | 400 | 400 | 300 | 325 | 250 | 340 | 0 | 0 | ... |

AVERP = anterograde effective refractory period; VAERP = retrograde effective refractory period; AVNRT = intra-AV nodal reentrant tachycardia; Before = before flecainide administration; After = after flecainide administration.
All measurements in milliseconds.

preexcitation where accessory pathway anterograde refractoriness was ≤265 ms during the control study, refractoriness increased insignificantly in 4 and showed a relative increase in the remaining 2 patients. By comparison, effective refractory periods of the atrial myocardium in these 9 patients changed insignificantly (191 ± 24 to 197 ± 30 ms).

Accessory pathway retrograde refractoriness was more markedly increased by flecainide administration. Retrograde accessory pathway block persisted in 8 patients, 7 of whom had accessory pathway retrograde refractory periods of ≥300 ms during the control study. In the 10 remaining patients, retrograde refractoriness (<300 ms in all cases during the control study) was increased in 5, unchanged in 1 (268 ± 24 to 322 ± 71 ms, difference not significant [NS]), relatively shortened in 1, and relatively increased in the remaining 3 patients. Right ventricular myocardial refractoriness in these 18 patients demonstrated a slight change from 217 ± 22 to 226 ± 24 ms ($p < 0.05$).

**Intra-AV nodal reentrant tachycardia (Tables I and III):** All patients with intra-AV nodal tachycardia had the typical variety of reentry comprising anterograde slow A-H pathway conduction and retrograde fast A-H pathway conduction with virtually simultaneous atrial and ventricular activation. Flecainide acetate successfully terminated intra-AV nodal reentrant tachycardia in 8 patients an average of 5 minutes (range 1 to 15) after administration began.

Tachycardia termination resulted from block in the retrograde limb of the tachycardia circuit in 7 patients and block in the anterograde (A-H) limb in the remaining patient. A typical example of tachycardia termination is illustrated in Figure 4. Flecainide increased intra-AV nodal reentrant tachycardia cycle lengths in all patients due to an increase in both AV and VA times (Fig. 2, Table I). However VA time was measurable in only 5 patients, the low right atrial deflection on the His bundle electrogram occurring simultaneously with and thus indistinguishable from the right ventricular deflection in the remaining 4 patients.

In 5 patients, intra-AV nodal reentrant tachycardia could be reinitiated during the post-drug study. In 3 of the 4 remaining patients, retrograde block of the fast A-H pathway persisted. After flecainide administration, the tachycardia initiation window using a single atrial extrastimulus decreased insignificantly. A single ventricular extrastimulus initiated tachycardia in 4 patients only during the control study and not after flecainide administration.

Flecainide markedly increased retrograde refractoriness of the fast A-H pathway, retrograde block persisting in 6 patients, remaining markedly prolonged in 7 patients, and unchanged in 2 (see Table III). The magnitude of this increase was not, however, related to the effective refractory period measured during the control study. Anterograde fast A-H pathway refractoriness (350 ± 52 to 355 ± 45 ms) was not significantly affected by flecainide. Similarly, refractoriness of the slow A-H pathway in both the anterograde and retrograde directions was not significantly affected by flecainide. The change in myocardial refractoriness of both the right atrium (200 ± 31 to 210 ± 30 ms) and right ventricle (225 ± 23 to 222 ± 21 ms) after flecainide administration in these 15 patients with functional A-H duality was not statistically significant.

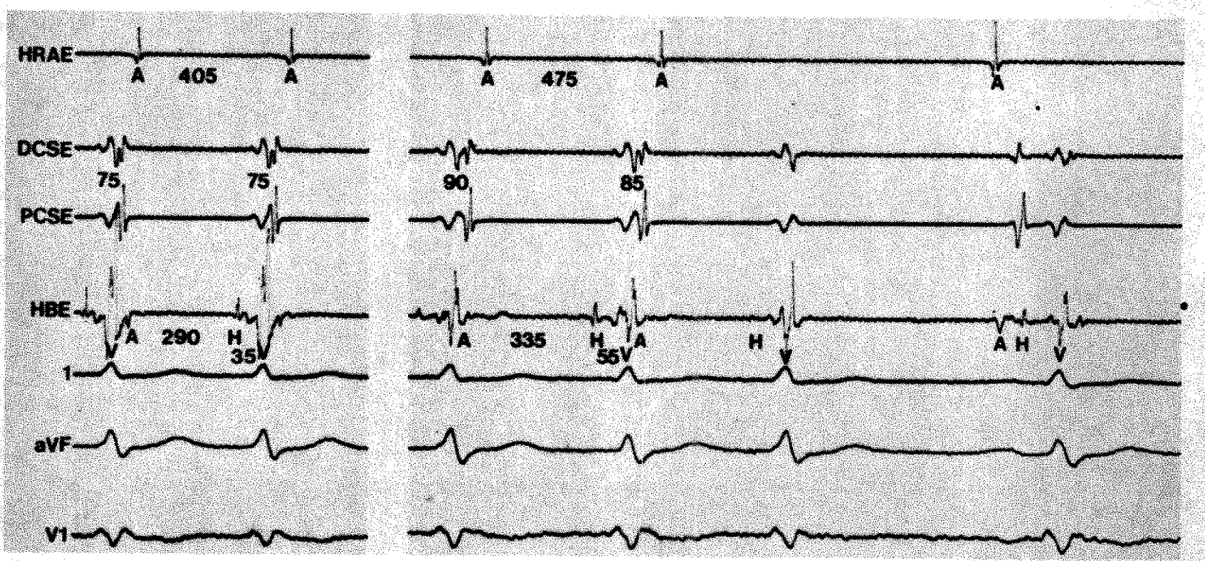



**FIGURE 4.** In this patient tachycardia termination occurred 85 seconds after flecainide administration began, that is, after 40 mg of a total dose of 140 mg had been given. Tachycardia termination occurred as a result of block in the retrograde limb (fast A-H pathway) of the tachycardia circuit, the last electrical event during tachycardia being ventricular depolarization. Before termination, the tachycardia cycle length increased from 405 to 475 ms due to conduction delay in both the anterograde and retrograde limbs of the tachycardia circuit. A = intracardiac atrial electrogram; DCSE = distal coronary sinus electrogram; H = intracardiac His bundle deflection; HBE = His bundle electrogram; HRAE = high right atrial electrogram; PCSE = proximal coronary sinus electrogram; L1, aVF, $V_1$, and $V_6$ = surface electrocardiographic leads; V = ventricular depolarization. All measurements in milliseconds.

**Adverse effects:** Two patients experienced major adverse effects. Antidromic AV reentrant tachycardia was initiated in 1 patient in whom it was only possible to initiate orthodromic AV reentrant tachycardia during the control study. In another patient, a single ventricular extrastimulus reproducibly initiated ventricular flutter and fibrillation only after flecainide administration. Minor adverse effects included numbness and paresthesia of the buccal mucosa in 28 patients, transient drowsiness or dizziness in 5 patients, and discomfort at the injection site in 3 patients.

## Discussion

The maintenance of reentrant "junctional" tachycardia depends upon tachycardia cycle length exceeding the refractory period of any 1 of the components of the reentry circuit. Hence, any pharmacologic agent which increases refractoriness within the reentry circuit beyond the cycle length of the tachycardia will prevent induction and maintenance of reentrant tachycardia. Ideally such an antiarrhythmic agent would selectively increase refractoriness within the anomalous pathways (fast A-H pathway or accessory AV pathway) without affecting conduction or refractoriness within the normal conduction system of the heart.

Many reports have described the efficacy of Vaughan Williams[19] class I and III antiarrhythmic agents in the management of the Wolff-Parkinson-White syndrome.[20–22] Disopyramide was shown to significantly increase both anterograde and retrograde accessory pathway refractoriness to a similar extent and to effectively terminate orthodromic AV reentrant tachycardia by blocking the retrograde limb of the circuit; however, conduction time through the accessory pathway was probably also increased.[23,24] Wellens et al[25,26] found that procainamide, quinidine, ajmaline and amiodarone had marked effects on anterograde refractoriness of accessory pathways with a lesser effect on retrograde refractoriness. The magnitude of the effects of these drugs on anterograde accessory pathway refractoriness was related to initial accessory pathway anterograde effective refractory period before drug administration,[27] a more marked lengthening of refractoriness occurring if the initial refractoriness was ≥270 ms. No such drug effect was observed with regard to retrograde refractoriness of accessory pathways in the same group of patients.

In our study, flecainide had a marked effect on both anterograde and retrograde accessory pathway refractoriness, its effects on retrograde refractoriness apparently being more marked. The response of accessory pathway anterograde refractoriness to flecainide also appears related to its resting value with short (<270 ms) refractory periods showing only modest lengthening after flecainide and longer (>270 ms) refractory periods showing more marked lengthening or anterograde conduction block (in all 3 of our patients with accessory pathway anterograde refractory periods of ≥300 ms anterograde conduction block developed). A similar response of accessory pathway retrograde refractoriness to flecainide was observed. When initial retrograde refractoriness was ≥300 ms, marked prolongation occurred (all 7 of our patients had accessory pathway retrograde block after flecainide administration), whereas the response to flecainide was much less marked when retrograde refractoriness was <300 ms. The more marked effect of many antiarrhythmic agents, including flecainide acetate, on accessory pathway refractoriness compared with their reduced effect on either atrial or ventricular refractoriness suggests that accessory pathways, although histologically similar to ventricular muscle,[28,29] have quite distinct electrophysiological characteristics.

Similarly, procainamide[30] and quinidine[31] were shown to selectively depress retrograde fast A-H pathway conduction in patients with intra-AV nodal reentrant tachycardia, with little or no effect on anterograde fast A-H pathway conduction and no significant effect on either anterograde or retrograde slow A-H pathway conduction.

This study has shown that flecainide effectively terminates intra-AV nodal reentrant tachycardias by selectively prolonging retrograde fast A-H pathway refractoriness. Its selective depressant effect on fast A-H pathway refractoriness with a negligible effect on either atrial or ventricular refractoriness in the same group of patients are findings which are strikingly similar to the effects observed with procainamide and quinidine and in agreement with the suggestion by Gomes,[32,33] Platt,[34] and their co-workers that the fast A-H pathway is electrophysiologically dissimilar to either the slow A-H pathway or the normal AV node and more characteristic of accessory or anomalous pathway tissue. In 6 of our patients, retrograde duality of AV nodal conduction only became evident after flecainide administration (Table II), presumably due to the selective impairment of retrograde fast A-H pathway conduction by flecainide.

Although slow pathway refractoriness was unaffected by flecainide, the A-H interval during intra-AV nodal reentry was prolonged markedly. Previous studies have shown that flecainide depresses conduction through the normal AV node.[10] Despite this the A-H interval during AV reentry remained unchanged, presumably a result of concomitant slowing of the tachycardia rate. The different response of the slow pathway may be related to an increased sensitivity to flecainide. Also this A-H interval is not a linear conduction time and is not directly comparable to the A-H interval during sinus rhythm or during AV reentry.

The significant depressant effect of flecainide on normal cardiac conduction pathways as well as anomalous pathways may theoretically tend to favor continuation of reentrant tachycardias, although at a slower rate. However, the disproportionate influence of flecainide on abnormal pathway refractoriness assured tachycardia termination in 20 of the 23 patients. Since flecainide appears to have relatively minor negative inotropic effects in both experimental models[1] and the normal human heart,[35] slowing the tachycardia rate should improve the clinical and hemodynamic state of patients with reentrant tachycardias.

In this study, flecainide acetate proved to be an extremely effective agent for the acute management of

reentrant junctional tachycardias which utilize either accessory AV pathways or dual A-H pathways. The usual mode of tachycardia termination in response to flecainide was marked prolongation of the retrograde effective refractory periods of these pathways such that refractoriness exceeded the increase in tachycardia cycle length. It is unlikely that tachycardia termination was spontaneous and coincidental with flecainide administration as all patients had previous histories of long and sustained episodes of tachycardia, tachycardia was well established in each patient before flecainide administration, and tachycardia termination was due to retrograde block in the anomalous pathway in all except 2 patients.

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## References


1. **Campbell Cowan J, Vaughan Williams EM.** Characterization of a new oral antiarrhythmic drug, flecainide (R818). Eur J Pharmacol 1981;73:333–342.
2. **Schmid JR, Seebeck BD, Henrie CL, Bannitt EH, Kvam DC.** Some antiarrhythmic actions of a new compound, R818, in dogs and mice (abstr). Fed Proc 1975;34:775.
3. **Verdouw PD, Deckers JW, Conard GJ.** Antiarrhythmic and hemodynamic actions of flecainide acetate (R818) in the ischaemic porcine heart. J Cardiovasc Pharmacol 1979;1:473–486.
4. **Hodess AB, Follansbee WP, Spear JF, Moore EN.** Electrophysiological effects of a new antiarrhythmic agent, flecainide, on the intact canine heart. J Cardiovasc Pharmacol 1979;1:427–439.
5. **Conard GJ, Carlson GL, Frost JW, Ober RE.** Human plasma pharmacokinetics of flecainide acetate (R818), a new antiarrhythmic, following single oral and intravenous doses (abstr). Clin Pharmacol Ther 1979;25:218.
6. **Conard GJ, Carlson GL, Frost JW, Ober RE, Leon AS, Hunninghake DB.** Human plasma elimination kinetics of R-818, a new antiarrhythmic (abstr). Proceedings of the 21st National Meeting APhA Academy of Pharmaceutical Sciences. Orlando, FL: APhA Academy of Pharmaceutical Sciences, 1976:106.
7. **Orning OM.** Electrophysiological effects of flecainide acetate in arrhythmias (abstr). In: Proceedings of VIII World Congress of Cardiology. Tokyo: Congress of Cardiology, 1978:480.
8. **Somani P.** Antiarrhythmic effects of flecainide. Clin Pharmacol Ther 1980;27:464–470.
9. **Anderson JL, Stewart JR, Perry BA, van Hamersveld DD, Johnson TA, Conard GJ, Chang SF, Kvam DC, Pitt B.** Oral flecainide acetate for the treatment of ventricular arrhythmias. N Engl J Med 1981;305:473–477.
10. **Hellestrand KJ, Bexton RS, Nathan AW, Spurrell RAJ, Camm AJ.** The acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man. Br Heart J 1982;48:140–148.
11. **Harrison DC, Winkle RA, Sami M, Mason JW.** Encainide: a new and potent antiarrhythmic drug. In: Harrison DC, ed. Cardiac Arrhythmias—a Decade of Progress. Boston, MA: GK Hall, 1981:316.
12. **Goldreyer BH, Bigger JT.** Spontaneous and induced reentrant tachycardia. Ann Intern Med 1969;70:87–98.
13. **Goldreyer BH, Bigger JT.** Site of reentry in paroxysmal supraventricular tachycardia in man. Circulation 1971;43:15–26.
14. **Goldreyer BH, Damato AN.** The essential role of A-V conduction delay in the initiation of paroxysmal supraventricular tachycardia. Circulation 1971;43:679–687.
15. **Denes P, Wu D, Dhingra RC, Chuquimia R, Rosen KM.** Demonstration of dual AV nodal pathways in patients with paroxysmal supraventricular tachycardia. Circulation 1973;48:549–555.
16. **Rosen KM, Metha A, Miller RA.** Demonstration of dual A-V nodal pathways in man. Am J Cardiol 1974;33:291–294.
17. **Damato AN, Lau SH, Patten RD, Steiner C, Berkowitz WD.** A study of A-V conduction in man using premature atrial stimulation and His bundle recordings. Circulation 1969;40:61–69.
18. **Josephson ME, Seides SF.** Clinical Cardiac Electrophysiology. Techniques and Interpretations. Philadelphia: Lea & Febiger, 1979:40.
19. **Vaughan Williams EM.** The classification of antiarrhythmic drugs. In: Sandoe E, Flensted-Jensen E, Olesen KH, eds. Symposium on Cardiac Arrhythmias. Sodertalje, Sweden: AB Astra, 1970:449–472.
20. **Mandel WJ, Laks MM, Obayashi K, Hayakawa H, Daley W.** The Wolff-Parkinson-White syndrome. Pharmacological effects of procainamide. Am Heart J 1975;90:744–754.
21. **Sellers TD, Campbell RW, Bashore TM, Gallagher JJ.** Effects of procainamide and quinidine sulfate in the Wolff-Parkinson-White syndrome. Circulation 1977;55:15–22.
22. **Rosenbaum MB, Chiale PA, Ryba D, Elizari MV.** Control of tachyarrhythmias associated with Wolff-Parkinson-White syndrome by amiodarone hydrochloride. Am J Cardiol 1974;34:213–223.
23. **Spurrell RAJ, Thorburn CW, Camm J, Sowton E.** Effects of disopyramide on electrophysiological properties of specialized conduction systems in man and on accessory A-V pathway in Wolff-Parkinson-White syndrome. Br Heart J 1975;37:861–868.
24. **Camm J, Ward D, Spurrell RAJ.** The effect of intravenous disopyramide phosphate on recurrent paroxysmal tachycardias. Br J Clin Pharmacol 1979;8:441–449.
25. **Wellens HJJ, Durrer D.** Effect of procainamide, quinidine, and ajmaline in the Wolff-Parkinson-White syndrome. Circulation 1974;50:114–120.
26. **Wellens HJJ, Lie KI, Bar FW, Wesdorp JC, Dohmen HJ, Duren DR, Durrer D.** Effect of amiodarone in the Wolff-Parkinson-White syndrome. Am J Cardiol 1976;38:189–194.
27. **Wellens HJJ, Bar FW, Dassen WRM, Brugada P, Vanagt EJ, Farre J.** Effect of drugs in the Wolff-Parkinson-White syndrome. Am J Cardiol 1980;46:665–669.
28. **Becker AE, Bouman LN, Janse MJ, Anderson RH.** Functional anatomy of the cardiac conduction system. In: Harrison DC, ed. Cardiac Arrhythmias—a Decade of Progress. Boston: GK Hall, 1981:3–24.
29. **Becker AE, Anderson RH, Durrer D, Wellens HJJ.** The anatomical substrates of Wolff-Parkinson-White syndrome: a clinicopathological correlation in seven patients. Circulation 1978;57:870–879.
30. **Wu D, Denes P, Bauernfeind R, Kehoe R, Amat-Y-Leon F, Rosen KM.** Effect of procainamide on A-V nodal reentrant paroxysmal tachycardia. Circulation 1978;57:1171–1179.
31. **Wu D, Hung J-S, Kuo C-T, Hsu K-S, Shieh W-B.** Effects of quinidine on A-V nodal reentrant paroxysmal tachycardia. Circulation 1981;64:823–831.
32. **Gomes JAC, Dhatt MS, Damato AN, Akhtar M, Holder CA.** Incidence, determinants and significance of fixed retrograde conduction in the region of the A-V node. Am J Cardiol 1979;44:1089–1098.
33. **Gomes JAC, Dhatt MS, Rubenson DS, Damato AN.** Electrophysiological evidence for selective retrograde utilization of a specialized conducting system in A-V nodal reentrant tachycardia. Am J Cardiol 1979;43:687–698.
34. **Platt M, Peter T, Mandel W.** New evidence for intranodal tracts. Effect of verapamil in paroxysmal supraventricular tachycardia (abstr). Paris: VIII European Congress of Cardiology, 1980:165.
35. **Hodges M, Hoback J, Graham E, Erlien D, Asinger R, Mikell F.** Cardiac function after oral dosing with flecainide acetate (abstr). Clin Pharmacol Ther 1981;29:251.

# Cardiac Effects of Treatment With Quinidine and Digoxin, Alone and in Combination

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**Systolic time intervals ($QS_2$-I and LVET-I) and echocardiographically determined ejection fraction and velocity of circumferential fiber shortening were recorded in 10 healthy volunteers as measures of inotropic effect during maintenance treatment with 4 consecutive drug regimens: (1) quinidine, 1,200 mg/day; (2) digoxin, average dose 0.31 mg/day; (3) the combination of (1) and (2); and (4) digoxin alone (average dose 0.65 mg/day) to provide the same steady-state serum concentration of digoxin as during the period with combination of digoxin and quinidine. The steady-state serum concentration of digoxin during the low-dose regimen increased from 0.72 ± 0.15 (mean ± standard deviation [SD]) to 1.63 ± 0.28 nmol/liter when quinidine was added. With the high dose of digoxin alone, the serum digoxin level reached 1.68 ± 0.50 nmol/liter. Skeletal muscle digoxin concentrations during these periods were 27.7 ± 8.3, 48.7 ± 16.2, and 51.6 ± 23.6 nmol/kg of dry weight, respectively. The skeletal muscle to serum concentration ratio of digoxin decreased significantly during quinidine treatment.**

**Systolic time intervals were significantly prolonged by quinidine alone and shortened by digoxin alone, the latter effect being dose-dependent. Subtracting the effect of quinidine itself, the induced increase in digoxin level caused a significant increase in inotropic effect. When these corrected values were compared with those attained during the period with the same steady-state digoxin concentration but in the absence of quinidine, no significant differences were found. Echocardiographically measured ejection fraction and velocity of circumferential fiber shortening showed trends for similar drug effects, as did the systolic time intervals.**

**This study, performed under steady-state conditions, demonstrates that the quinidine-induced increase in steady-state serum digoxin concentration will, with due consideration to quinidine's own pharmacodynamic properties, be accompanied by increased cardiac effects. This indicates that quinidine is not interfering with active receptor sites in the heart for digoxin.**

Recent studies have documented that the steady-state concentration of digoxin in plasma/serum increases markedly during co-medication with quinidine[1–3] due to reduced renal[4–6] and nonrenal digoxin clearance.[5,7] The cardiac effects of the increased serum digoxin concentrations are not fully clarified. Clinical reports indicate that cardiac as well as extracardiac adverse effects of digoxin occur as a result of the interaction with quinidine.[2,6,8–10] In 2 experimental studies in man, a reduced inotropic effect of single doses of digoxin was reported during treatment with quinidine.[11,12] The present study was undertaken to evaluate the cardiac effects of digoxin in volunteers during quinidine treatment employing conditions of drug therapy approaching those of the clinical situation.

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## Methods

**Subjects and procedures:** Ten healthy male volunteers (mean age 31 years, range 24 to 38) gave informed consent to participate in the study (most of them were colleagues). (The Ethical Committee of the Karolinska Hospital approved the investigation.) Results of physical examination, routine blood study, including electrolytes, serum creatinine, blood count, and sedimentation rate, electrocardiograms, blood pressure, systolic time intervals, and echocardiograms were normal.

The subjects were investigated on 6 occasions (Fig. 1): before intake of quinidine and digoxin (control I); after 4 days' intake of quinidine, 1,200 mg/day (Quinidine Durules®, Hässle-Astra, Sweden); after 2 to 3 weeks' intake of digoxin in a low dose (0.31 ± 0.07 [mean ± SD] mg/day) to produce a steady-state serum level of 0.6 to 1.0 nmol/liter; and after a

4-day period with the same low digoxin dose combined with 1,200 mg/day of quinidine. (It has been documented that the steady state of digoxin is reached after approximately 4 days of combination treatment.[6,8,13]) The final period consisted of 2 to 3 weeks with a higher dose of digoxin alone (0.65 ± 0.14 mg/day), monitored to give the same serum digoxin concentration as that attained during the combination treatment. At least 6 weeks after discontinuing digoxin treatment a second control investigation without medication was performed (control II).

Blood samples, skeletal muscle biopsies, blood pressure, electrograms, systolic time intervals, and echocardiographic measurements were all taken after at least 45 minutes of rest with the patient in the supine position and approximately 24 hours after the last dose of digoxin. The 3 biopsy samples were taken from the quadriceps femoris muscle (vastus lateralis) with the percutaneous needle biopsy technique of Bergström.[14] The needle was inserted into the muscle through a small incision made in locally anesthetized skin.

During the first 24 hours of the combination treatment all subjects were in hospital and monitored with electrocardiography. There was close contact between the investigators and the subjects during the different test periods to monitor potential untoward reactions.

**Determination of skeletal muscle and serum digoxin concentrations:** The skeletal muscle samples were freeze-dried and carefully freed from connective tissue and fat. Two pieces from each biopsy sample were weighed and homogenized in phosphate buffer; afterwards, digoxin was extracted from the tissue with dichloromethane. After evaporation of the dichloromethane phase, the residue was redissolved in human serum, and the digoxin concentration was measured by radioimmunoassay with a commercial iodine-125 radioimmunoassay kit (New England Nuclear, Boston, Massachusetts). The method has previously been described in detail.[15,16] The serum digoxin concentration was measured with the iodine-125 radioimmunoassay kit without any extraction procedure. The coefficients of variation for duplicate analyses of skeletal muscle and serum digoxin were 11 and 6, respectively. The skeletal muscle and serum concentrations given are the mean values of duplicate determinations. The digoxin concentrations in skeletal muscle were obtained from 9 volunteers as the muscle biopsy samples from the 10th subject were lost.

**Quinidine analyses:** The quinidine concentrations in plasma were determined by the method of Cramér and Isaksson.[17]

**Electrocardiograms:** The electrocardiograms were recorded at a paper speed of 100 mm/s with a Mingograph 62 (Siemens-Elema). Heart rate, P-Q interval, QRS duration and Q-T interval corrected for heart rate ($QT_c$) according to Bazett[18] were measured in 10 consecutive beats in lead II and the same complexes were included in the calculation of the systolic time intervals. The electrocardiographic measurements were done by 1 of the investigators without knowledge of the corresponding drug regimen. There were no significant differences in measurements performed by an independent observer who, also blindly, reviewed random tracings.

**Systolic time intervals of the left ventricle:** The systolic time intervals were measured from simultaneous records of the lead II electrocardiogram, phonocardiogram, and external carotid arterial pulse. A piezoelectric crystal microphone (EMT 25B, Siemens-Elema) was used to record the heart sounds. The carotid pulse was recorded using an airborne system with a funnel shaped pick-up attached by polyethylene tubing to a piezoelectric pressure transducer (EMT 510C, Siemens-Elema). The tracings were made at a paper speed of 100 mm/s with a Mingograph 62. The total electromechanical systole ($QS_2$) and left ventricular ejection time (LVET) were calculated from the mean values of 10 consecutive heart beats, corrected for heart rate according to Weissler et al[19,20] and presented as systolic time interval indexes ($QS_2$-I, LVET-I.[21]) Systolic time intervals were analyzed by the same investigator without knowledge of the drug period at hand. No significant differences in measurements by an independent, also blinded, investigator were observed.

**Echocardiography:** The echocardiograms were performed with an ATL (Seattle, Washington) Mark 3 ultrasonoscope utilizing a 3.0 MHz transducer with optimal focus between 3 and 8 cm. The printouts were recorded on a Honeywell LS fiberoptic recorder with a paper speed of 50 mm/s. The subjects were examined while in the partial left lateral decubitus position. The transducer was placed in the third, fourth, or fifth intercostal space parasternally. Each examination was preceded by a 2-dimensional study for general survey of the left ventricle. The left ventricular view was taken at or just below the tips of the mitral leaflets. Throughout the study, care was taken to reestablish the identical position of the patient and the transducer. The left ventricular echocardiographic dimensions were measured from the endocardial echo of the posterior wall to that of the left side of the septum. Measurements at end-diastole were made at the peak of the R-wave; measurements at end-systole were made at the point of the smallest distance separating septum from posterior wall.

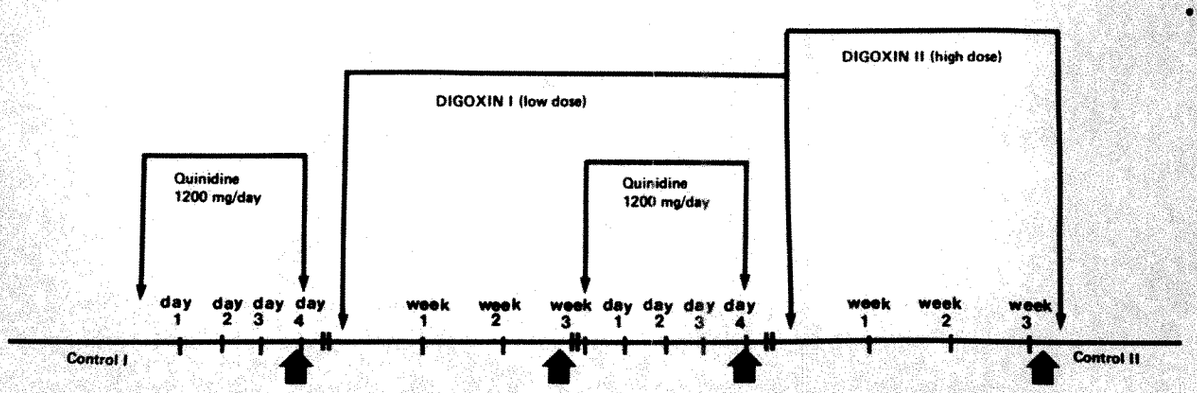



**FIGURE 1.** Study design. Cardiac effects in 10 healthy volunteers during treatment with quinidine and digoxin. **Heavy arrows** indicate the times cardiac effects and drug concentrations were measured.

The mean rates of circumferential fiber shortening and left ventricular ejection fraction were calculated by conventional techniques.[22] All the calculations were made using the average obtained from 5 consecutive cardiac cycles.

**Statistical analyses:** Values are given as the mean ± SD. Two-tailed Student's *t* test for paired observations was used to evaluate the statistical significance of differences between treatments. P values >0.05 were considered nonsignificant (NS).

## Results

**Adverse reactions:** The 2 different doses of digoxin were tolerated well without significant adverse effects by all 10 subjects. Quinidine treatment caused a light to modest tiredness in several volunteers and in a few cases minor anticholinergic reactions. No differences in these regards were noted during the quinidine-digoxin combination period compared with treatment with quinidine alone. No ventricular arrhythmias were recorded and no changes in blood pressure were registered during the treatment periods.

**Serum digoxin concentration:** When quinidine was added to the low digoxin dose, the mean serum digoxin concentration increased from 0.72 ± 0.15 nmol/liter to 1.63 ± 0.28 nmol/liter (126% increase, p <0.001) (Table I). With the high digoxin dosage the mean serum digoxin concentration was 1.68 ± 0.40 nmol/liter (Table I), which was not significantly different from that reached during combined treatment with quinidine and the low digoxin dose.

**Skeletal muscle digoxin concentration:** The steady-state digoxin concentration in skeletal muscle was 27.7 ± 8.3 nmol/kg of dry weight during the period with the lower digoxin dose. Skeletal muscle digoxin increased to 48.7 ± 16.2 nmol/kg of dry weight (76% increase, p <0.001) during the combination therapy with quinidine. This was not significantly different from the value attained (51.6 ± 23.6 nmol/kg of dry weight) during the period with digoxin alone in the higher dose (Table I).

**TABLE I Serum and Skeletal Muscle Concentrations of Digoxin at Steady State During the Different Test Periods (Mean ± SD, n = 10)**

| | Digoxin I | Digoxin I + Quinidine | Digoxin II |
|---|---|---|---|
| Digoxin dose (mg/day) | 0.31 ± 0.07 | 0.31 ± 0.07 | 0.65 ± 0.14 |
| Serum digoxin (concentration (nmol/liter) | 0.72 ± 0.15 | 1.63 ± 0.28† | 1.68 ± 0.40† |
| | | NS | |
| Skeletal muscle digoxin concentration* (nmol/kg dry weight) | 27.7 ± 8.3 | 48.7 ± 16.2‡ | 51.6 ± 23.6‡ |
| | | NS | |

* n = 9.
† Significantly different from digoxin I, p <0.001.
‡ Significantly different from digoxin I, p <0.005.
Digoxin I = low digoxin dose; Digoxin II = high digoxin dose.

The mean *ratio* of the digoxin concentration in skeletal muscle to that in serum decreased from 39.1 ± 12.0 to 30.7 ± 13.4 (22% decrease, p <0.02) when quinidine was added to the lower digoxin dose. During period of the high digoxin dose this ratio was 31.1 ± 18.1, which was not significantly different from either of the other 2 periods.

**Quinidine concentration:** The mean predose quinidine concentration in plasma was 4.9 ± 1.5 μmol/liter during treatment with quinidine alone in a daily dose of 1,200 mg, and 4.8 ± 1.2 μmol/liter during the combination with digoxin with the same quinidine dose.

**Cardiac effects:** *Control periods:* The mean values of the systolic time intervals and echocardiographic measurements from the 2 control periods did not differ significantly, nor did the values for their standard deviations. The individual values were within the normal ranges.[18–21]

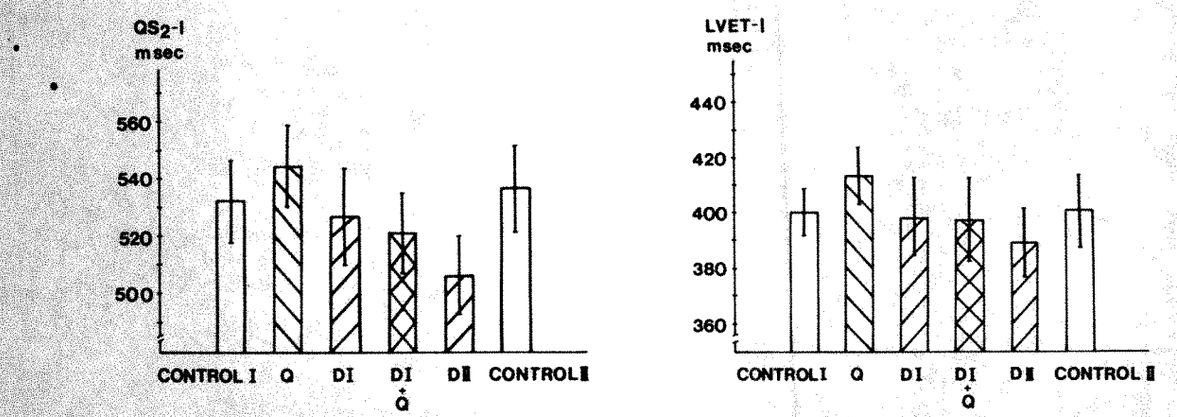



**FIGURE 2.** Heart rate-corrected electromechanical systole ($QS_2$-I) **(left panel)** and left ventricular ejection time (LVET-I) **(right panel)** in 10 volunteers during the following test periods: control periods before (control I) and after (control II) drug administration; Q, maintenance treatment with quinidine 1,200 mg/day; DI, maintenance treatment with the low digoxin dose; DI + Q, maintenance treatment with the low digoxin dose in combination with quinidine; and DII, maintenance treatment with the high digoxin dose. During the periods DI + Q and DII the digoxin concentrations were similar. Values are means ± SD.

**TABLE II Electrocardiographic, Systolic Time Intervals, and Echocardiographic Measurements at Steady State During the Different Test Periods (Mean ± SD, n = 10)**

| | Control I | Quinidine | Digoxin I | Digoxin I + Quinidine | Digoxin II | Control II |
|---|---|---|---|---|---|---|
| Heart rate | 61 ± 10 | 59 ± 9 | 57 ± 9 | 59 ± 8 | 53 ± 7* | 57 ± 8 |
| $QT_c$ (ms) | 37 ± 2 | 42 ± 3* | 36 ± 1 | 40 ± 3†† | 34 ± 1 | 37 ± 2 |
| $QS_2$-I (ms) | 533 ± 15 | 545 ± 14† | 527 ± 17†† | 521 ± 14† | 516 ± 13* | 537 ± 15 |
| | | | p <0.05 | | | |
| LVET I (ms) | 400 ± 9 | 413 ± 10* | 398 ± 14 | 397 ± 15 | 389 ± 12† | 401 ± 13 |
| | | | NS | | | |
| Vcf (circ/s) | 1.2 ± 0.1 | 1.1 ± 0.1†† | 1.2 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1 | 1.1 ± 0.1 |
| EF (%) | 72 ± 4 | 70 ± 4 | 73 ± 4 | 75 ± 3 | 74 ± 3 | 72 ± 5 |

* Statistically significant from control period, p <0.001.
† Statistically significant from control period, p <0.01.
†† Statistically significant from control period, p <0.05.
Digoxin I = low digoxin dose; Digoxin II = high digoxin dose; EF = ejection fraction; Vcf = circumferential fiber shortening.

*Electrocardiographic measurements:* The heart rate did not change significantly during the different test periods except for a decrease with the high digoxin dose (Table II). $QT_c$ was significantly prolonged compared with the control period during treatment with quinidine alone and also with quinidine in combination with the low digoxin dose. The high digoxin dose was associated with a shortening of $QT_c$ (Table II). The P-Q interval and the QRS duration were not significantly altered during any treatment period.

*Systolic time intervals:* Heart rate corrected $QS_2$ and LVET ($QS_2$-I and LVET-I) are presented in Table II and Figure 2. During the quinidine period the systolic time intervals were significantly longer than during the control periods. In contrast, when quinidine was added during digoxin treatment, a slight shortening of $QS_2$-I was recorded (p <0.05), whereas LVET-I was not significantly changed compared with the low digoxin dose alone period.

The low digoxin dose caused a shortening of $QS_2$-I (p <0.05), but no statistically significant decrease in LVET-I. This inotropic effect was more marked with the higher digoxin dose ($QS_2$-I, p <0.001; LVET-I, p <0.002). Compared with the effect of quinidine alone, the addition of digoxin significantly shortened both $QS_2$-I and LVET-I (p <0.001).

During 2 treatment periods (combination low digoxin dose and quinidine, and high digoxin dose), serum as well as skeletal muscle digoxin concentrations were similar. After individual correction for the effect of quinidine, the effects of digoxin on the systolic time intervals were similar. This is illustrated for $QS_2$-I in Figure 3.

*Echocardiographic measurements:* During quinidine treatment there was a slight but significant reduction (p <0.05) in the mean velocity of circumferential fiber shortening, whereas the ejection fraction was not significantly changed (Table II, Fig. 4). During the combined treatment with quinidine and digoxin there was a significant increase in both mean velocity of circumferential fiber shortening and ejection fraction compared with treatment with quinidine alone (p <0.01). Digoxin alone did not induce any statistically significant change in velocity of circumferential fiber shortening or ejection fraction, although a tendency for values to increase was observed with both doses compared with the control period.

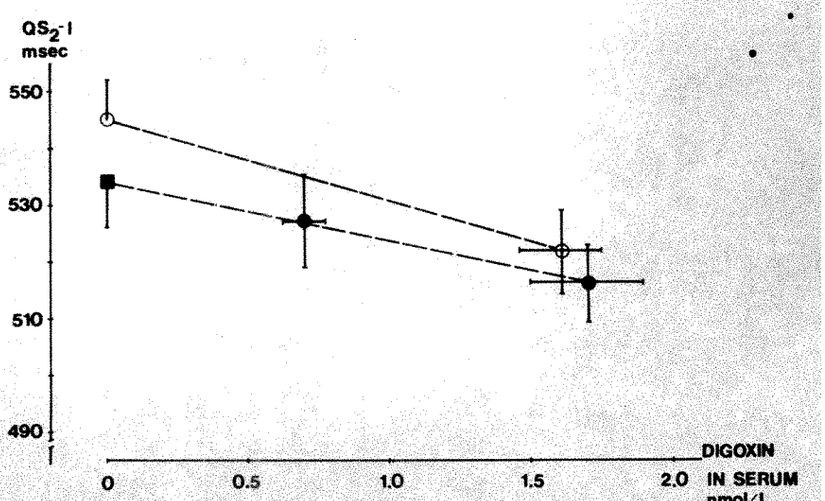



**FIGURE 3.** Electromechanical systole ($QS_2$-I) related to the steady-state serum digoxin concentration. **Solid square,** control period without drugs; **open circles,** quinidine treatment; **closed circles,** no quinidine treatment. Values are means ± SD.

End-diastolic diameters were not changed during the different drug periods.

## Discussion

In the present study, left ventricular performance has been measured noninvasively during treatment with digoxin and quinidine, alone and in combination, in healthy volunteers. The design involved maintenance treatment with normal therapeutic doses of the drugs to mimic the clinical situation. A treatment period with digoxin alone, monitored to yield the same steady-state serum digoxin concentration as during the combination of quinidine and digoxin, enabled us to assess the responsiveness of the heart to a given concentration of digoxin in the absence and in the presence of quinidine.

In accordance with previous studies, quinidine treatment approximately doubled the steady-state concentration of digoxin in serum,[1–3,6,7] and caused a lesser increase in skeletal muscle.[23] The ratio of the digoxin concentration in skeletal muscle to that in serum therefore decreased by about 22% confirming our previous findings with a decreased ratio of 23%.[23] However, this decrease in the ratio does not mean a reduced tissue digoxin concentration. On the contrary, because of the quinidine-induced increase in the total body load of digoxin, the digoxin concentration in skeletal muscle was increased by approximately 75%.

Left ventricular performance is mainly dependent upon preload, afterload, and contractility (inotropy). Preload and afterload—measured as left ventricular end-diastolic diameter and systemic blood pressure, respectively—were unchanged during the study; therefore, drug effects on the noninvasive variables may be considered changes in contractility of the left ventricle. Heart rates did not change during the different test periods except for during the period with a high digoxin dose, where a significantly decreased heart rate was recorded in comparison with the control period.

As previously known, quinidine decreased and digoxin increased contractility measured as changes in systolic time intervals.

When quinidine was administered to the subjects during maintenance digoxin treatment, contractility measured as shortening of $QS_2$-I was slightly enhanced, whereas LVET-I and the echocardiographic measures were not significantly changed. Thus, since the negative effect of quinidine on contractility was of the same magnitude as the positive effect of the induced increase in digoxin level, the effects cancel out and net contractility remains essentially unchanged. Quinidine therefore causes a shift to the right of the serum concentration-effect curve for digoxin with regard to contractility (Fig. 3). Such a shift may, however, not occur for adverse effects of digoxin. The net effect of the combination treatment therefore could be a decrease in the therapeutic index of digoxin.

Subtracting the negative inotropic effects of quinidine alone, the quinidine-induced increase in digoxin in the body caused a significant improvement in contractility measured as changes in systolic time intervals

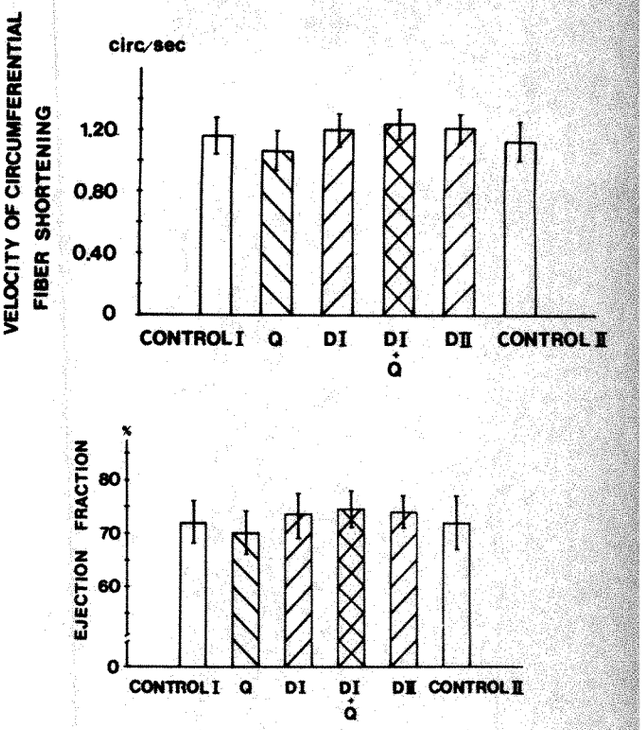



**FIGURE 4.** Echocardiographic measurements in 10 healthy volunteers during test periods, as in Figure 2. **Top panel,** velocity of circumferential fiber shortening (circ/s). **Bottom panel,** ejection fraction. Values are means ± SD.

compared with the control period. When these values are compared with those attained during the period with the same steady-state digoxin level but in the absence of quinidine, no significant differences appear. Therefore, the contractile responsiveness of the heart to a given steady-state serum concentration of digoxin is probably not affected by quinidine. This would exclude a major and clinically significant interference of quinidine with the binding and action of digoxin at active sites in the heart, supporting recent in vitro studies.[24–27] These results may seem to contradict the reported decrease in the ratio of the digoxin concentration in skeletal muscle to that in serum. However, the decrease in the ratio was very moderate (about 20%). Furthermore, it is not known whether the decrease in total digoxin binding to skeletal muscle is accompanied by a decreased binding to active sites in the heart.

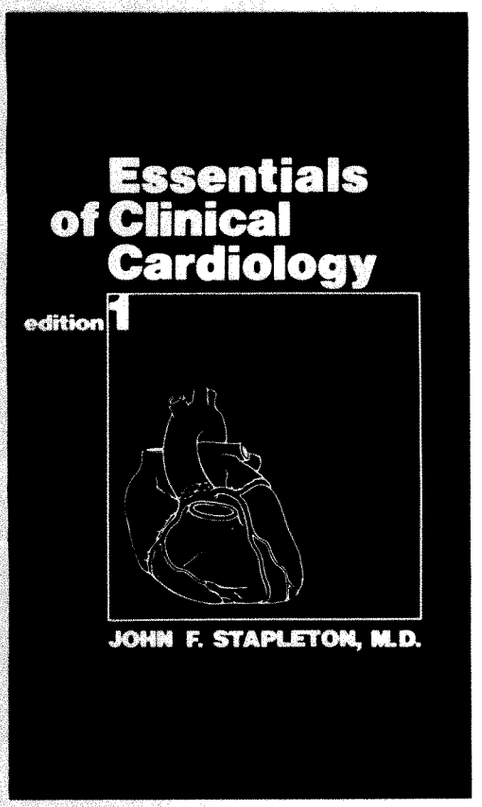
Concerning the inotropic effects of digoxin and quinidine, results similar to ours were recently presented by Belz et al[28] in a preliminary report, whereas partly contradictory conclusions were reached in 2 other experimental studies in man.[11,12] However, the conclusions from the present study and that by Belz et al[28] are strengthened by their experimental design measuring effects at steady state and distribution equilibrium and by their use of more rigorous crossover control periods.

**Acknowledgment:** We thank Annika Thorsson for excellent assistance.

## References


1. **Ejvinsson G.** Effect of quinidine on plasma concentrations of digoxin. Br Med J 1978;1:279–280.
2. **Leahey EB Jr, Reiffel JA, Drusin RE, Heissenbuttel RH, Lovejoy WP, Bigger JT Jr.** Interaction between quinidine and digoxin. JAMA 1978;240:533–534.
3. **Doering W, Könige E.** Ansteig der Digoxinkonzentration im Serum unter Chinidinmedikation. Med Klin 1978;72:1085–1088.
4. **Hooymans PM, Merkus HM.** Effect of quinidine on plasma concentration of digoxin (letter). Br Med J 1978;2:1022.
5. **Hager WD, Fenster P, Mayersohn M, Perrier D, Graves P, Marcus EI, Goldman S.** Digoxin-quinidine interaction. Pharmacokinetic evaluation. N Engl J Med 1979;300:1238–1241.
6. **Dahlqvist R, Ejvinsson G, Schenck-Gustafsson K.** Effect of quinidine on plasma concentration and renal clearance of digoxin: a clinically important drug interaction. Br J Clin Pharmacol 1980;9:413–418.
7. **Schenck-Gustafsson K, Dahlqvist R.** Pharmacokinetics of digoxin in patients subjected to the quinidine-digoxin interaction. Br J Clin Pharmacol 1981; 11:181–186.
8. **Doering W.** Quinidine-digoxin interaction. Pharmacokinetics: underlying mechanism and clinical implications. N Engl J Med 1979;303:400–404.
9. **Leahey EB Jr, Reiffel JA, Giardina EG, Bigger JT Jr.** The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. Ann Intern Med 1980;92:605–608.
10. **Cody RJ, Jr, Walker AM, Greenblatt DJ, Hershel J.** Increased digoxin toxicity during quinidine administration (abstr). Circulation 1980;63:Suppl III:183.
11. **Steiness E, Waldorff S, Hansen PB, Kjaergård H, Buch J, Egeblad H.** Reduction of digoxin-induced inotropism during quinidine administration. Clin Pharmacol Ther 1980;27:791–795.
12. **Hirsh PD, Weiner HJ, North RL.** Further insights into digoxin-quinidine interaction. Lack of correlation between serum digoxin concentration and inotropic state of the heart. Am J Cardiol 1980;46:863–867.
13. **Mungall DR, Robichaux RP, Perry W, Scott JW, Robinson A, Burelle T, Hurst D.** Effects of quinidine on serum digoxin concentration. Ann Intern Med 1980;93:689–693.
14. **Bergström J.** Muscle electrolytes in man: determined by neutron activation analysis on needle biopsy specimens: a study on normal subjects, kidney patients and patients with chronic diarrhea. Scand J Clin Lab Invest 1962;14(Suppl 68):1–110.
15. **Jogestrand T.** Digoxin concentration in right atrial myocardium skeletal muscle and serum in man: influence of atrial rhythm. Eur J Clin Pharmacol 1980;17:243–250.
16. **Jogestrand T, Sundqvist K.** Skeletal muscle digoxin concentration and its relation to serum digoxin concentration and cardiac effect in healthy man. Eur J Clin Pharmacol 1981;19:89–95.
17. **Cramér G, Isaksson B.** Quantitative determination of quinidine in plasma. Scand J Clin Lab Invest 1963;15:353–356.
18. **Bazett HC.** An analysis of the time relations of electrocardiograms. Heart 1920;7:353–370.
19. **Weissler AM, Harris SW, Schoenfeld CD.** Systolic time intervals in heart failure in man. Circulation 1968;37:149–150.
20. **Weissler AM, Lewis RP, Lightin RF, Bush ChA.** Comparative responses to the digitalis glycosides in man. In: Marks BH, Weissler AM, eds. Basic and Clinical Pharmacology of Digitalis. Springfield, IL: Charles C Thomas, 1972:260–280.
21. **Lewis RR, Rittges SE, Forester WF, Boudolas H.** A critical review of the systolic time intervals. Circulation 1977;56:146–158.
22. **Feigenbaum H.** Echocardiography. 3rd ed. Philadelphia: Lea & Febiger, 1981:134.
23. **Schenck-Gustafsson K, Jogestrand T, Nordlander, R, Dahlqvist R.** Effect of quinidine on digoxin concentration in skeletal muscle and serum in patients with atrial fibrillation. N Engl J Med 1981;305:209–211.
24. **Kim D-H, Akera T, Brody T.** Effects of quinidine on the cardiac-glycoside sensitivity of guinea-pig and rat heart. J Pharmacol Exp Ther 1981;217: 559–565.
25. **Kim D-H, Akera T, Brody T.** Interactions between quinidine and cardiac glycosides involving mutual binding sites in the guinea-pig. J Pharmacol Exp Ther 1981;218:108–114.
26. **Bali JV, Tse-Eng D, Wallick ET, Bilezikian JP, Scwartz A, Butler VP.** Effect of quinidine on the digoxin receptor in vitro. J Clin Invest 1981;68:1065–1074.
27. **Williams JF, Mathew B.** Effects of quinidine on positive inotropic action of digoxin. Am J Cardiol 1981;47:1052–1055.
28. **Belz CG, Doering W, Aust PE, Heinz M, Belz G.** Quinidine-digoxin-interaction: a crossover double blind study on cardiac efficacy of increasing serum digoxin concentrations (abstr). Circulation 1981;64:Suppl IV-135.

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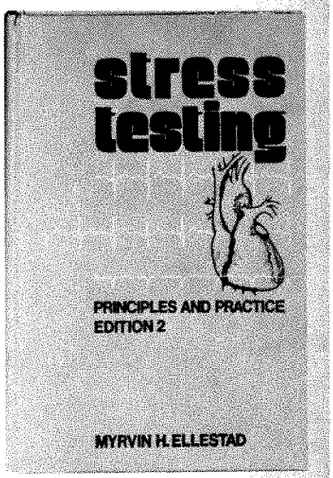
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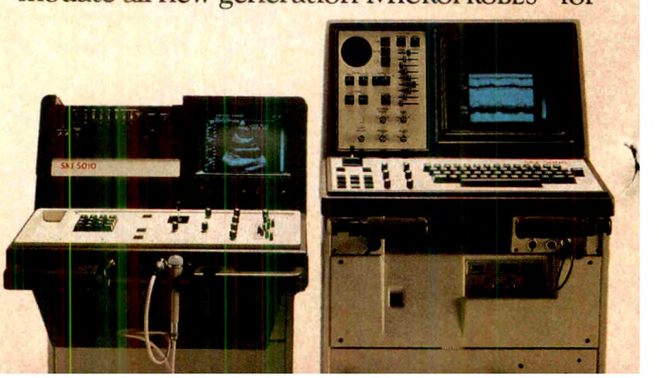
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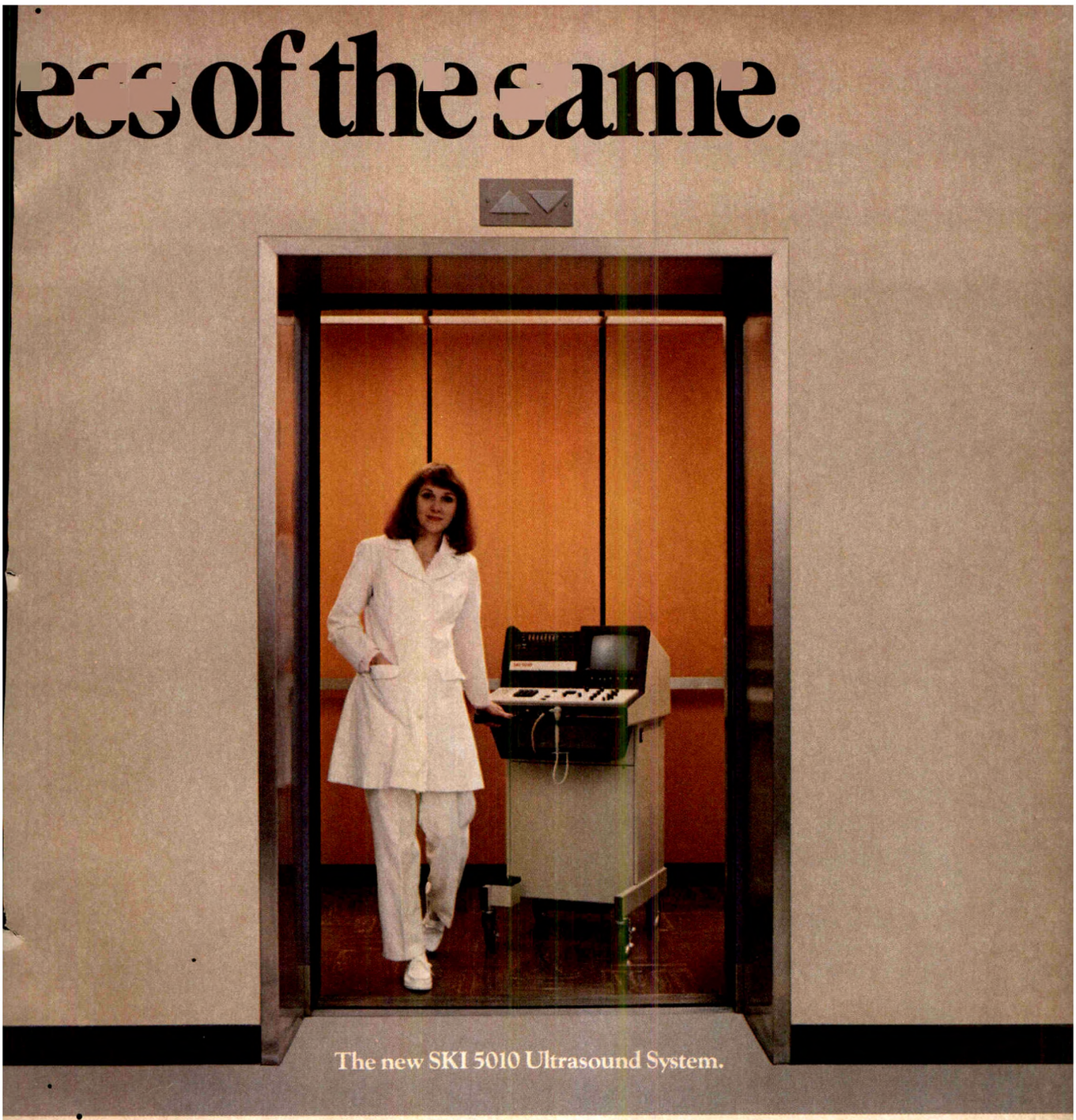
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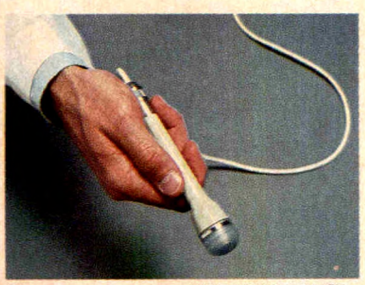


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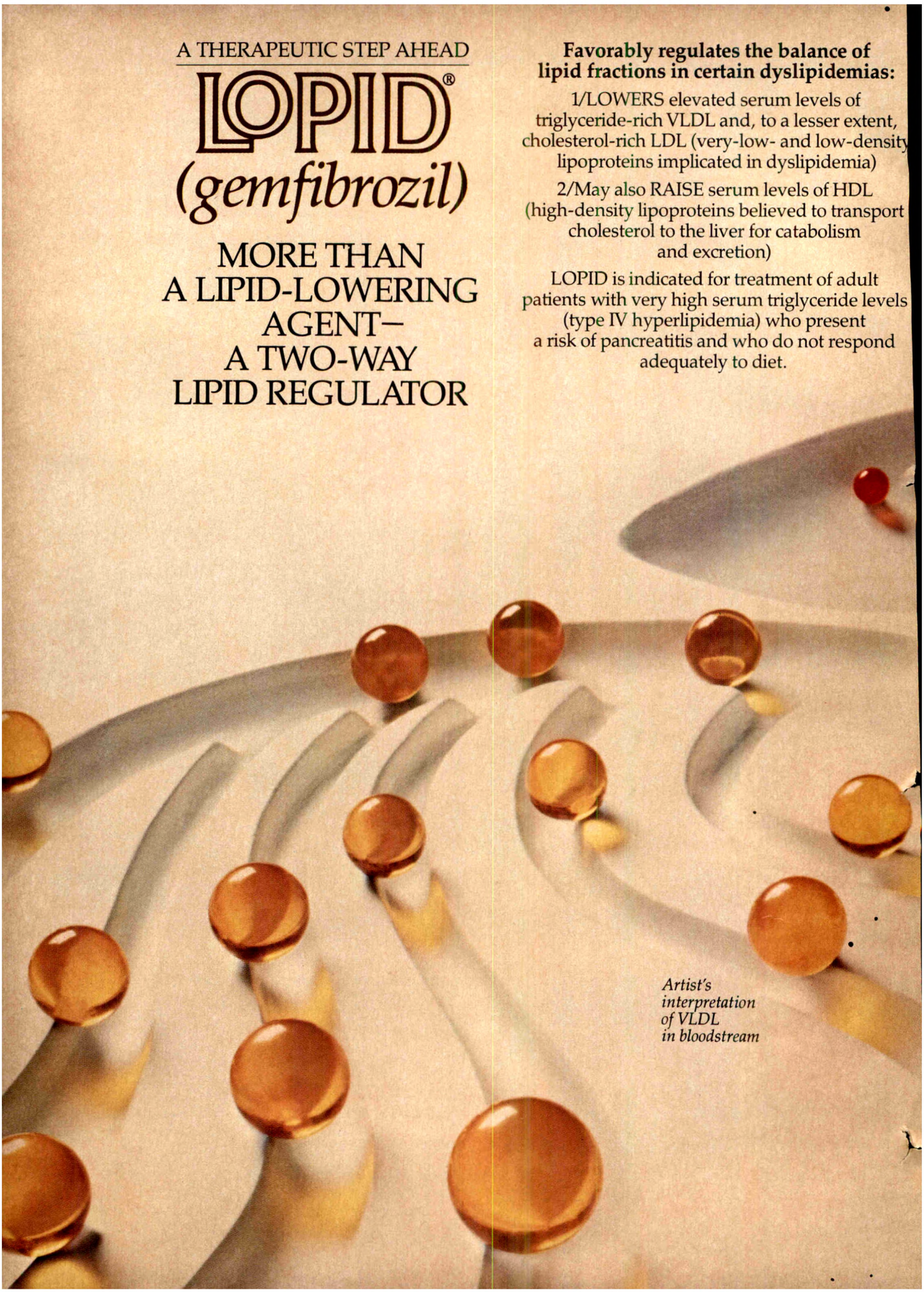
## MORE THAN A LIPID-LOWERING AGENT— A TWO-WAY LIPID REGULATOR

**Favorably regulates the balance of lipid fractions in certain dyslipidemias:**

1/LOWERS elevated serum levels of triglyceride-rich VLDL and, to a lesser extent, cholesterol-rich LDL (very-low- and low-density lipoproteins implicated in dyslipidemia)

2/May also RAISE serum levels of HDL (high-density lipoproteins believed to transport cholesterol to the liver for catabolism and excretion)

LOPID is indicated for treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to diet.

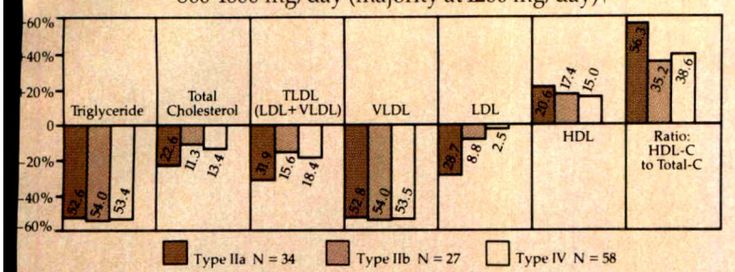


*Artist's interpretation of VLDL in bloodstream*

## Lipid-regulating efficacy demonstrated in 1,437 patients with dyslipidemia[1]

Results of open-label phase of US multicenter study (119 patients) at end of 12 lunar months*

Average % change from baseline at doses ranging from 800-1600 mg/day (majority at 1200 mg/day)†




*Visit every 4 weeks during long-term use of LOPID.
†Data cited on this graph reflect clinical experience based on the multicenter trial. They do not imply an indication for Types IIa and IIb dyslipidemias.

## Well tolerated, well accepted in clinical trials[1]

Profile of side effects similar to that of placebo.

No significant abnormalities seen in clinical and laboratory evaluations.

Less than 1% patient dropout in largest US study.

## Convenient BID dosage

*Diet, exercise, and weight loss are the first choice in therapy of lipid disorders.*


Reference:
1. Data on file, Medical Affairs Dept, Parke-Davis.


*Artist's interpretation of HDL in bloodstream*

# LOPID®

300-mg capsules

*(gemfibrozil)*

**PARKE-DAVIS**

Please see following pages for brief summary of prescribing information.


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# LOPID®
## (gemfibrozil)
## A LIPID REGULATOR

**LOPID® (gemfibrozil) Capsules**

**Before prescribing, please see full prescribing information.**
**A Brief Summary follows:**

**CLINICAL PHARMACOLOGY.** LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

| HLP Type | TRIGLYCERIDE | CHOLESTEROL | | | | RATIO |
|---|---|---|---|---|---|---|
| | | Total | VLDL | LDL | HDL | HDL Cholesterol / Total Cholesterol |
| IIa | −44% | −4.2% | −44.3% | −5.8% | +24.6% | +33% |
| IIb | −45% | −8.6% | −45.0% | −6.4% | +19.5% | +34% |
| IV | −40% | −1.8% | −40.8% | +14.6% | +17.4% | +23% |

**INDICATIONS AND USAGE.** Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (See WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

**CONTRAINDICATIONS.** 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

**WARNINGS.** 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p$ greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis — LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants — Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

**PRECAUTIONS.** 1. **Initial Therapy** — Before instituting LOPID (gemfibrozil) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy** — Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels** — LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility** — Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B** — Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** — Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** — Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function** — Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias** — Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children** — Safety and efficacy in children have not been established.

**ADVERSE REACTIONS.** In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

**Integumentary:** rash, dermatitis, pruritus, urticaria
**Central Nervous System:** headache, dizziness, blurred vision
**Musculoskeletal:** painful extremities
**Hematopoietic:** anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

**Other reactions were:**

**Gastrointestinal:** dry mouth, constipation, anorexia, gas pain, dyspepsia
**Musculoskeletal:** back pain, arthralgia, muscle cramps, myalgia, swollen joints
**Central Nervous System:** vertigo, insomnia, paresthesia, tinnitus
**Clinical Laboratory:** hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)
**Miscellaneous:** fatigue, malaise, syncope

**DOSAGE AND ADMINISTRATION.** The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

**DRUG INTERACTIONS.** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

**MANAGEMENT OF OVERDOSAGE.** While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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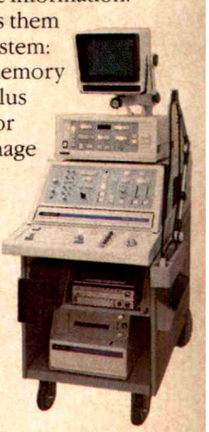
# New Insights

## Toshiba SSH-40A Ultrasound Scanner
## The Complete Cardiac Lab.

How do you measure commitment? With words? Toshiba prefers to have the products make the point. Newest proof: the Toshiba SSH-40A Cardiac Ultrasound Laboratory, a vivid example of our commitment to echocardiographic diagnostics.

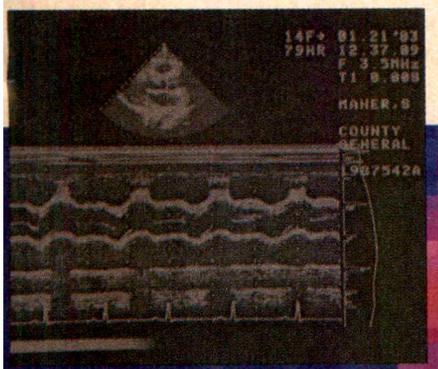
Clinical versatility is the watchword for the SSH-40A. It means independent or simultaneous display of 2-D echocardiograms, M-Mode and Doppler images for faster, more complete diagnosis. It means you can scan with various probes for the best image quality in all patient sizes and specialized procedures. Perform two dimensional, multi-gate array Doppler flow studies and perform all cardiac function computations instantly.

Image quality? Startling. Low level echoes contain the most significant diagnostic information. The SSH-40A captures and displays them with a unique, low-noise digital system: dual microprocessors and more memory than any ultrasound instrument. Plus the powerful Digital Scan Processor provides optimum control over image quality.



Such insights, frankly, defy words. That's why we're eager to provide you with a demonstration of the SSH-40A's powerful capabilities. Then you can complete the picture yourself.

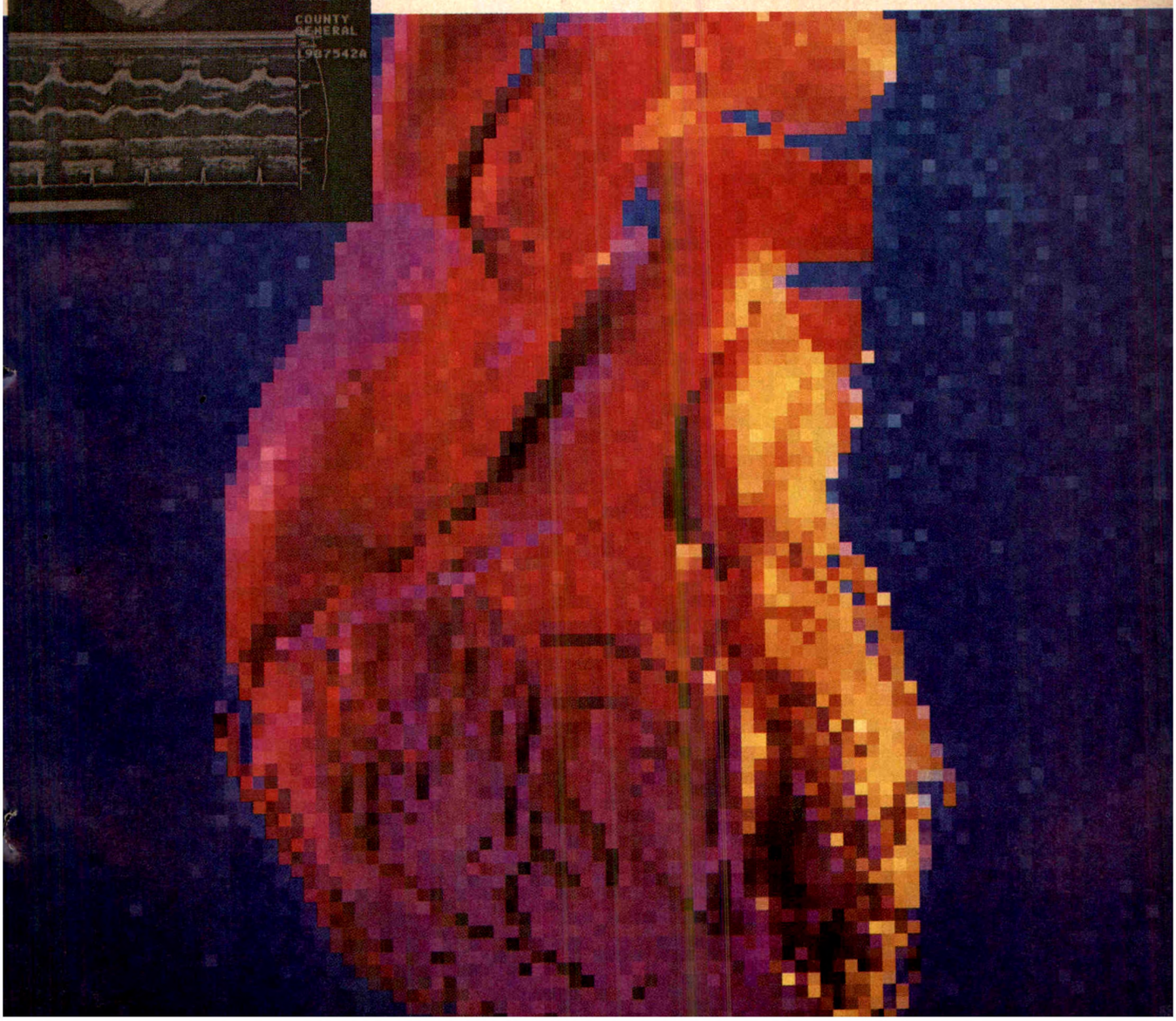
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# New Insights

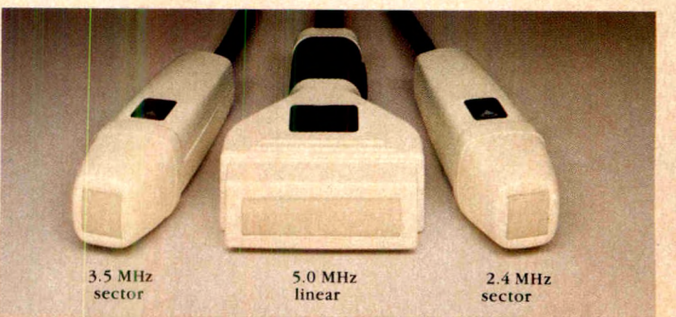
## TOSHIBA SSH-40A CARDIAC ULTRASOUND LABORATORY.

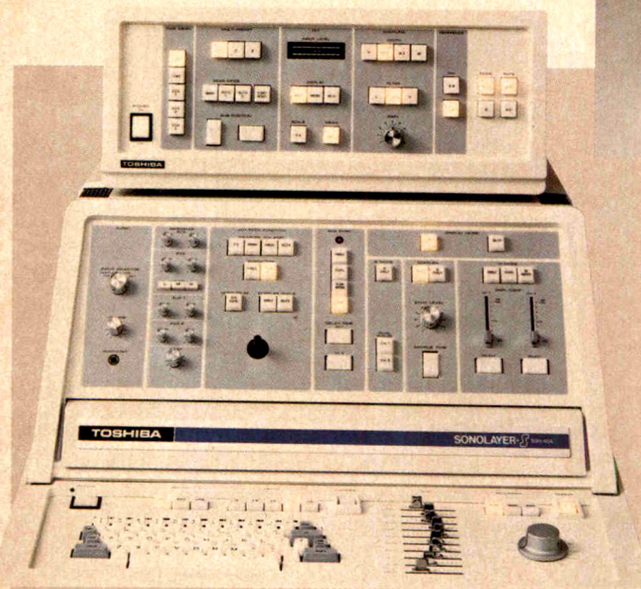
The Toshiba SSH-40A is a complete cardiac ultrasound laboratory that combines clinical versatility, superior image quality and powerful digital scan processing to provide a host of features for new insights into cardiac diagnoses.

The SSH-40A is available with a standard 3.5 MHz probe and optional 5 MHz linear scan probe and 2.4 MHz sector scan probe to enable accurate examinations of all patients, from neonates to adults. All pertinent image and exam data, including results from computations, can be displayed. And the unique two dimensional multigate array Doppler capability enables the operator to perform flow studies, to display frequency spectrum from the digital FFT analyzer and to compute flow rate, velocity and other cardiac function data. Extensive computational algorithms are on-line to ensure fast, accurate analyses.

Superb image quality results from the advanced scanning technology incorporated in the SSH-40A. A new receiver design and a new digital scan processor provide optimized image quality with clearly defined edge differentiation and excellent tissue differentiations. A faithful display of low level echoes provides excellent gray scale resolution.

The SSH-40A delivers the image processing functions cardiologists require. Echo enhancement, post processing and other echo processing operations, synchronous freezing of two phases of a cardiac cycle, slow motion display and measurement of distances and areas on frozen images are all well within the range of this remarkable system's capabilities.




- Simultaneous 2-D imaging and dual M-Mode or Doppler operation ensures more exact correlation, faster diagnosis and state-of-the-art performance.
- Cardiac function (SV, EF, FS, CO and others), area, circumference, slope and distance can be computed at the touch of a keyboard, thanks to a selection of stored algorithms.
- Simultaneous display of two images, strobed from two selected points on the ECG cycle, allows detection of abnormal wall motion.
- Comprehensive exam data display permits date, time, frequency and patient data and image annotation to be included for more complete patient records.

For further information on the SSH-40A electronic sector scanner, or other Toshiba Medical Systems' products, please call toll free 800-421-1968, in California call (714) 730-5000 or write Toshiba Medical Systems, 2441 Michelle Drive, Tustin, CA 92680.

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# Immediate Hemodynamic Effects of a New Calcium-Channel Blocking Agent (Nitrendipine) in Essential Hypertension

HECTOR O. VENTURA, MD, FRANZ H. MESSERLI, MD, WILLIE OIGMAN, MD, FRANCIS G. DUNN, MD, EFRAIN REISIN, MD, and EDWARD D. FROHLICH, MD

**The immediate hemodynamic effects of a new calcium-channel blocking agent nitrendipine were studied in 12 patients with mild established essential hypertension. According to the response to mean arterial pressure, patients were classified into responders (decrease >10 mm Hg, 7 patients) and nonresponders (≤10 mm Hg, 5 patients). The decrease in arterial pressure in responders was associated with a significant ($p < 0.01$) decrease in total peripheral resistance and a significant ($p < 0.05$) increase in heart rate, cardiac index, and left ventricular ejection rate. The plasma norepinephrine level was significantly ($p < 0.05$) increased in the responders. The response to upright tilt was qualitatively similar to pretreatment values. Thus, nitrendipine lowered arterial pressure as a result of arteriolar dilatation associated with a reflexive increase in heart rate and cardiac index. These hemodynamic properties make the drug particularly apt for use in combination with beta-adrenergic blockade for the treatment of arterial hypertension.**

The place of calcium-channel blocking agents in the medical management of coronary heart disease has been well established over the last few years.[1–6] These agents act by inhibiting calcium ion entrance into the vascular smooth muscle cell,[7,8] thereby promoting vasodilation.[9] Since essential hypertension is hemodynamically characterized by an increased vascular resistance, it is not surprising that calcium-channel blocking agents have also been used with success in the treatment of systemic hypertension.[10–12] For example, nifedipine has been shown to be an effective form of therapy both in hypertensive emergencies[13] and in less severe forms of hypertension.[14,15]

However, various calcium-channel blocking agents seem to have disparate effects on cardiac contractility and electrophysiology. Accordingly, the hemodynamic response to these compounds is not uniform.[16] The present study was designed to evaluate the immediate effects of a new calcium-channel blocking agent, nitrendipine, a compound that is structurally similar to nifedipine.

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## Methods

Twelve patients (10 men and 2 women) with mild established essential hypertension were included in the present study. Each subject provided informed consent to a protocol previously approved by our institution's review committee. All subjects were evaluated to exclude secondary forms of hypertension[17] and other concomitant disorders. Patients were enrolled if, after discontinuation of all medications for at least 3 weeks, the diastolic pressure (Phase V of Korotkoff sounds) in the supine and standing positions was 90 to 114 mm Hg.

As previously described in detail,[17] systemic hemodynamics were determined before and then 60 and 120 minutes after oral administration of nitrendipine (20 mg). Intraarterial and venous pressures were monitored continuously and supine cardiac output was determined in triplicate using indocyanine green dye (5 mg) in the postabsorptive state.[17]

Plasma volume was determined with radioactive iodine-125 human serum albumin.[17] Blood samples were withdrawn for determination of plasma renin activity[18] and catecholamine (epinephrine, norepinephrine, and dopamine) concentrations[19] 1 hour after insertion of the intravascular catheters, and 60 and 120 minutes after the administration of the agent. In addition, M-mode echocardiography[20] was performed before and 60 and 120 minutes after nitrendipine administration. Response to upright tilt (45°) for 5 minutes was also studied in eight patients. Cuff blood pressures were recorded in all patients for an additional 3 hours after completion of the hemodynamic study. Statistical evaluation was done by analysis of variance with repetitive measurements and a subsequent Tukey's honestly significant difference test.[21]

**TABLE I Clinical Characteristics of the Patients**

| | Responders | Nonresponders |
|---|---|---|
| Number | 7 | 5 |
| Age (yr) | 45 ± 7 | 43 ± 18 |
| Sex (male:female) | 6:1 | 4:1 |
| Race (white:black) | 5:2 | 3:2 |
| Height (cm) | 172 ± 8 | 178 ± 8 |
| Weight (kg) | 84 ± 1 | 91 ± 2 |
| BSA ($m^2$) | 1.96 ± 0.1 | 2.08 ± 0.3 |
| SAP | 158 ± 7 | 147 ± 5 |
| DAP | 101 ± 3 | 93 ± 1 |
| MAP | 120 ± 4 | 111 ± 1 |

BSA = body surface area; DAP = diastolic arterial pressure; MAP = mean arterial pressure; SAP = systolic arterial pressure.

## Results

According to the response of mean arterial pressure 2 hours after the drug administration, patients were classified into responders (decrease ≥10 mm Hg in mean arterial pressure, average −14 ± 2, 7 patients) or nonresponders (≤10 mm Hg decrease in mean arterial pressure, average +4 ± 3, 5 patients). Clinical characteristics of the 2 groups are detailed in Table I. Except for a somewhat lower arterial pressure in the nonresponding patients, no significant pretreatment differences between the 2 groups were found. The mean arterial pressure decrease in the responding patients was accompanied by an increase in heart rate, cardiac output, and a decrease in total peripheral resistance (Fig. 1). Arterial distensibility as measured by pulse pressure divided by stroke volume[22] also changed after nitrendipine administration. The velocity of circumferential fiber shortening and the ejection fraction remained unchanged during the 2-hour study, although the left ventricular ejection rate increased (Table II).

The responses of circulating humoral substances to nitrendipine (Table III) primarily reflected a significant ($p < 0.05$ after 2 hours) increase in plasma norepinephrine level; there was no change in plasma epinephrine, dopamine, or renin activity. Arterial pressure remained at a low level in responding patients throughout the 3-hour period of observation after completion of the hemodynamic assessment.

The response to upright tilt (Table IV) was qualitatively unchanged (except for mean arterial pressure) with nitrendipine when compared with pretreatment values. Comparison between responding and nonresponding patients was not appropriate in view of the small number involved.

## Discussion

The present data show that the immediate antihypertensive effect of an oral dose of 20 mg of nitrendipine was associated with a significant decrease in total peripheral resistance and an increase in cardiac output, heart rate, and left ventricular ejection rate in the responding group. These findings are in agreement with reports of other calcium-channel inhibiting agents,[14,23,24] indicating that the decrease in arterial pressure is due to a decreased vascular resistance produced by predominantly arteriolar dilatation. Since postural hypotension was not produced during upright tilt, significant peripheral venodilation seemed unlikely.

The increase in heart rate and cardiac output associated with the decrease in arterial pressure that occurred in our study has also been observed with nifedipine administration.[14,23,24] Although both nifedipine and nitrendipine increase cardiac output, the increase is produced by an elevation of heart rate only with the latter, whereas both heart rate and stroke volume become elevated with nifedipine. Since calcium-channel blockers exert negative direct chronotropic and inotropic[25] effects under in vitro conditions, it is fair to conclude that the cardioacceleration (and the increase in cardiac output) occurred secondary to augumented sympathetic or decreased baroreceptor mediated vagal activity. Indeed, the observed increase in norepinephrine of >50% above pretreatment levels lends support to this concept.

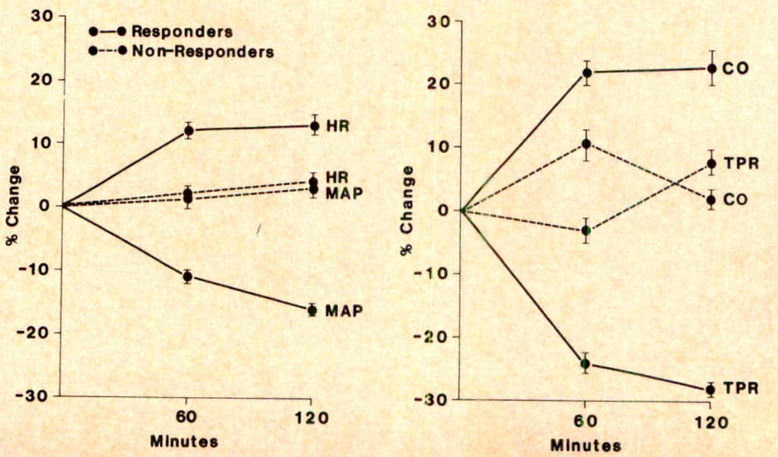



**FIGURE 1.** Immediate hemodynamic effect of oral administration of nitrendipine (20 mg) on (**left**) mean arterial pressure (MAP) and heart rate (HR), and (**right**) cardiac output (CO) and total peripheral resistance (TPR).

**TABLE II Hemodynamic Responses to Nitrendipine (Mean ± Standard Error of the Mean)**

| | Baseline | | 60 Minutes | | 120 Minutes | |
|---|---|---|---|---|---|---|
| | Responders | Nonresponders | Responders | Nonresponders | Responders | Nonresponders |
| MAP (mm Hg) | 113 ± 5 | 104 ± 3 | 101 ± 5 | 107 ± 3 | 95 ± 3† | 108 ± 5 |
| HR (beats/min) | 72 ± 5 | 65 ± 4 | 82 ± 6* | 66 ± 5 | 83 ± 6* | 67 ± 5 |
| CI (liters/min/m$^2$) | 2.80 ± 0.1 | 2.96 ± 0.2 | 3.45 ± 0.2* | 3.20 ± 0.4 | 3.45 ± 0.3* | 2.88 ± 0.3 |
| SI (ml/m$^2$) | 40 ± 3 | 45 ± 1 | 42 ± 3 | 48 ± 3 | 43 ± 3 | 43 ± 3 |
| TPRI (units) | 41 ± 3 | 36 ± 2 | 31 ± 2† | 35 ± 4 | 29 ± 2† | 39 ± 4 |
| PP/SV (mm Hg/ml) | 0.92 ± 0.1 | 0.75 ± 0.1 | 0.73 ± 0.1* | 0.79 ± 0.1 | 0.69 ± 0.1† | 0.81 ± 0.1 |
| LVERI (ml/min/m$^2$) | 130 ± 9 | 141 ± 9 | 147 ± 6* | 154 ± 10 | 154 ± 9† | 141 ± 11 |
| VCF (circ/s) | 1.25 ± 0.1 | 1.22 ± 0.1 | 1.26 ± 0.1 | 1.35 ± 0.1 | 1.26 ± 0.1 | 1.34 ± 0.1 |
| EF (%) | 73 ± 3 | 74 ± 2 | 71 ± 3 | 74 ± 2 | 71 ± 4 | 74 ± 3 |

* $p < 0.05$ versus baseline.
† $p < 0.01$ versus baseline.
CI = cardiac index; EF = ejection fraction; HR = heart rate; LVERI = left ventricular ejection rate index; MAP = mean arterial pressure; PP/SV = pulse pressure/stroke volume; SI = stroke index; TPRI = total peripheral resistance index; VCF = velocity of circumferential fiber shortening.

**TABLE III Humoral and Biochemical Responses to Nitrendipine**

| | Baseline | | 60 Minutes | | 120 Minutes | |
|---|---|---|---|---|---|---|
| | Responders | Nonresponders | Responders | Nonresponders | Responders | Nonresponders |
| PRA (ng/ml/min) | 1.07 ± 0.3 | 0.68 ± 0.2 | 1.00 ± 0.4 | 0.31 ± 0.1 | 0.89 ± 0.5 | 0.33 ± 0.1 |
| NE (pg/ml) | 310 ± 66 | 357 ± 80 | 400 ± 68 | 467 ± 90 | 481 ± 66* | 424 ± 95 |
| E (pg/ml) | 103 ± 32 | 89 ± 50 | 128 ± 38 | 88 ± 35 | 88 ± 42 | 123 ± 38 |
| D (pg/ml) | 71 ± 28 | 68 ± 41 | 79 ± 32 | 82 ± 40 | 60 ± 24 | 130 ± 40 |

* $p < 0.05$ versus baseline.
D = dopamine; E = epinephrine; NE = norepinephrine; PRA = plasma renin activity.

**TABLE IV Head-Up Tilt**

| | Responders | | | | Nonresponders | | | |
|---|---|---|---|---|---|---|---|---|
| | Before | | After | | Before | | After | |
| | Supine | Tilt | Supine | Tilt | Supine | Tilt | Supine | Tilt |
| MAP (mm Hg) | 113 ± 5 | 116 ± 8 | 99 ± 4 | 92 ± 7 | 104 ± 3 | 110 ± 5 | 108 ± 6 | 114 ± 5 |
| CI (liters/min/m$^2$) | 2.79 ± 0.2 | 2.32 ± 0.1 | 3.63 ± 0.1 | 2.80 ± 0.2 | 2.90 ± 0.2 | 2.56 ± 0.2 | 2.90 ± 0.2 | 2.66 ± 0.1 |
| HR (beats/min) | 72 ± 5 | 80 ± 7 | 83 ± 6 | 98 ± 9 | 65 ± 3 | 70 ± 4 | 67 ± 4 | 73 ± 5 |
| TPRI (units) | 43 ± 2 | 48 ± 3 | 27 ± 2 | 34 ± 2 | 36 ± 3 | 44 ± 3 | 38 ± 3 | 43 ± 3 |

CI = cardiac index; HR = heart rate; MAP = mean arterial pressure; TPRI = total peripheral resistance index.

The response of cardiac output, heart rate, and total peripheral resistance to upright tilt was qualitatively similar during nitrendipine when compared with the pretreatment period. However, although mean arterial pressure showed a slight decrease under nitrendipine no orthostatic hypotension was observed, indicating that the venous return to the heart remained unchanged after nitrendipine administration. Thus, the compound seems to predominantly affect the arteriolar vascular bed. Indeed, Olivari et al,[11] measuring pressures in the right side of the heart during nifedipine administration, were unable to document any significant drug effects.

Since we did not measure the drug concentration in the plasma, the reason for the lack of effect in the nonresponding patients remains speculative. Conceivably, they might not have absorbed the drug, or the receptor concentration of the compound might not have been high enough to produce vasodilatation.

*In conclusion*, the antihypertensive effect of nitrendipine is related to an arteriolar dilation associated with a reflexive increase in heart rate and cardiac index. Accordingly, its combination with beta-blocking agents would be beneficial in the treatment of arterial hypertension.

## References

1. **Mizuno Y, Yasui S.** Effects of nifedipine treatment of ischemic diseases. In: Hashimoto K, Kimura E, Kobayashi T, eds. New Therapy of Ischemic Heart Disease. Tokyo: University of Tokyo Press, 1975:163.
2. **Ebner F.** Survey and summary results obtained during the world wide clinical investigations of Adalat (nifedipine). In: Lockner W, Braash W, Kronenberg G, eds. New Therapy of Ischemic Heart Disease. Berlin: Springer-Verlag, 1975:348.
3. **Muller JE, Gunther SJ.** Nifedipine therapy for Prinzmetal's angina. Circu-

lation 1978;57:137.
4. **Andreasen F, Boye E, Christoffersen E, et al.** Assessment of verapamil in the treatment of angina pectoris. Eur J Cardiol 1975;2:443–452.
5. **Pawdi O, Maseri A, Simonetti I.** Management of unstable angina at rest by verapamil—a double blind crossover study in the coronary care unit. Br Heart J 1979;41:167–174.
6. **Hausen JF, Sandol E.** Treatment of Prinzmetal's angina due to coronary artery spasm using verapamil: a report of three cases. Eur J Cardiol 1978;7:327–335.
7. **Fleckenstein A.** Specific pharmacology of calcium in myocardial cardiac pacemakers and vascular smooth muscle. Ann Rev Pharmacol Toxicol 1977;17:149–166.
8. **Thorens S, Haeusler G.** Effects of some vasodilators on calcium translocation in intact and fractioned vascular smooth muscle. Eur J Pharmacol 1979;54:79–91.
9. **Ross G, Jorgensen CR.** Cardiovascular actions of ypoveatril. J Pharmacol Exp Ther 1967;158:504.
10. **Krikler D.** Verapamil in cardiology. Eur J Cardiol 1974;2:3.
11. **Olivari M, Bartocelli C, Polese A, Furentini C, Moruzzi L, Guazzi MD.** Treatment of hypertension with nifedipine, a calcium antagonistic agent. Circulation 1979;59:1056.
12. **Burris JF, Notargiacomo AV, Papademetriou V, Freis ED.** Acute and short-term effects of a new calcium antagonist in hypertension. Hypertension 1982;4(Suppl II):II-32–II-35.
13. **Kuwajima I, Veda K, Kamata C, et al.** A study on effects of nifedipine in hypertensive crisis on severe hypertension. Jpn Heart J 1978;19:455–467.
14. **Guazzi M, Olivari MT, Polese A, Fioretini C, Magrini F, Moruzzi P.** Nifedipine, a new antihypertensive with rapid action. Clin Pharmacol Ther 1977;22:528–532.
15. **Laaser V, Meurerr KA, Kaufmann W.** Zur klinischen bewertung der kombinations behandlung von nifedipin mit verschiedenen. Antihypertensiva. Arzneimittelforsch 1977;27:676–681.
16. **Henry PD.** Comparative pharmacology of calcium antagonists: nifedipine, verapamil, and dialtiazem. Am J Cardiol 1980;46:1047–1057.
17. **Messerli FH, DeCarvalho JGR, Christie B, Frohlich ED.** Systemic and regional hemodynamics in low, normal and high cardiac output borderline hypertension. Circulation 1978;58:441.
18. **Sealey JE, Laragh JH, Gerten-Banes T, Aceto RM.** The measurement of plasma renin activity in man. In: Laragh JH, ed. Hypertension Manual. New York: Yorke, 1974:621–640.
19. **Peuler JD, Jonson GA.** Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. Life Sci 1977;21:625.
20. **Dunn FG, Chandraratna PAN, DeCarvalho JGR, Basta LL, Frohlich ED.** Pathophysiological assessment of hypertensive heart disease with echocardiography. Am J Cardiol 1977;39:789–795.
21. **Snedecor GW, Cochran WG.** Statistical Methods. 6th ed. Ames, Iowa: Iowa State University Press, 1967.
22. **Tarazi RC, Magrin IF, Dustan HP.** The role of aortic distensibility in hypertension. In: Miller P, Safar MA, eds. Monaco: Boehringer-Ingelheimk, International Symposium on Hypertension, 1975;133:45.
23. **D'Oliveira T, Calderon NR, Garcilazo E, Patricio T, Tenreyro E.** Hemodynamic changes after a single dose of nifedipine (Adalat) in patients catheterized for coronary disease. Proceedings of the 2nd International Adalat Symposium. Ref 2:145.
24. **Murakami M, Murakami E, Takeboshi N, et al.** Antihypertensive effect of 4-(2 Nihsphenyl) 2-6-dimethyl, 4 dihydropyndine-3,5 dicarbonic acid dimethyllesser (nifedipine Bay a 1040), a new coronary dilator. Jpn Heart J 1972;13:128.
25. **Schwartz A, Grupp G, Millard RW, et al.** Calcium channel blockers: possible mechanisms of protective effects on the ischemic myocardium. In: Weiss GB, ed. Clinical Physiology Series Monograph. Bethesda, MD: American Physiological Society, 1981:191–210.

# Predictability of Blood Pressure Response to Isometric Stress

ROBERT H. CHANEY, MD and STEPHAN ARNDT, PhD

**Isometric exercise causes transient systemic hypertension, but with individual differences. An attempt was made to delineate predictors of those differences by analyzing the blood pressure (BP) response in terms of variables readily measured in clinical practice. For each of 270 office patients, we determined blood pressure, heart rate (HR), electrocardiographic findings, and symptoms in response to maximal isometric and maximal dynamic exercise. For systolic BP response as the predicted measure, 4 predictor variables in combination, including age, sex, resting systolic BP, and maximal treadmill systolic BP, yielded 70% predictability. For diastolic BP, 5 predictors in combination, including handgrip strength, resting diastolic BP, treadmill HR, systolic BP, and diastolic BP, allowed 66% prediction. Not predictive of either were resting HR, abnormality of treadmill test, presence of heart disease, and certain other medical diagnoses.**

Since Alam and Smirk[1] 4 decades ago described the increase in systemic blood pressure (BP) during exercise of muscle groups with compromised circulation, there has been increasing interest in the cardiovascular response to isometric stress. While Alam and Smirk[1] restricted circulation in contracting muscles by overwork or vascular occlusion, others[2–4] have demonstrated that isometric exercise itself restricts blood flow in the contracting muscles and causes transient systemic arterial hypertension. However, Alam and Smirk[1] also described individual variation in BP response to isometric stress, and this has received much less interest. Yet some individuals develop extreme transient hypertension with isometric exercise, such as that frequently performed in occupational and recreational activities. In observing BP during maximal handgrip contraction, we found great individual differences. We therefore attempted to determine whether the responses were related to, and predicted by, any or a combination of readily measured variables. It has been stated that an increase in BP with isometric exercise is a predictable function of the intensity of the stress.[2,5] Other factors, usually tested singly, also have been reported to influence this response, including age,[4,6–8] sex,[9] systemic hypertension,[10–12] body fat content,[13] and heart disease.[14] We therefore determined the association of BP response in isometric stress with several noninvasive clinical factors in combination and singly.

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## Methods

Each of 270 office patients was subjected once to 1 minute of maximal isometric handgrip stress. They included 194 men (72%) and 76 women (28%) aged 20 to 79 years (mean 52, standard deviation 10.07). A Kolmogorov-Smirnov test[15] was used to ensure the normalcy of the age distribution and demonstrated that this distribution did not depart significantly from the normal curve ($D = 0.042$, $p < 0.15$). Of the 270 patients, 33% had arteriosclerotic coronary heart disease, 17% had had myocardial infarcts, 22% had controlled hypertension, and 19% were receiving digitalis and antihypertensive or antiarrhythmic agents (including beta-adrenergic blocking agents). However, none had severe hypertension, serious arrhythmia, myocardial infarction within 2 months, crescendo angina, or active cerebrovascular disease. Other precautions included informed consent, continuous electrocardiographic monitoring, and presence of a crash cart and personnel trained in basic life support.

After baseline measurements of heart rate (HR) and BP and electrocardiography, each patient, standing with a hand dynamometer (Smedley, Stoelting, Chicago) adjusted to the right hand, squeezed for 2 or 3 seconds, 3 different times, to obtain a maximal reading. The patient was then instructed to sustain maximal exertion for 60 seconds, at the same time relaxing all other muscle groups and breathing normally. At 30 and 50 seconds he was again urged to do his best and was told the remaining time. Blood pressure usually increased through the minute of sustained contraction. Although fatigue

**TABLE I Blood Pressure Response to Isometric Handgrip Exercise (n = 270)**

| | Resting (mm Hg) | | Maximal on HG (mm Hg) | | Absolute Increase (mm Hg) | | % of Resting | |
|---|---|---|---|---|---|---|---|---|
| BP | Range | Mean | Range | Mean | Range | Mean | Range | Mean |
| Systolic | 68–200 (SD 19.36) | 123 | 90–260 (SD 26.26) | 166 | 0–90 (SD 16.76) | 43 | 100–180 (SD 14.56) | 136 |
| Diastolic | 40–110 (SD 12.00) | 82 | 70–150 (SD 15.31) | 110 | −10–+58 (SD 10.43) | 28 | 88–200 (SD 15.46) | 135 |

BP = blood pressure; HG = handgrip; SD = standard deviation.

caused a decrease in actual handgrip pressure over the minute, we were concerned only that the effort was maximal for each subject. During this minute, BP was repeatedly measured and the highest reading toward the end of the static effort was recorded. The patient and the oscilloscope were watched for evidence of complications, and in the last 5 seconds an assistant obtained a 4-lead electrocardiographic write-out. The method was reproducible. Intrasubject reliability was demonstrated by retesting 74 of the subjects approximately 1 year later. The correlations for systolic BP and diastolic BP were 0.673 and 0.664, respectively (both p values <0.001). The dynamic exercise was a graded, interrupted, multistage, maximal treadmill test, with HR, BP, and 4-lead electrocardiogram recorded each minute of exercise and rest.

Analysis of the data was made by 2 stepwise multiple regression analyses. One regression used systolic BP response to isometric stress as the predicted variable and the other analysis involved diastolic BP reaction. For both analyses the following variables were included as potential predictors: resting HR, resting systolic BP, resting diastolic BP, maximal HR and systolic BP and diastolic BP on the treadmill test, handgrip strength, age, sex, presence or absence of heart disease, whether or not the treadmill test was abnormal, presence or absence of hypertension, normal/abnormal resting electrocardiographic results, and cardiovascular medication. Other medical diagnoses were also considered, including diabetes mellitus (n = 15), chronic obstructive pulmonary disease (n = 10), hyperuremia (n = 11), hyperlipidemia (n = 18), and peptic ulcer (n = 35). Effects coding[16] was used for all of these diagnostic categories so that they could be tested as a group and then, if significant, inspected individually. This procedure is frequently useful to control for excessively liberal interpretation of the statistical tests.

**TABLE II Measures of Importance for Significant Variables in Predicting Systolic BP and Diastolic BP Response to Isometric Stress (n = 270)**

| Variable | Beta Weight | Change in $R^2$ | Simple r | B Coefficient |
|---|---|---|---|---|
| **Systolic BP Response** | | | | |
| Age | 0.105* | 0.011† | 0.227† | 0.27 |
| Sex (1 male; 2 female) | −0.113† | 0.012† | −0.255† | −6.59 |
| Resting systolic BP | 0.456† | 0.594† | 0.771† | 0.62 |
| Maximal systolic BP on treadmill | 0.387† | 0.084† | 0.765† | 0.36 |
| Constant | ... | ... | ... | 21.99 |
| **Diastolic BP Response** | | | | |
| Handgrip strength (kg) | 0.206† | 0.029† | 0.342† | 0.27 |
| Resting diastolic BP | 0.385† | 0.539† | 0.734† | 0.49 |
| Maximal heart rate on treadmill | −0.082* | 0.006* | 0.113* | −0.05 |
| Maximal systolic BP on treadmill | 0.176† | 0.064† | 0.644† | 0.37 |
| Maximal diastolic BP on treadmill | 0.287† | 0.024† | 0.715† | 0.09 |
| Constant | ... | ... | ... | 15.43 |

* p <0.05.
† p <0.01.
BP = blood pressure.

## Results

The BP response to isometric stress varied greatly among individual patients, as seen in Table I. For instance, diastolic BP reaction ranged from a decrease in 1 patient to a 2-fold increase in another. It is noteworthy that individual variability of the systolic BP response to isometric exertion (standard deviation 26.21) was significantly greater than the sample's variability of resting systolic BP (standard deviation 19.33; $t(268) = 7.94$; $p < 0.001$). This difference was also true for diastolic BP (standard deviation 15.28 and 11.97 for reactions to isometric stress and resting values, respectively; $t(268) = 5.94$; $p < 0.001$).

In order to predict both systolic BP and diastolic BP during isometric stress, 2 stepwise multiple regressions were performed. As predictor variables (for example, resting diastolic BP and age) were stepped into the regression, the improvement in $R^2$ (an index of predictability)[16] was tested for significance. This procedure continued only as long as adding a new variable increased prediction significantly. The presence or absence of other medical diagnoses was treated as a single group of variables during this phase of the analysis. This resulted in the best set of variables which could be used to determine the maximal blood pressure response to the isometric stress.

The multiple R with systolic response as the dependent measure proved highly significant ($R = 0.837$; $F(4,265) = 155.04$; $p < 0.001$; SDe = 14.45) with 4 independent variables which included age, sex, systolic BP at rest, and systolic BP on maximal treadmill exercise. Indeed, the analysis was able to account for 70% of the individual variation in systolic BP response. The 4 variables are listed in Table II along with alternate measures of the variables' relative importance in prediction.

Neither HR nor diastolic BP during rest or during treadmill exercise was predictive of systolic BP reaction. No other variable was significant. For example, neither strength, the presence or absence of heart disease, abnormality of treadmill exercise, nor the presence of other medical diagnoses added to the prediction of systolic BP during the isometric stress. In interpretation of the beta weights, the individual who is likely to have high systolic BP during isometric stress can be described as having high systolic BP while at standing rest as well as high systolic BP on the maximal treadmill test. Age and sex were also significantly descriptive, although to a lesser extent, with older patients and male patients reaching higher systolic BP levels.

The results with diastolic BP response also showed predictability. The multiple R for the diastolic BP was 0.814 ($F[5,264] = 103.45$; $p < 0.001$; SDe = 8.97) and included 5 predictor variables (Table II). These predictors were handgrip strength, resting diastolic BP, treadmill HR, systolic BP, and diastolic BP. In this analysis, 66% of the patient variability in diastolic BP reaction to isometric stress was explained.

In predicting systolic BP reaction to isometric stress, the best predictor was the resting systolic BP. Similarly, the best estimate of diastolic BP reaction was afforded by the resting diastolic BP level. As with systolic BP response, a description can be made of individuals expected to have a high diastolic BP response. Such persons had a high diastolic BP while resting as well as a high diastolic and systolic BP during the treadmill test. Furthermore, these persons had a lower maximal heart rate on the treadmill test and tended to have stronger handgrip. As with systolic BP, the presence or absence of heart disease, abnormality of the treadmill exercise, and other medical diagnoses were not associated with the diastolic BP reaction. In contrast, however, neither age, sex, nor resting systolic BP contributed to diastolic BP prediction.

Based on the first order correlation, sex was a significant predictor of diastolic BP response. However, after the strength variable entered the regression, sex ceased being significantly related. This suggests that although generally men have higher diastolic BP responses, this is because they are also stronger, with strength being the deciding factor.

The last column in Table II, labeled "B coefficient," presents the basis for formulating the prediction of both systolic and diastolic BP during isometric stress. A predicted score can be calculated by multiplying the value of each variable by the appropriate B coefficient, then summing, and adding the constant. For instance, a 50-year-old woman with a resting systolic BP of 123 mm Hg and a maximal systolic BP of 175 mm Hg would have a predicted maximal systolic BP during handgrip stress as follows: Predicted systolic BP = 50(0.27) + 2(−6.59) + 123(0.62) + 175(0.36) + 21.99 = 162 mm Hg.

B coefficients will vary with different samples of persons, and these formulas will not be totally generalizable. They do, however, predict well for subjects in our sample, and should predict for similar subjects.

## Discussion

The stimulus for this study was the observation of marked individual variation in blood pressure response to isometric stress. The major question was whether or not the response could be predicted by basic clinical information. The answer to our question is yes in that BP reactions could be predicted with 70% of systolic BP and 66% of diastolic BP variation accounted for. Different sets of variables are required for predicting systolic and diastolic BP reactions, and there are patterns that are important to prediction. The most important information for predicting systolic BP reaction is systolic BP with the subject at standing rest. Likewise, resting diastolic BP is the strongest predictor of diastolic BP response. The patients' maximal BP reactions on the treadmill contribute additional information. Maximal systolic BP on the treadmill is useful for estimating the systolic BP reaction to isometric stress, whereas both the systolic BP and the diastolic BP, as well as HR, on the treadmill are important for predicting the diastolic BP. However, we found an inverse relation between HR on the treadmill and diastolic BP during handgrip; lower HR is associated with higher diastolic BP reactions.

While sex and age are relevant only to systolic BP response, strength is only involved in predicting diastolic BP response. The weak relation of age with systolic BP and the lack of relation to diastolic BP during isometric stress is interesting since previous reports[4,6–8] have indicated as association in subjects of comparable age. Further caution in predicting is indicated by our finding that although strength related well to diastolic BP, several patients with weakest strength had the greatest BP increase relative to resting levels, and some with greatest strength had the smallest increase.

Of importance was the nonsignificance of the presence or absence of heart disease to either systolic BP or diastolic BP reaction in our series. Heart disease tended to predispose to higher systolic BP response with handgrip exercise, but without statistical significance. This is consistent with the findings of Kino et al,[7] who reported no difference between BP response in older normal persons and that in older patients with heart disease. Fisher et al,[14] on the other hand, found a greater increase in BP in persons with normal left ventricular function than in those with abnormal function. Our results agree with those of others[10,11] in that hypertensive patients had greater increases in BP with isometric stress than nonhypertensive patients. Strong et al[12] found in youngsters aged 7 to 14 years an inverse relation between resting BP and *percent* change with exercise.

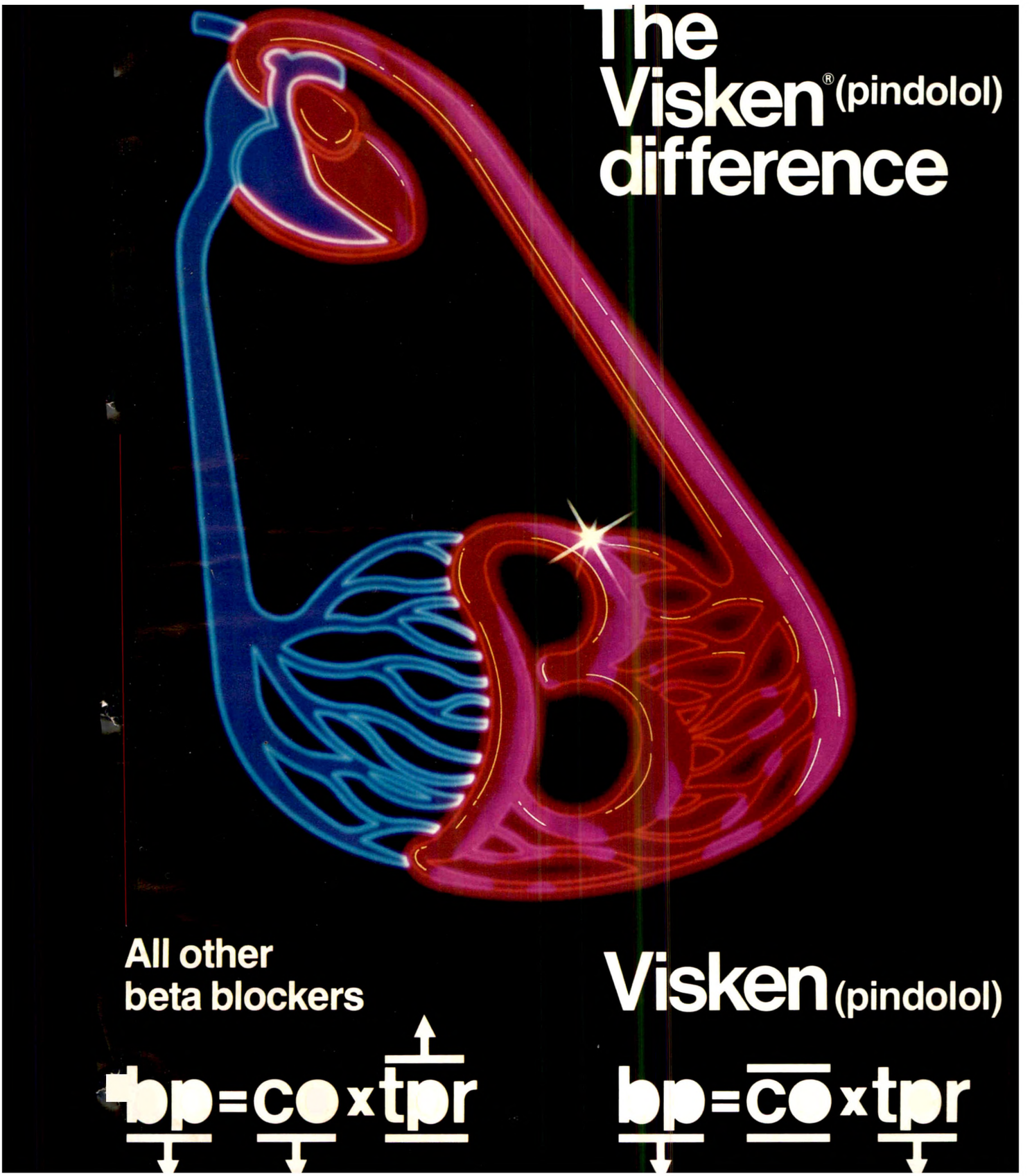
Although it has become popular to emphasize the dangers of isometric exercise,[3,17–19] we found infrequent S-T depressions, no significant arrhythmia, and no angina or other notable symptoms in our patients. Other workers have also spoken to the safety of isometric testing.[20–22] While isometric stress does increase myocardial oxygen consumption,[22] coronary flow has been shown to increase,[3,23] presumably meeting[3] or even

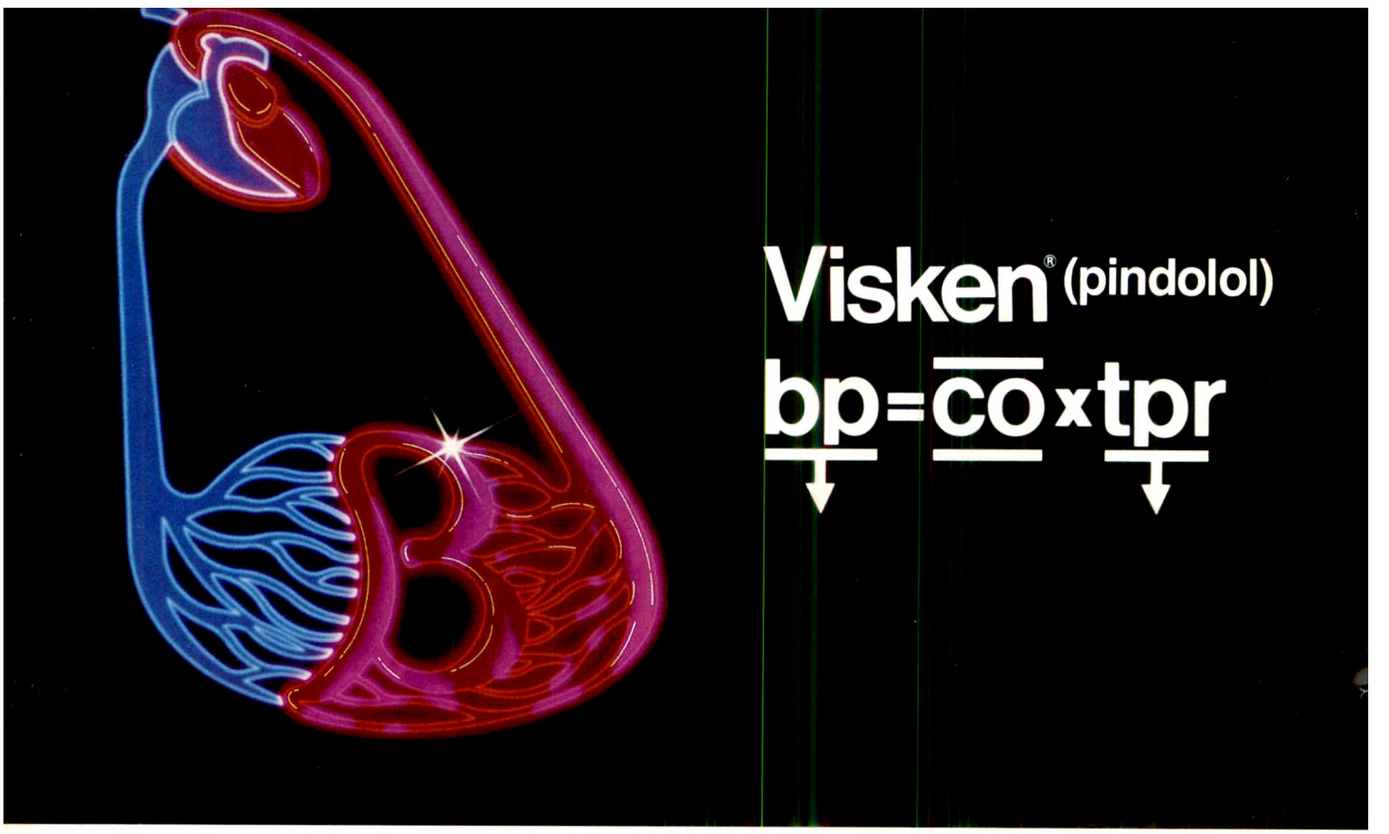
exceeding[24] the increased myocardial oxygen consumption. We have found isometric stress, as we have employed it, monitored for electrocardiogram and symptoms as well as BP, a safe and practical noninvasive test. It appears, then, that such testing is neglected at times when it might be useful. Many variables affect BP increase with this type of exertion; we found that patterns of readily obtained clinical variables can account for two thirds of the variation in BP response.

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## References

1. **Alam M, Smirk FH.** Observations in man upon a blood pressure raising reflex arising from the voluntary muscles. J Physiol (Lond) 1937;89:372–383.
2. **Humphreys PW, Lind AR.** Blood flow through active and inactive muscles of the forearm during sustained handgrip contractions. J Physiol (Lond) 1963;166:120–135.
3. **Kivowitz C, Parmley WW, Donoso R, Marcus H, Ganz W, Swan HJC.** Effects of isometric exercise on cardiac performance. Circulation 1971; 44:994–1002.
4. **Lind AR, McNicol GW.** Muscular factors which determine the cardiovascular responses to sustained and rhythmic exercise. Can Med Assoc J 1967; 96:706–715.
5. **Mitchell JH, Wildenthal K.** Static (isometric) exercise and the heart; physiological and clinical considerations. Annu Rev Med 1974;25:369–381.
6. **Lind AR, McNicol GW, Donald KW.** Circulatory adjustments to sustained (static) muscular activity. In: Evang K, Andersen KL, eds. In: Proc Sympos Physical Activity in Health and Disease. Oslo: Universitatsforlaget, 1966: 36–63.
7. **Kino M, Lance VQ, Shahamatpour A, Spodick DH.** Effects of age on response to isometric exercise. Am Heart J 1975;90:575–581.
8. **MacDonald HR, Sapru RP, Taylor SH, Donald KW.** Effects of intravenous propanolol (Inderal) on the systemic circulatory response to sustained handgrip. Am J Cardiol 1966;18:333–344.
9. **Petrofsky JS, Burse RL, Lind AR.** Comparison of physiological responses of women and men to isometric exercise. J Appl Physiol 1976;38:863–868.
10. **Larnid S, Wolff FW.** Drug failure in reducing pressor effect of isometric stress test in hypertension. Am Heart J 1973;86:211-215.
11. **Lorimer AR, Macfarlane PW, Provan G, Duffy T, Laurie TDV.** Blood pressure and catecholamine responses to "stress" in normotensive and hypertensive subjects. Cardiovasc Res 1971;5:169–173.
12. **Strong WB, Miller MD, Striplin M, Salehbhai M.** Blood pressure response to hypertension and dynamic exercise in healthy black children. Am J Dis Child 1978;132:587–595.
13. **Petrofsky JS, Lind AR.** Isometric strength, endurance, and the blood pressure in heart rate responses during isometric exercise in healthy men and women, with special reference to age and body fat content. Pflugers Arch 1975;360:49–61.
14. **Fisher ML, Nutter DO, Jacobs W, Schlant RC.** Hemodynamic responses to isometric exercise (handgrip) in patients with heart disease. Br Heart J 1973;35:422–432.
15. **Stephens MA.** Use of the Kolmogorov-Smirnov, Cramer-Von Mises and related statistics without extensive tables. J Am Statistic Assoc 1974; 69:730–737.
16. **Cohen J, Cohen P.** Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum Associates, 1975:135–144, 188–195.
17. **Atkins JM, Matthews OA, Blomqvist CG, Mullins CB.** Incidence of arrhythmias induced by isometric and dynamic exercise. Br Heart J 1976; 38:465–471.
18. **Matthews OA, Blomqvist G, Cohen LS, Mullins CB.** Left ventricular function during isometric (handgrip): significance of an atrial gallop. Am Heart J 1974;88:686–693.
19. **Siegle W, Gilbert CA, Nutter DO, Schlant RC, Hurst JW.** Use of isometric handgrip for the indirect assessment of left ventricular function in patients with coronary atherosclerotic heart disease. Am J Cardiol 1972;30:48–54.
20. **Helfant RH, DeVilla MA, Meister SG.** Effect of sustained isometric handgrip exercise on left ventricular performance. Circulation 1971;44:982–993.
21. **Lowe DK, Rothbaum DA, McHenry PL, Corya BC, Knoebel SB.** Myocardial blood flow response to isometric (handgrip) and treadmill exercise in coronary heart disease. Circulation 1975;51:126–131.
22. **Nutter DO, Schlant RC, Hurst JW.** Isometric exercise and the cardiovascular system. Mod Concepts Cardiovasc Dis 1972;41:11–15.
23. **Kerber RE, Miller RA, Najjar SM.** Myocardial ischemic effects of isometric, dynamic and combined exercise in coronary artery disease. Chest 1975; 67:388–394.
24. **Braunwald E, Sarnoff SJ, Case RB, Stainsby WN, Welch GH Jr.** Hemodynamic determinants of coronary flow: effect of changes in aortic pressure and cardiac output on the relationship between myocardial oxygen consumption and coronary blood flow. Am J Physiol 1958;192:157–163.


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3) cardiogenic shock
4) second- and third-degree heart block
5) severe bradycardia

*See clinical significance statement.

**References:**
1. Data on file, Sandoz Pharmaceuticals.
2. Wilcox CS, Lewis PS, Peart WS, et al: Renal function, body fluid volumes, renin, aldosterone, and noradrenaline during treatment of hypertension with pindolol. *J Cardiovasc Pharmacol* 3:598-611, 1981.

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Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

**WARNINGS**
**Cardiac Failure:** Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

**In Patients Without A History of Cardiac Failure:** In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal:** Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers:** Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

**Major Surgery:** Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

**Diabetes and Hypoglycemia:** Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

**Thyrotoxicosis:** Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

**PRECAUTIONS**
**Impaired Renal or Hepatic Function:** Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

**Information for Patients:** Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

**Drug Interactions:** Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

**Pregnancy—Category B:** Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**CLINICAL LABORATORY**
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

**ADVERSE REACTIONS**
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

| Body System/ Adverse Reaction | Total (Volunteered and Elicited) Visken (pindolol) (N = 322) % | Active Controls* (N = 188) % | Plac (N = % |
|---|---|---|---|
| Central Nervous System | | | |
| Anxiety | 4 | <1 | |
| Bizarre or Many Dreams | 8 | 3 | |
| Dizziness | 17 | 23 | |
| Fatigue | 15 | 19 | 1 |
| Hallucinations | 1 | 0 | |
| Insomnia | 19 | 8 | 1 |
| Lethargy | 3 | 6 | |
| Nervousness | 11 | 5 | |
| Weakness | 7 | 5 | |
| Autonomic Nervous System | | | |
| Paresthesia | 5 | 2 | |
| Visual Disturbances | 4 | 3 | |
| Cardiovascular | | | |
| Dyspnea | 9 | 8 | 9 |
| Edema | 11 | 9 | 3 |
| Heart Failure | 2 | <1 | 0 |
| Palpitations | 2 | 2 | 0 |
| Weight Gain | 3 | 5 | 0 |
| Musculo-Skeletal | | | |
| Chest Pain | 5 | 3 | 5 |
| Joint Pain | 11 | 6 | 8 |
| Muscle Cramps | 8 | 2 | 0 |
| Muscle Pain | 12 | 12 | 9 |
| Gastrointestinal | | | |
| Abdominal Discomfort | 7 | 7 | 5 |
| Nausea | 7 | 4 | 1 |
| Skin | | | |
| Pruritus | 2 | <1 | 0 |
| Rash | 2 | 3 | 3 |

*Active Controls: Patients received either propranolol, ∝-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

The following selected (potentially important) adverse reactio were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

**POTENTIAL ADVERSE EFFECTS**
In addition, other adverse effects not listed above have been r ported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

**Central Nervous System:** Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

**Cardiovascular:** Intensification of AV block. See CONTRAINDICATIONS.

**Allergic:** Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

**Hematologic:** Agranulocytosis; thrombocytopenic and nonthrombocytopenic purpura.

**Gastrointestinal:** Mesenteric arterial thrombosis; ischemic colitis.

**Miscellaneous:** Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

**OVERDOSAGE**
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

**Excessive Bradycardia:** administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

**Cardiac Failure:** digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

**Hypotension:** administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

**Bronchospasm:** administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ⩾80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

**DOSAGE AND ADMINISTRATION**
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 10 mg b.i.d. alone or in combination with other antihypertensive agents. Many patients will respond to 15 mg per day (5 mg t.i.d.). The antihypertensive response usually occurs within the first week of treatment. If a satisfactory reduction in blood pressure does not occur within 2-3 weeks, the dose may be adjusted in increments of 10 mg per day at 2-3 week intervals up to a maximum of 60 mg per day.

**HOW SUPPLIED**
White, round, scored tablets: 5 mg and 10 mg, packages of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" on one side, and "78-73" and scored on other side (NDC 0078-0073-05). [VIS-Z2 9/1/82]

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# Clonidine in Congestive Heart Failure: A Vasodilator With Negative Inotropic Effects

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**Fourteen patients with moderately severe congestive heart failure (CHF) were given clonidine orally (0.2 and 0.4 mg doses) to determine the hemodynamic effects of a typical centrally acting vasodilator. The 0.2 mg dose significantly reduced mean systemic (15%) and mean pulmonary artery (20%) pressure; the corresponding reductions in vascular resistance were not as great because of a diminished cardiac output. Pulmonary capillary wedge pressure decreased significantly (27%). Heart rate decreased 11% and stroke volume remained unchanged. At a higher dose (0.4 mg), clonidine augmented these reductions but increased stroke volume modestly (15%). Isovolumic developed pressure/duration of isovolumic contraction and the duration of the preejection period were used as indexes of inotropy. After both doses, isovolumic developed pressure/duration of isovolumic contraction decreased dramatically (≥33%) and the preejection period increased substantially (≥18%) (both $p < 0.05$).**

**Compared with currently employed vasodilating agents, the centrally acting agent clonidine appears unique in that the drug-induced systemic and pulmonary arterial vasodilation are not accompanied by a commensurate improvement in ventricular systolic function. This lack of improvement appears to be a result of negative inotropic effects.**

Peripherally acting vasodilators are now commonly used in the management of congestive heart failure (CHF). Many classes of agents (adrenergic blockers, nonspecific vasodilators, and angiotensin-converting enzyme inhibitors) have been extensively examined over the past decade. Numerous studies have demonstrated that these agents augment stroke volume and cardiac output, primarily by reducing ventricular afterload.[1,2]

In contrast to the peripheral class of compounds, centrally acting vasodilators have received little attention in the setting of low output CHF. One typical centrally acting agent is clonidine. Clonidine is used predominantly in hypertensive patients, in whom it effectively reduces systemic blood pressure, systemic vascular resistance, and heart rate.[3-5] It induces its antihypertensive effect by attenuating sympathetic outflow by way of a complex interaction with the central alpha-adrenergic system.[6,7]

We postulated that clonidine may be an effective vasodilator since it does reduce sympathetic activity, a major cause of the elevated ventricular afterload accompanying CHF. This study was designed to determine the acute hemodynamic properties of oral clonidine in patients with chronic CHF.

From the Division of Cardiology, Ohio State University College of Medicine, Columbus, Ohio. This study was supported in part by the James D. Casto Cardiovascular Research Fund and the S. J. Roessler Foundation, Ohio State University, College of Medicine, Columbus, Ohio. Manuscript received September 10, 1982; revised manuscript received November 30, 1982, accepted December 1, 1982.

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## Methods

**Patient population:** Fourteen patients with moderately severe CHF were studied. The mean age was 53 years (range 19 to 73); 2 patients were women. The diagnosis of dilated cardiomyopathy was confirmed by cardiac catheterization performed in each patient within 2 months before the onset of study. Thirteen patients had dilated cardiomyopathy and 1 patient had severe occlusive atherosclerotic coronary artery disease with ischemic cardiomyopathy. Twelve patients were categorized as functional class III and 2 patients as functional class IV (New York Heart Association). All those studied were receiving a digitalis preparation (daily digoxin dose of 0.25 mg in 6 patients, 0.125 mg in 7 patients, and digitoxin 0.1 mg in 1 patient) and furosemide (daily dose range 40 to 120 mg). Several patients had previously received vasodilators (isosorbide dinitrate 20 mg every 6 hours in 5 patients and hydralazine 75 mg every 8 hours in 3 patients). All vasodilators were discontinued at least 48 hours before study. The digitalis and diuretics were continued throughout the study with afternoon doses to avoid peak effect.

**Measurements:** On the first study day, a triple-lumen flow-directed catheter was introduced percutaneously into the subclavian vein and placed in the pulmonary artery for the measurement of pulmonary artery pressure, pulmonary

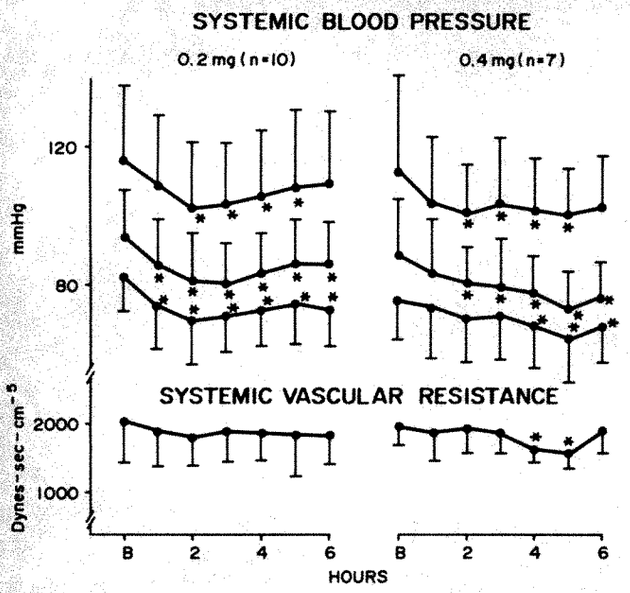



**FIGURE 1.** Both doses of clonidine significantly lowered systolic, mean, and diastolic systemic blood pressures. Only the 0.4 mg dose reduced vascular resistance. Data are presented as mean ± 1 standard deviation. * $p < 0.05$; B = baseline control.

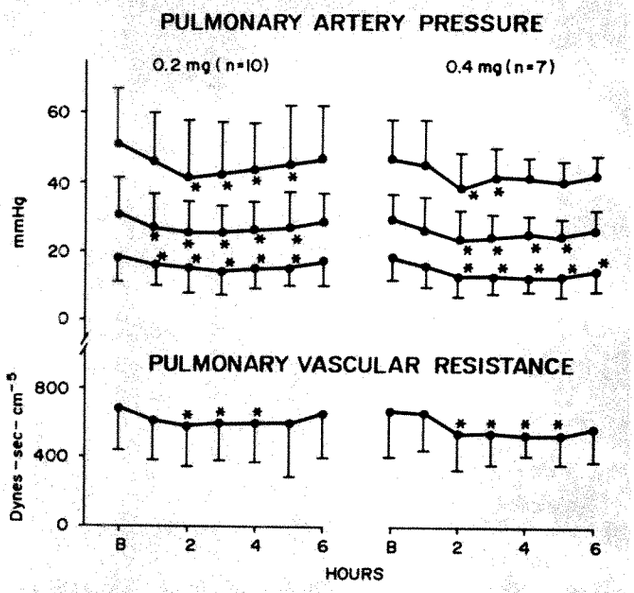



**FIGURE 2.** Pulmonary arterial pressure decreased significantly after clonidine administration. Pulmonary vascular resistance decreased as well. Data are presented as mean ± 1 standard deviation. * $p < 0.05$; B = baseline control.

capillary wedge pressure, and cardiac output (thermodilution technique). The pulmonary artery and capillary wedge pressures were measured with Becton-Dickinson Electrodyne PR-18A pressure amplifiers and ST-149 and WR-4D recording systems. The cardiac outputs were computed with an Instrumentation Laboratory computer unit 601 and recorder unit 602, and were obtained in triplicate (5 measurements were made if variation exceeded 10%). Systemic blood pressure was measured by a cuff and a mercury column sphygmomanometer. Heart rate was obtained from continuous electrocardiographic monitoring. Systolic time intervals, derived from the simultaneous recording of a carotid pulse tracing, a precordial phonocardiogram, and an electrocardiogram, were obtained with an Electronics for Medicine Echo IV unit using specifications previously outlined.[8] Standard formulas were used to determine vascular resistances. Additional calculated variables included the following: diastolic time = R-R interval minus total electromechanical systole ($QS_2$)[9]; preejection period index (milliseconds) = preejection period index corrected for heart rate[8]; and isovolumic developed pressure/duration of isovolumic contraction,[10–12] where developed pressure during isovolumic contraction = systemic diastolic blood pressure minus pulmonary capillary wedge pressure, and isovolumic contraction time = preejection period minus electromechanical delay (Q wave of the electrocardiogram to upstroke of left ventricular impulse on the apexcardiogram). The preejection period index and the isovolumic developed pressure/duration of isovolumic contraction were used as indexes of inotropy.[10–12]

**Protocol:** The patients were studied over 3 days. Day 1 was utilized for catheter placement and served as an equilibration period. On Day 2, 0.2 mg of clonidine was administered, and on Day 3, the patients received 0.4 mg. Clonidine was administered orally in the postabsorptive state. In 10 patients, hemodynamic variables (cardiac output, heart rate, pulmonary capillary wedge pressure, systemic blood pressure, and pulmonary artery pressure) were obtained before and at hourly (×6) intervals after each clonidine dose. Two of these 10 patients and 4 additional ones also underwent hemodynamic, preejection period index, and isovolumic developed pressure/duration of isovolumic contraction measurements at baseline control and 3 hours after clonidine administration.

**Statistical analysis:** The hemodynamic data were compared with control values for each dose with analyses of variance for repeated measures. The 3-hour isovolumic developed pressure/duration of isovolumic contraction and systolic time interval data were compared with control values using the *t* test for paired data.

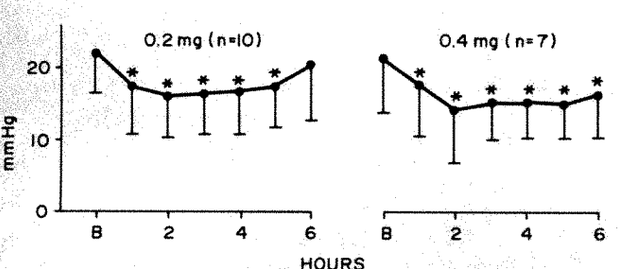



**FIGURE 3.** Pulmonary capillary wedge pressure was significantly reduced by clonidine. Data are presented as mean ± 1 standard deviation. * $p < 0.05$; B = baseline control.

## Results

The results of the hemodynamic studies are presented in Figures 1 through 5. There was no significant difference between any of the baseline control measurements of the 2 doses. After both doses there was a substantial reduction of systolic, mean, and diastolic systemic blood pressures (Fig. 1). All 10 patients who participated in the 6-hour protocol received the 0.2 mg dose, while only 7 were given 0.4 mg because hypotension (systolic blood pressure ≤90 mm Hg) developed in

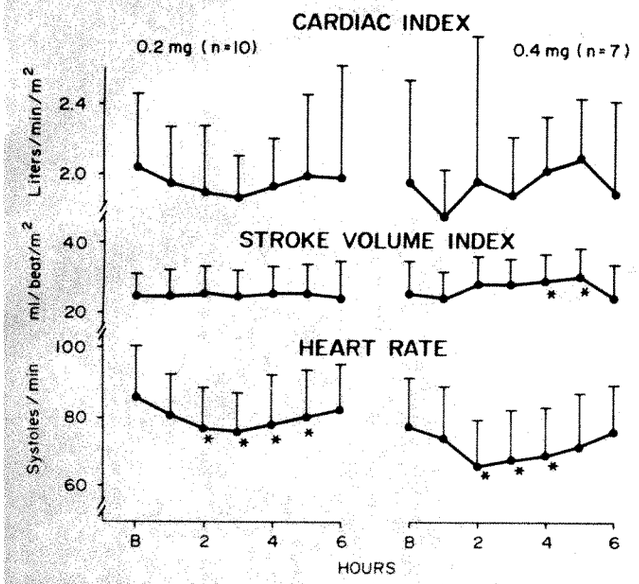



**FIGURE 4.** Clonidine did not alter cardiac index. Stroke volume increased slightly after the 0.4 mg dose, at 4 and 5 hours after drug administration. Both doses significantly lowered heart rate. Data are presented as mean ± 1 standard deviation. * $p < 0.05$; B = baseline control.

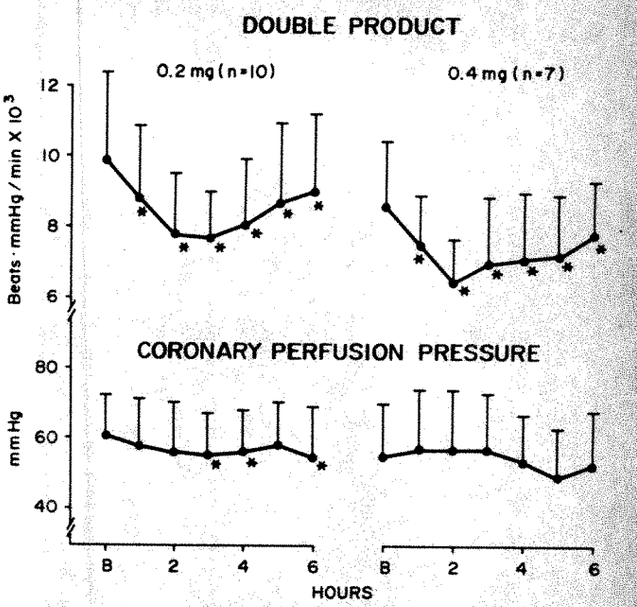



**FIGURE 5.** Double product, a calculated estimation of myocardial oxygen consumption, decreased substantially. Coronary perfusion pressure (diastolic blood pressure − pulmonary capillary wedge pressure) decreased slightly after 0.2 mg and was not altered by the higher dose. Data are presented as mean ± 1 standard deviation. *p $< 0.05$; B = baseline control.

3 patients after the lower dose. The decrease in systemic blood pressure was not accompanied by a comparable reduction of systemic vascular resistance. Pulmonary artery pressure decreased after clonidine administration; moreover, pulmonary vascular resistance decreased after both doses (Fig. 2). Pulmonary capillary wedge pressure decreased substantially (Fig. 3). Clonidine also evoked a significant negative chronotropic response; heart rate decreased 11 and 15% after the respective 0.2 and 0.4 mg doses (Fig. 4). Cardiac index was not significantly altered, and stroke volume increased only modestly 3 and 4 hours after the 0.4 mg dose. Since heart rate and systolic blood pressure both decreased, the double product, an estimate of myocardial oxygen consumption, decreased (Fig. 5). Coronary perfusion pressure (diastolic blood pressure minus pulmonary capillary wedge pressure) was slightly reduced with 0.2 mg, and was not altered by the higher dose. Diastolic perfusion time increased significantly after both doses (Table I). Isovolumic developed pressure/duration of isovolumic contraction and systolic time intervals were obtained in 6 patients. There was a dramatic reduction in isovolumic developed pressure/duration of isovolumic contraction for each patient after both doses (Fig. 6). Although the isovolumic developed pressure did not change significantly, duration of isovolumic contraction was prolonged substantially (Table I). The preejection period index lengthened significantly in each patient (Fig. 6). The ratio of the preejection period to left ventricular ejection time increased significantly after clonidine administration (Table I); this increase was secondary to a consistent prolongation of the preejection period and some shortening of the left ventricular ejection time (Table I).

All patients had somnolence after both doses of clonidine. Four patients noted dry mouths. Three patients has systemic hypotension; 1 of these patients had

**TABLE I Systolic and Diastolic Time Intervals, Isovolumic Developed Pressure (ΔP), and Isovolumic Contraction Time (Δt) Measurements Obtained at Baseline Control and 3 Hours After Clonidine (n = 6)**

| | Control | 0.2 mg | Control | 0.4 mg |
|---|---|---|---|---|
| $QS_2I$ (ms) | 528 ± 11 | 530 ± 14 | 521 ± 18 | 525 ± 18 |
| Diastolic time (ms) | 332 ± 63 | 422* ± 72 | 399 ± 109 | 528* ± 128 |
| LVETI (ms) | 368 ± 18 | 351 ± 21 | 356 ± 35 | 348 ± 32 |
| PEP/LVET | 0.56 ± 0.09 | 0.71* ± 0.16 | 0.53 ± 0.08 | 0.74* ± 0.13 |
| ΔP (mm Hg) | 63 ± 7 | 57 ± 13 | 59 ± 6 | 56 ± 7 |
| Δt (ms) | 91 ± 14 | 117* ± 21 | 89 ± 14 | 128* ± 18 |

Values are presented as mean ± 1 standard deviation.
LVETI = left ventricular ejection time index; PEP/LVET = preejection period/left ventricular ejection time; $QS_2I$ = duration of electromechanical systole index.

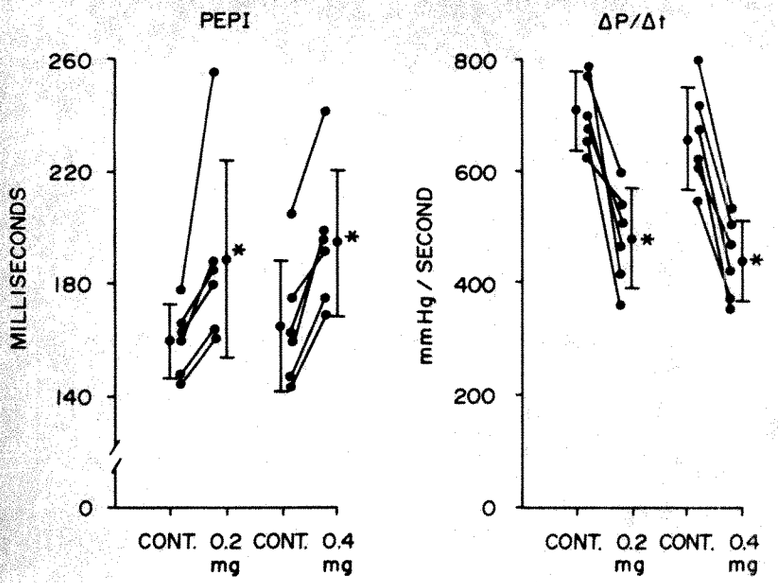



**FIGURE 6.** The preejection period index (PEPI) decreased substantially while the developed pressure during isovolumic contraction/isovolumic contraction time ($\Delta P/\Delta t$) decreased dramatically after clonidine. These changes in inotropic indexes occurred in each patient after both doses. Individual data (n = 6) are presented with brackets indicating ± 1 standard deviation and * $p < 0.05$; CONT. = control.

symptoms of postural hypotension. Intermittent right bundle branch block and first degree atrioventricular block was noted in 3 patients.

## Discussion

Clonidine evoked significant hemodynamic effects in these patients with CHF. This centrally acting vasodilator reduced systemic blood pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure. Heart rate decreased significantly after clonidine administration. Cardiac and stroke volume indexes did not change substantially. Clonidine appeared to favorably affect the myocardial oxygen supply-demand ratio by minimally altering coronary perfusion pressure, increasing diastolic perfusion time, and reducing the double product and inotropic state of the ventricle.

Since stroke volume changed little after clonidine administration, the decrease in systemic blood pressure was probably secondary to systemic arteriolar vasodilatation. The systemic arteriolar vasodilatation after clonidine administration was not reflected in changes in calculated systemic vascular resistance since cardiac output either did not change or tended to decrease. Systemic vascular resistance, the major contributing factor to the state of ventricular afterload, is generally used as an approximation of afterload. Ventricular wall tension during systole, formulated by the Laplace equation as ventricular systolic pressure × ventricular volume (at the designated pressure) ÷ wall thickness, is another expression (and probably a more precise one) of ventricular afterload. Clonidine substantially decreased systolic pressure. Its effects on ventricular volume were not measured; however, since ventricular systolic and diastolic pressures decreased, ventricular volume probably either decreased or remained unaltered. Therefore, using the ventricular wall tension formulation for afterload, clonidine probably elicited a reduction in ventricular afterload despite minimal to no changes in calculated systemic vascular resistance. Certainly, clonidine effected systemic arteriolar dilatation.

The inability of the failing ventricle to increase stroke volume in response to systemic arteriolar vasodilatation (or afterload reduction) may be caused by 1 or more factors, such as, excessive preload reduction, end-stage ventricular dysfunction, provocation of ventricular ischemia, or drug-related negative inotropic effects. The degree of preload reduction (approximated by the decrease in pulmonary capillary wedge pressure) was not excessive in this population, but quite similar to the reduction effected by some of the peripheral vasodilators.[12-14] None of the patients demonstrated end-stage ventricular dysfunction and, when subsequently tested, most responded favorably (augmentation of stroke volume and cardiac index) to various peripheral vasodilators. None of the patients demonstrated clinical evidence of "rebound" after discontinuation of their vasodilator therapy (≥48 hours prestudy), although more subtle hemodynamic changes cannot be excluded. It is unlikely that a mild "rebound" effect would account for the lack of augmentation of ventricular function; in this setting, the response to clonidine might be even more favorable. It is unlikely that clonidine elicited myocardial ischemia, since all but 1 of the subjects had angiographically normal coronary anatomy and, as previously indicated, clonidine tended to favorably alter the determinants of myocardial oxygen supply-demand. Clonidine did, however, decrease isovolumic developed pressure/duration of isovolumic contraction and increase the preejection period and preejection period/left ventricular ejection time in all subjects tested at both doses indicating that this compound evoked negative inotropic effects.

The decrease in isovolumic developed pressure/duration of isovolumic contraction with clonidine was secondary to lengthening of the isovolumic contraction time. The isovolumic contraction time and the pre-

ejection period by themselves correlate well with other indexes of inotropy, although independent changes of ventricular filling and systemic pressure can profoundly alter these variables.[8,10–12,15–17] That is, without a change in contractility, an isolated reduction of ventricular filling pressure can increase the preejection period and the isovolumic contraction time, and an isolated reduction of diastolic blood pressure would shorten them. While ventricular filling pressure did decrease with clonidine administration, this drug effected a parallel reduction in systemic diastolic pressure; the resultant isovolumic developed pressure remained unchanged. Therefore, the increase in preejection period and isovolumic contraction time and the consequent decrease in isovolumic developed pressure/duration of isovolumic contraction noted after clonidine administration indicates that this drug elicited a negative inotropic effect.

Clonidine's central site of action[6,7,18,19] probably accounts for most of the differences between the hemodynamic effects of this drug and those of the peripheral vasodilating agents. Clonidine's central effects elicit an overall reduction in sympathetic nervous system outflow to cardiovascular target organs including vascular smooth muscle (generalized vasodilation), specialized conduction tissue (negative chronotropy), and myocardium (resultant negative inotropy). Clonidine has been shown to reduce circulating cathecholamines and also retard renin release (resultant decrease in angiotensin activity).[20,21] The vasodilation is not likely to be a consequence of direct peripheral action, because its peripheral effects are predominantly vasopressor.[22] The negative chronotropic effects may be partly related to heightened parasympathetic activity, since clonidine appears to exert some parasympathomimetic effects.[23] The negative inotropic effects are, in large part, mediated indirectly through reduced myocardial adrenergic tone; clonidine itself does not directly reduce inotropy.[24]

Elevated sympathetic activity is an important compensatory mechanism in maintaining adequate cardiac function in moderate to severe CHF.[25] Although norepinephrine levels of neurons innervating the heart are reduced and the number and sensitivity of $beta_1$-adrenergic receptors are attenuated, cardiac function remains quite dependent on heightened sympathetic support.[25–27] Unlike clonidine, the peripheral vasodilators act primarily at vascular or peripheral vascular innervation sites and, therefore, do not elicit myocardial depression; for example, hydralazine induces vasodilation by acting directly on arterioles, and prazosin, an $alpha_1$-antagonist, postsynaptically blocks norepinephrine at vascular innervation sites. It is possible that clonidine's overall hemodynamic effects may be more favorable in patients with heart failure of lesser severity and with less dependence on sympathetic nervous system support.

The clinical role of clonidine in CHF is likely to be restricted because of its inability to improve ventricular systolic function. Since it reduces double product, inotropy, and pulmonary capillary wedge pressure and increases diastolic perfusion time, it may be useful in patients with ischemic cardiomyopathy who have high ventricular filling pressure with mild ventricular systolic dysfunction. While its role in the treatment of CHF is probably limited, clonidine is an unusual vasodilator which has provided valuable insights into the role of the central sympathetic nervous system in human CHF.

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## References

1. **Cohn JN.** Vasodilator therapy for heart failure: the influence of impedance on left ventricular performance. Circulation 1973;48:5–8.
2. **Mason DT.** Afterload reduction and cardiac performance: physiologic basis of systemic vasodilators as a new approach in the treatment of congestive heart failure. Am J Med 1978;65:106–125.
3. **Onesti G, Schwartz AM, Kim KE, Schwartz C, Brest AN.** Pharmacodynamic effects of a new antihypertensive drug, Catapres (ST-155). Circulation 1969;39:219–228.
4. **Muir AL, Burton JL, Lawrie DM.** Circulatory effects at rest and exercise of clonidine, an imidazoline derivative with hypotensive properties. Lancet 1969;2:181–184.
5. **McRaven DR, Kroetz FW, Kioschos JM, Kirkendall WM.** The effect of clonidine on hemodynamics in hypertensive patients. Am Heart J 1971; 81:482–489.
6. **Sharma JN, Sandrew B, Wang SC.** CNS site of clonidine induced hypotension: a micro iontophoretic study of cardiovascular neurons. Brain Res 1978;151:127–133.
7. **Tadepalli AS, Mills E.** Contribution of supracollicular structures of the brain to the central depression of cardiovascular function by clonidine. J Pharmacol Exp Ther 1978;205:693–701.
8. **Lewis RP, Leighton RF, Forester WF, Weissler AM.** Systolic time intervals. In: Noninvasive Cardiology. New York: Grune & Stratton, 1974:301–314.
9. **Boudoulas H, Lewis RP, Rittgers SE, Leier CV, Vasko JS.** Increased diastolic time: an important factor in the beneficial effect of propranolol in patients with coronary artery disease. J Cardiovasc Pharmacol 1979;1: 503–513.
10. **Diamond G, Forrester JS, Chatterjee K, Wegner S, Swan HJC.** Mean electromechanical $\Delta P/\Delta t$. Am J Cardiol 1972;30:338–342.
11. **Agress CM, Wegner S, Forrester JS, Chatterjee K, Parmley WW, Swan HJC.** An indirect method for evaluation of left ventricular function in acute myocardial infarction. Circulation 1972;46:291–297.
12. **Leier CV, Desch CE, Magorien RD, Triffon DW, Unverferth DV, Boudoulas H, Lewis RP.** Positive inotropic effects of hydralazine in human subjects: comparison with prazosin in the setting of congestive heart failure. Am J Cardiol 1980;46:1039–1044.
13. **Levine TB, Franciosa JA, Cohn JN.** Acute and long-term response to an oral converting enzyme inhibitor, captopril, in congestive heart failure. Circulation 1980;62:35–42.
14. **Leier CV, Bambach D, Thompson MJ, Cattaneo SM, Goldberg RJ, Unverferth DV.** Central and hemodynamic effects of intravenous isosorbide dinitrate, nitroglycerin and nitroprusside in patients with congestive heart failure. Am J Cardiol 1981;48:1115–1123.
15. **Talley RC, Meyer JF, McNay JL.** Evaluation of the preejection period as an estimation of myocardial contractility in dogs. Am J Cardiol 1971;27: 384–391.
16. **Metzger CC, Chough CB, Kroetz FW, Leonard JJ.** True isovolumic contraction time. Am J Cardiol 1970;25:434–442.
17. **Boudoulas H, Karayannacos PE, Lewis RP, Leier CV, Vasko JS.** Effect of afterload changes on left ventricular performance. Eur Congress Non-Invasive Cardiovasc Dynamics 1980;12:89–91.
18. **Kobinger W, Walland A.** Investigations into the mechanism of the hypotension effect of 2- (2,6-dichlorophenylamino)-2-imidazoline-HCl. Eur J Pharmacol 1967;2:115–162.
19. **Schmitt H, Schmitt H.** Localization of the hypotensive effects of 2(-2,6-dichlorophenylamino)-2-imidazoline-hydrochloride. Eur J Pharmacol 1969;6:8–12.
20. **Hokfelt B, Hedeland H, Hansson BG.** The effect of clonidine and penbutolol respectively on cathecholamines in blood and urine, plasma renin activity and urinary aldosterone in hypertensive patients. Arch Int Pharmacodyn Ther 1975;213:307–321.
21. **Reid IA, MacDonald DM, Pachnis B, Ganong WF.** Studies concerning the mechanism of supppession of renin secretion by clonidine. J Pharmacol Exp Ther 1975;192:713–721.
22. **Haeusler G.** Studies on the possible contribution of a peripheral presynaptic action of clonidine and dopamine to their vascular effects under in vivo conditions. N Sch Arch Pharmacol 1976;295:191–202.
23. **Lobson RD, Kaplan HR, LaForce S.** An investigation into the bradycardiac effects of St-155 2-(2,6-dichlorphenylamino)-2-imidazoline HCl in the anesthetized dog. J Pharmacol Exp Ther 1969;169:120–131.
24. **Motz W, Ippisch R, Strauer BE.** Clonidine exerts no direct myocardial depressant effect. Chest 1982;82:214.
25. **Vogel JHK, Chidsey CA.** Cardiac adrenergic activity in experimental heart failure assessed by beta receptor blockade. Am J Cardiol 1969;24:198–208.
26. **Chidsey CA, Sonnenblick E, Morrow AG, Braunwald E.** Norepinephrine stores and contractile force of papillary muscle from the failing human heart. Circulation 1966;33:43–51.
27. **Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WS, Lurie K, Billingham ME, Harrison DC, Stinson EB.** Decreased catecholamine sensitivity and $\beta$-adrenergic receptor density in failing human hearts. N Engl J Med 1982;307:205–211.

# In Vivo Quantitation of Platelet Deposition on Human Peripheral Arterial Bypass Grafts Using Indium-111–Labeled Platelets

## Effect of Dipyridamole and Aspirin

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**Indium-111–labeled autologous platelets, injected 48 hours after operation, were used to evaluate the thrombogenicity of prosthetic material and the effect of platelet inhibitor therapy in vivo. Dacron® double-velour (Microvel®) aortofemoral artery bifurcation grafts were placed in 16 patients and unilateral polytetrafluoroethylene femoropopliteal grafts were placed in 10 patients. Half the patients in each group received platelet inhibitors before operation (dipyridamole, 100 mg 4 times a day) and after operation (dipyridamole, 75 mg, and acetylsalicylic acid, 325 mg 3 times a day); the rest of the patients served as control subjects. Five-minute scintigrams of the graft region were taken with a gamma camera interfaced with a computer 48, 72, and 96 hours after injection of the labeled platelets. Platelet deposition was estimated from the radioactivities of the grafts and expressed as counts per 100 pixels per microcurie injected.**

**Dipyridamole and aspirin therapy significantly reduced the number of platelets deposited on Dacron grafts and prevented platelet accumulation over 3 days. With the small amount of platelet deposition on polytetrafluoroethylene femoropopliteal artery grafts even in control patients, platelet inhibitor therapy had no demonstrable effect on platelet deposition on these grafts.**

**It is concluded that (1) platelet deposition on vascular grafts in vivo can be quantitated by noninvasive methods, and (2) dipyridamole and aspirin therapy reduced platelet deposition on Dacron aortofemoral artery grafts.**

The success of vascular surgery is limited by the substantial number of arterial grafts in which the development of thrombosis results in occlusion.[1] Studies showing accelerated consumption of platelets in patients with vascular prostheses provide indirect evidence that platelets may be important in this process.[2] More direct evidence of increased platelet deposition on prosthetic grafts compared with normal vascular endothelium is derived from imaging techniques using indium-111–labeled platelets.[3,4] In animal studies platelet deposition can be quantitated by removing the graft and measuring its radioactivity in a gamma counter.[5] Currently, however, only a qualitative assessment of platelet deposition on arterial grafts in human subjects can be made from gamma camera images.

For evaluation of the thrombogenicity of prosthetic biomaterials and the effect of antithrombotic therapy in human subjects, methods of quantitation are necessary. We report herein a quantitative, noninvasive method of measuring platelet deposition in man and the effect of platelet inhibitor therapy on platelet deposition on both Dacron aortofemoral and polytetrafluoroethylene femoropopliteal grafts in patients in the days immediately after operation.

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**TABLE I Characteristics of Control and Treated Patients**

| | Bilateral Aortofemoral Grafts | | Unilateral Femoropopliteal Grafts | |
|---|---|---|---|---|
| | Control (n = 8) | Treated (n = 8) | Control (n = 5) | Treated (n = 5) |
| Sex | 4M 4F | 6M 2F | 5M 0F | 4M 1F |
| Age (yr)* | 58.6 ± 10.9 | 59.5 ± 7.8 | 70.2 ± 12.7 | 65.8 ± 7.4 |
| Height (cm)* | 164.8 ± 9.9 | 167.6 ± 13.3 | 165.1 ± 12.1 | 167.2 ± 6.5 |
| Weight (kg)* | 73.0 ± 15.8 | 72.9 ± 15.8 | 74.9 ± 7.2 | 81.5 ± 19.8 |

* Mean ± standard deviation.

## Methods

**Patients studied:** Twenty-six patients (19 men and 7 women) with a mean age of 62 years (range 44 to 79) were studied after informed consent had been obtained. Their characteristics are listed in Table I.

Sixteen patients underwent aortobifemoral operation with insertion of a 12 mm (n = 2), 14 mm (n = 11), or 16 mm (n = 3) preclotted Dacron double-velour (Microvel®) bifurcation graft. The diameter of the limbs of the graft was half that of the proximal anastomosis—that is, 6, 7, or 8 mm. The grafts extended from the bifurcation of the aorta to the common femoral artery on each side.

Ten additional patients underwent unilateral femoropopliteal artery operation in which an expanded polytetrafluoroethylene Gore-Tex® (W. L. Gore and Associates) graft of 6 mm diameter was anastomosed proximally to the common femoral artery and distally to the popliteal artery.

**Platelet labeling and imaging procedures:** Forty-eight hours postoperatively 43 ml of blood was collected in 7 ml of acid citrate dextrose (ACD) anticoagulant (Squibb). The platelets were separated and labeled with indium-111 oxine according to the method of Heaton et al.[6] Platelet-aggregation function is preserved by this method[7] as we have also observed in previous unpublished studies. After resuspension in 6 ml of plasma, the platelets were reinfused into the patient. The mean labeling efficiency was 68.5% (range 25 to 80) and the mean injected dose of radiolabel was 426 μCi (range 305 to 500).

On the fourth, fifth, and sixth days postoperatively, that is, 48, 72, and 96 hours after platelet labeling, scintigrams of the operated region were obtained with a gamma camera interfaced with a Medical Data Systems computer. The imaging period was exactly 5 minutes. A medium-energy parallel hole collimator was used and the gamma ray spectrometer was adjusted to include the 174 and 247 keV peaks of indium-111 radionuclide. The camera was placed as close to the skin as possible without actual contact, and the whole graft was included in the image.

**Qualitative analysis:** Two observers viewed all graft images blinded as to whether they were from treated or control patients. Visually enhanced radioactivity was recorded for a proximal or distal anastomosis if both observers agreed that the anastomosis had more radioactivity than the visually estimated average radioactivity of the remainder of the graft on at least 2 of the 3 days of imaging.

**Method of quantitation:** Platelet deposition on the graft was measured by outlining the image of the whole graft with a light pen. Anastomoses taken from a 2 mm segment at each end of the graft image were outlined separately. The computer-generated images were then used to quantitate counts per 100 pixels in the 3 regions of interest: proximal anastomosis, graft, and distal anastomosis. The differences in dose of radioactivity between patients were then normalized by dividing the activity by the injected activity corrected for decay. Hence, results are expressed as counts per 100 pixels per microcurie injected. Background radioactivity was estimated in patients with femoropopliteal artery operation by measuring the radioactivity from an area of thigh image 3 mm by 10 mm located 2 mm lateral to the graft. No background activity was measured on patients with aortofemoral artery grafts.

**Treatment groups:** *Treated patients:* Eight patients undergoing Dacron aortobifemoral (12 mm, n = 1; 14 mm, n = 5; 16 mm, n = 2) and 5 patients undergoing polytetrafluoroethylene femoropopliteal artery grafting procedures received platelet-inhibitor therapy based on a dosage schedule that improves a shortened platelet survival[8–11] and reduces aortocoronary vein bypass graft occlusion[12]: dipyridamole 100 mg was given orally 4 times in the 24 hours before operation, orally at 6 A.M. on the day of operation, and down the nasogastric tube at 1 hour after operation; then aspirin, 325 mg, in combination with dipyridamole, 75 mg, was administered 3 times a day starting down the nasogastric tube 8 hours postoperatively and orally when able.

*Control patients:* Eight patients undergoing Dacron aortobifemoral (12 mm, n = 1; 14 mm, n = 6, 16 mm, n = 1) and 5 patients undergoing polytetrafluoroethylene femoropopliteal artery grafting procedures received no platelet inhibitor drugs and served as the controls.

**Statistical analysis:** A close correlation existed between the measured activity in the right and left limbs of the Dacron

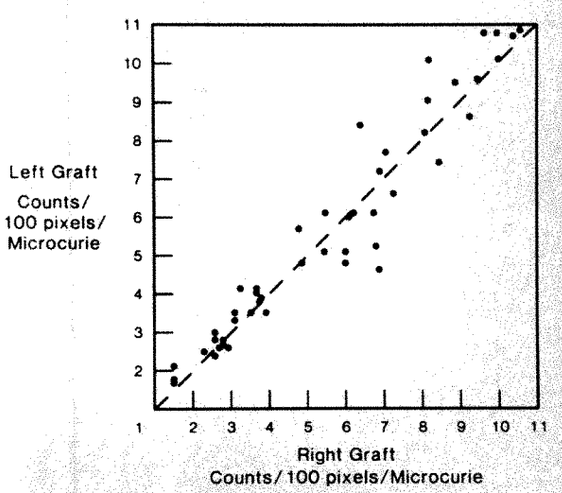



**FIGURE 1.** Correlation between radioactivity in right and left Dacron aortofemoral artery grafts on 3 consecutive days of imaging.

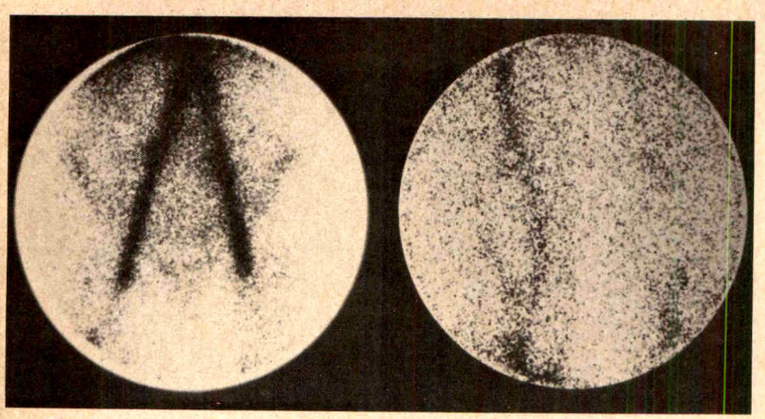


**FIGURE 2.** Examples of images obtained of aortofemoral artery Dacron bifurcation graft (**left panel**) and polytetrafluoroethylene femoropopliteal artery graft (left side of **right panel**) after injection of indium-111–labeled platelets.

aortofemoral artery grafts ($r = 0.96$, $n = 48$, $p < 0.001$) (Fig. 1). Therefore, in these patients the analysis was made on the mean value of the activities from the limbs of each graft. Results are expressed as median values, and the Mann-Whitney U test for comparison of independent samples was used for statistical analysis.

## Results

**Platelet deposition on Dacron and polytetrafluoroethylene grafts:** All grafts remained patent during the study, and they were all easily visualized as areas of increased radioactivity compared with the adjacent native artery (Fig. 2). Platelet activity was not uniform along the length of the graft. The Dacron aortofemoral artery grafts were more distinct against the background than were the polytetrafluoroethylene femoropopliteal artery grafts (Fig. 2); the less distinct polytetrafluoroethylene grafts had a median ratio of radioactivity of graft to adjacent thigh of 3.5 (range 2.9 to 6.0) to 1.

Platelet deposition in control patients was significantly greater on Dacron aortofemoral artery grafts than on polytetrafluoroethylene femoropopliteal artery grafts (see Fig. 3 for median values, range, and p values). Quantitative measurement of radioactivity of control grafts showed that only on the Dacron aortofemoral artery grafts was the radioactivity significantly increased at 96 hours compared with 48 hours for proximal anastomoses ($p < 0.01$) and for grafts ($p < 0.05$) (see Fig. 3, middle and upper panels, for values for Dacron).

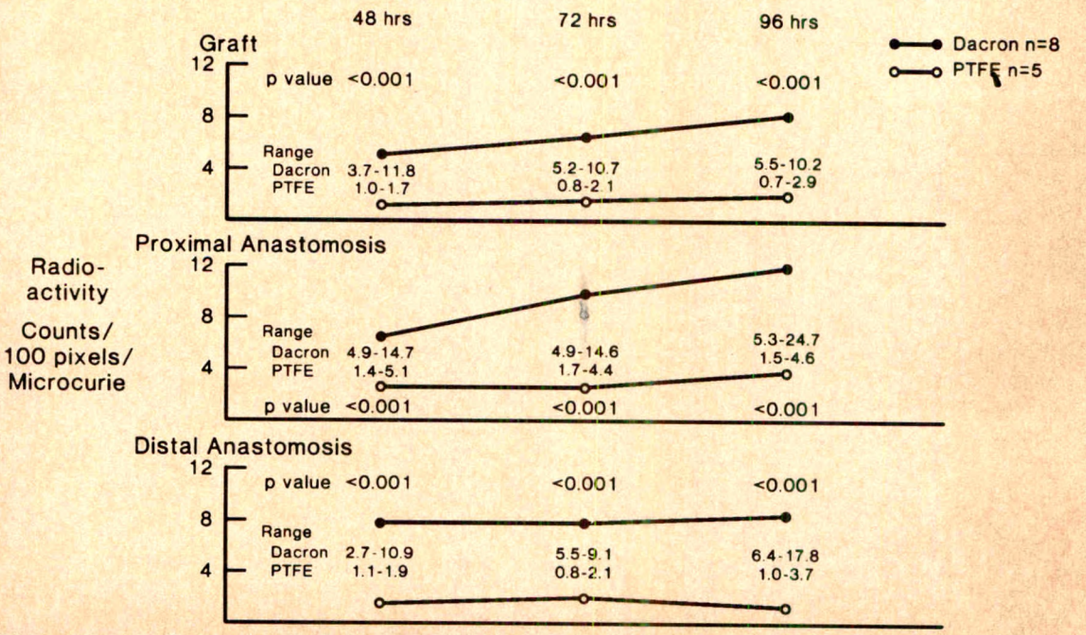



**FIGURE 3.** Graphs of median radioactivities of grafts (**upper panel**) and anastomoses (**middle and lower panels**) of Dacron aortofemoral artery prostheses compared with those of polytetrafluoroethylene (PTFE) femoropopliteal artery prostheses 48, 72, and 96 hours after injection of indium-111–labeled platelets in control patients. Ranges of radioactivity are listed in each panel for each of the 3 days.

As seen in Table II, visual estimation of enhanced radioactivity at the artery-graft anastomosis compared with the rest of the graft showed that approximately half of all anastomoses showed enhanced radioactivity.

**Effect of platelet inhibitor therapy:** *Dacron grafts:* Significantly fewer platelets were deposited on the aortofemoral artery grafts during each of the 3 days of imaging in treated patients (Fig. 4) compared with control patients. This effect was seen on the graft and on both proximal and distal anastomoses. There was no increase in radioactivity from 48 to 96 hours for proximal anastomoses or for grafts in the treated group.

*Polytetrafluoroethylene grafts:* No reduction in platelet deposition on the femoropopliteal grafts occurred in treated patients from the already low levels observed in control patients (Fig. 5).

**TABLE II Consensus Reading of Graft Images to Determine Visually Whether Artery-Graft Anastomoses Show Enhanced Radioactivity (ER) Compared With the Remainder of the Graft**

| | Anastomoses | | | |
|---|---|---|---|---|
| | Proximal | | Distal | |
| | Number | Number With ER | Number | Number With ER |
| Aortobifemoral grafts (Dacron) | | | | |
| Control | 8 | 5 | 16 | 8 |
| Treated | 8 | 3 | 16 | 6 |
| Femoropopliteal grafts (PTFE) | | | | |
| Control | 5 | 2 | 5 | 4 |
| Treated | 5 | 3 | 5 | 3 |
| Total | 26 | 13 | 42 | 21 |

PTFE = polytetrafluoroethylene.

## Discussion

**Quantitation of graft imaging:** In agreement with other investigators,[13,14] we found that both aortofemoral artery and femoropopliteal artery prosthetic grafts were readily visualized by the use of indium-111–labeled platelets. Platelet deposition along the graft was not uniform and especially tended to be enhanced at artery-graft anastomoses in both control and treated patients; this emphasizes the need to outline the whole graft, rather than just a section of it, and the need for quantifying platelet deposition.

The anastomoses might be expected to be regions of greater platelet accumulation compared with the rest of the graft. Both the presence of sutures and the differences in compliance between the native artery and the graft lead to turbulence which stimulates platelet adhesion. By injecting the platelets 48 hours after operation, postoperative bleeding does not contribute to any increase in extraluminal activity seen in these regions.

Any noninvasive method for measuring differences in radioactivity between patients encounters the problems of background blood pool activity and tissue attenuation. Our studies in dogs[5] demonstrated that as early as 3 hours after insertion the activity of a patent polytetrafluoroethylene graft can be up to 10 times that of the circulating blood. In addition, the half-life of indium-111 is short. By imaging 2 to 4 days after platelet

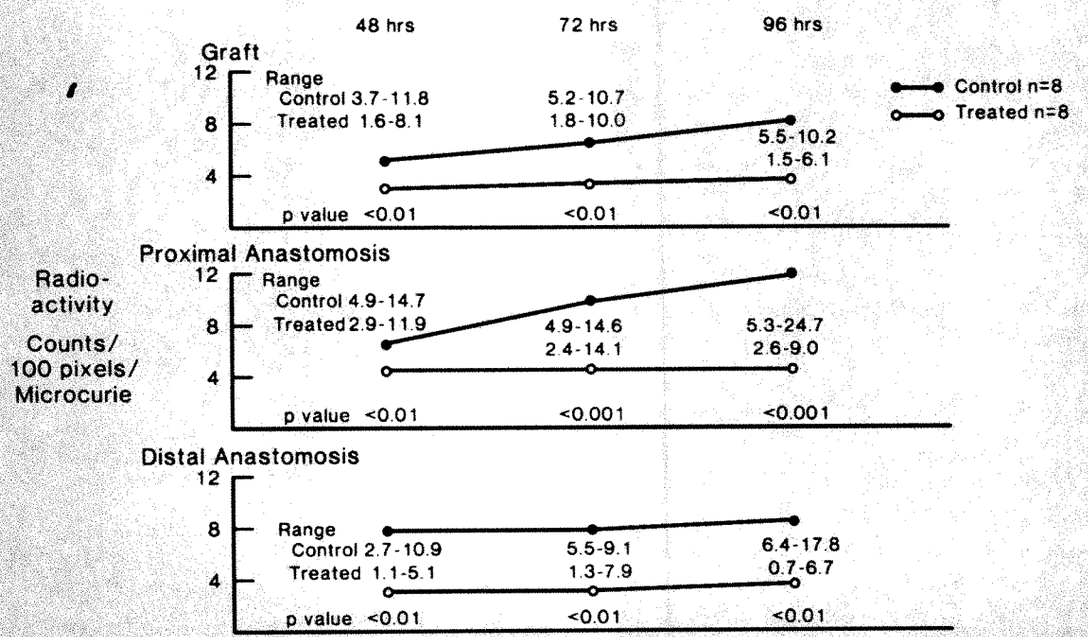



**FIGURE 4.** Graphs of median radioactivities of Dacron aortofemoral artery grafts (**upper panel**) and anastomoses (**middle and lower panels**) in control patients compared with those in patients treated with platelet inhibitors 48, 72, and 96 hours after injection of indium-111–labeled platelets. Ranges of radioactivity are listed in each panel for each of the 3 days.

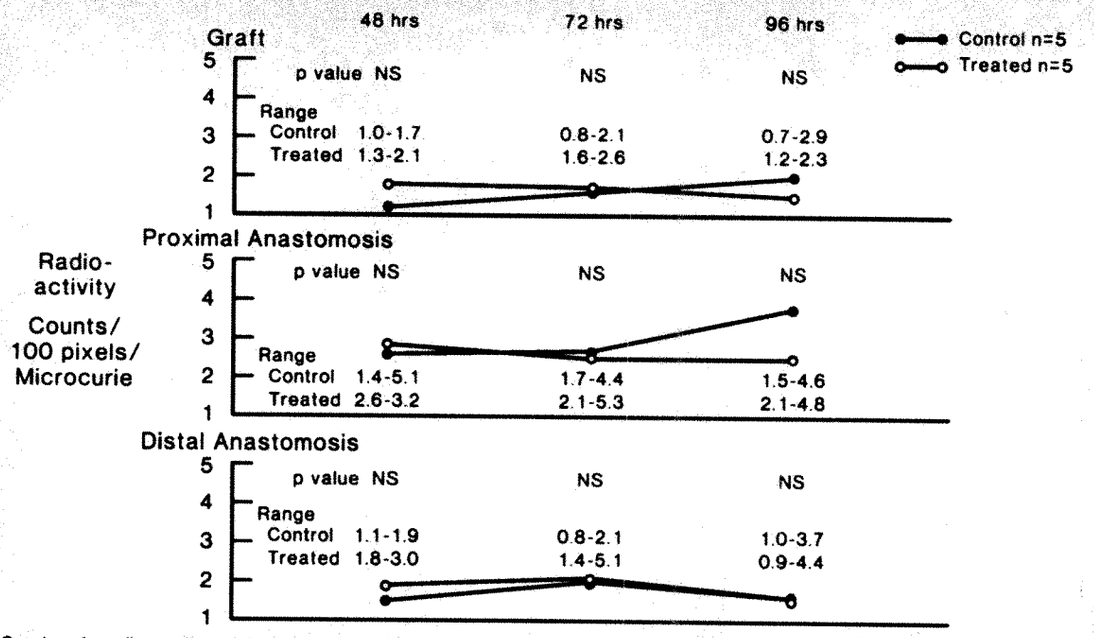



**FIGURE 5.** Graphs of median radioactivities of polytetrafluoroethylene femoropopliteal artery grafts (**upper panel**) and anastomoses (**middle and lower panels**) in control patients compared with those in patients treated with platelet inhibitors 48, 72, and 96 hours after injection of indium-111–labeled platelets. Ranges of radioactivity are listed in each panel for each of the 3 days.

labeling, the activity of the blood was at a minimum. Thus, the platelets deposited on the graft, rather than those circulating in the blood, contributed principally to the image of the graft.

Because the diameter of each femoropopliteal artery graft was the same and 7 of 8 of the aortofemoral artery grafts were also of equal diameter (the other differed by only 1 mm), the blood volumes per unit length of graft were similar in each group of patients. Furthermore, we standardized differences in blood pool activity between patients by incorporating the decay-corrected injected dose into the calculated figure.

The smaller diameter of the femoropopliteal artery grafts also results in less radioactivity per unit area of image, but this does not account for all of the difference in activity between the polytetrafluoroethylene and Dacron grafts. Platelets may be less adherent to polytetrafluoroethylene than to Dacron, as reported by others,[14] but this conclusion cannot be drawn from this study because the different graft materials were placed in different anatomic locations. Blood flow is greater in the aortofemoral position, so more platelets per unit of time come into contact with these grafts than with those in the femoropopliteal position.

Differences in tissue absorption of radioactivity may reduce the validity of comparisons between patients. The anatomic position of the aorta and the femoral artery remains relatively constant although the body habitus and amount of subcutaneous tissue may vary. The bifurcation of the aorta is anterior to the vertical column, and the graft passes anteriorly and inferiorly to just under the skin below the inguinal ligament. Because there was little difference in the body habitus between patients in the control and those in the treated groups (Table I), the variation in tissue attenuation was not large and would not be expected to account for the differences observed in the treated and control patients. By contrast, the anatomic position of the femoropopliteal artery grafts can vary, lying either subcutaneously or deep within the muscle layer. Furthermore, because the background tissue activity from the bone marrow may contribute to the measured activity of the graft, measurements of these grafts with low levels of platelet deposition may be subject to greater error.

To avoid these problems, some investigators[14] use activity ratios, comparing the grafts with the contralateral artery; such a comparison presupposes that in the contralateral artery the platelet endothelial interaction is normal, the luminal diameter is almost the same as that of the graft, and the blood flow is almost the same as that in the grafts, all of which assumptions are unlikely in a disease so diffuse as atherosclerosis.

**Platelet inhibitor therapy:** Dipyridamole and aspirin therapy has been shown to reduce platelet deposition and thrombosis in vein grafts both in dogs[15–17] and in patients.[12] In this study a similar drug regimen to that which showed a beneficial effect on the early occlusion rate of aortocoronary saphenous vein bypass grafts[12] in patients was associated with less deposition along the aortofemoral grafts, including the anastomoses, compared with the control grafts. However, the amount of platelet deposition on polytetrafluoroethylene femoropopliteal artery grafts was small, even in the control patients, and may have been below the level at which an effect of platelet inhibitor drugs could be observed.

Dipyridamole and its combination with aspirin takes advantage of the potentiation of the 2 drugs[9,10,18] with

interference of platelet metabolism at different levels,[9] allowing smaller dipyridamole doses with less expense and better tolerance, and enhanced dipyridamole absorption.[19] The maximal inhibition of platelet deposition in flowing blood in rabbits was obtained by using intermediate doses of dipyridamole (3 mg/kg) and aspirin (10 mg/kg).[18] The accumulation of salicylate may protect vascular prostacyclin from inhibition by aspirin.[20] Likewise, intermediate doses of dipyridamole (225 mg/day) and aspirin (1 g/day)[8,9,11] or larger doses of dipyridamole alone (400 mg/day)[10] prolong a shortened platelet survival in patients toward normal and appear to show in vivo suppression of platelet-arterial wall or platelet-prosthetic material interaction.[5,8–12,15] In our view suppression of this in vivo interaction in patients and animals is a good approach for choosing drugs and drug doses that may be of clinical antithrombotic benefit and value in a clinical trial.[12,21]

The clinical importance of this study is uncertain, although it suggests that this method may be an important way of screening for effective platelet inhibitor drugs in man. We have demonstrated that the percentage of injected dose per unit area, computed from the graft image, is a normalized variable that can be used to compare differences in platelet deposition. Longitudinal studies are necessary to establish whether late occlusion correlates with the level of platelet deposition observed in the early postoperative period.

## References


1. **Perdue GD, Smith RB, Veazey CR, Ansley JD.** Revascularization for severe limb ischemia. Arch Surg 1980;115:168–171.
2. **Harker LA, Slichter SJ, Sauvage LR.** Platelet consumption by arterial prostheses. Effects of endothelialization and pharmacologic inhibition of platelet function. Ann Surg 1977;186:594–601.
3. **Callow AD, Ledig CB, O'Donnell TF, Kelly JJ, Rosenthal D, Korwin S, Hotte C, Kahn PC, Vecchione JJ, Valeri CR.** A primate model for the study of the interaction of $^{111}$In-labeled baboon platelets with Dacron arterial prostheses. Ann Surg 1980;191:362–366.
4. **Agarwal KC, Wahner HW, Dewanjee MK, Fuster V, Puga FJ, Chesebro JH, Feldt RH.** Imaging of platelets in right sided extracardiac conduits in humans. J Nucl Med 1982;23:342–347.
5. **Pumphrey CW, Fuster V, Dewanjee M, Chesebro JH, Vlietstra RE, Kaye MP.** Comparison of the antithrombotic action of calcium antagonist drugs with dipyridamole in dogs. Am J Cardiol 1983;51:591–595.
6. **Heaton WA, Davis HH, Welch MJ, Mathias CJ, Joist JH, Sherman LA, Siegel BA.** Indium-111: a new radionuclide label for studying human platelet kinetics. Br J Haematol 1979;42:613–622.
7. **Joist JH, Baker RK, Thakar ML, Welch MJ.** Indium-111–labeled human platelets: uptake and loss of label and in vitro function of labeled platelets. J Lab Clin Med 1978;92:829–836.
8. **Fuster V, Chesebro JH, Frye RL, Elveback LR.** Platelet survival and the development of coronary artery disease in the young adult: effects of cigarette smoking, strong family history and medical therapy. Circulation 1981;63:546–551.
9. **Fuster V, Chesebro JH.** Pharmacologic effects of platelet-inhibitor drugs. Mayo Clin Proc 1981;56:185–195.
10. **Harker LA, Slichter SJ.** Studies of platelet fibrinogen kinetics in patients with prosthetic heart valves. N Engl J Med 1970;283:1302–1305.
11. **Ritchie JL, Harker LA.** Platelet and fibrinogen survival in coronary atherosclerosis. Response to medical and surgical therapy. Am J Cardiol 1977;39:595–598.
12. **Chesebro JH, Clements IP, Fuster V, Elveback LR, Smith HC, Bardsley WT, Frye RL, Holmes DR, Vlietstra RE, Pluth JR, Wallace RB, Puga FJ, Orszulak TA, Piehler JM, Schaff HV, Danielson GK.** A platelet-inhibitor-drug trial in coronary-artery bypass operations: benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein-graft patency. N Engl J Med 1982;307:73–78.
13. **Ritchie JL, Stratton JR, Thiele B, Hamilton GW, Warrick LN, Huang TW, Harker LA.** Indium-111 platelet imaging for detection of platelet deposition in abdominal aneurysms and prosthetic arterial grafts. Am J Cardiol 1981;47:882–889.
14. **McCollum CN, Norcott HC, Hawker RJ, Goldman M, Snape E, Drolc Z.** The influence of materials and platelet inhibition on the thrombogenicity of arterial grafts in man (abstr). Thromb Haemost 1981;46:101.
15. **Fuster V, Dewanjee MK, Kaye MP, Josa M, Metke MP, Chesebro JH.** Noninvasive radioisotope technique for detection of platelet deposition in coronary artery bypass grafts in dogs and its reduction with platelet inhibitors. Circulation 1979;60:1508–1512.
16. **Metke MP, Lie JT, Fuster V, Josa M, Kaye MP.** Reduction of intimal thickening in canine coronary bypass vein grafts with dipyridamole and aspirin. Am J Cardiol 1979;43:1144–1148.
17. **Josa M, Lie JT, Bianco RL, Kaye MP.** Reduction of thrombosis in canine coronary bypass vein with dipyridamole and aspirin. Am J Cardiol 1981;47:1248–1256.
18. **Mondada S, Korbut R.** Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. Lancet 1978;1:1286–1289.
19. **Tyce GM, Fuster V, Owen CA Jr.** Dipyridamole levels in plasma of man and other species. Res Commun Chem Pathol Pharmacol 1979;26:495–508.
20. **Dejana E, Cerletti C, DeCastellarnau C, Livio M, Galletti F, Latini R, DeGaetamo G.** Salicylate-aspirin interaction in the rat: evidence that salicylate accumulating during aspirin administration may protect vascular prostacyclin from aspirin-induced inhibition. J Clin Invest 1981;68:1108–1112.
21. **Chesebro JH, Fuster V.** Drug trials in prevention of occlusion of aorta-coronary artery vein grafts. J Thorac Cardiovasc Surg 1982;83:90–93.

# Cardiovascular Effects of a Newly Synthesized Cardiotonic Agent (TA-064) on Normal and Diseased Hearts

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**A new inotropic agent, TA-064, (−)-α-(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzylalcohol, was shown to have strong effects in experimental animals. Its effectiveness and associated adverse effects were tested in humans invasively (n = 6) and noninvasively (n = 17). Increasing doses of intravenous infusion (1, 2, and 4 μg/kg/min) increased plasma levels to 15, 35, and 82 ng/ml, respectively, resulting in marked increases in the peak rate of left ventricular pressure rise (dP/dt) (1,450 ± 63 to 3,042 ± 349 mm Hg/s) (mean ± standard error of the mean [SEM], p <0.01) and the ratio of dP/dt to left ventricular pressure at a developed pressure of 40 mm Hg (25 ± 3 to 39 ± 2 $s^{-1}$) (p <0.01), with a reduction in left ventricular end-diastolic pressure (12 ± 2 to 4 ± 1 mm Hg) (p <0.01). Minimal or no changes were seen in heart rate and left ventricular systolic pressure. After a single oral dose (10 mg), the plasma level reached its peak at 90 minutes (16 ± 9 ng/ml, n = 17). A positive inotropic effect was confirmed echocardiographically in both healthy volunteers (n = 8) and patients with congestive heart failure (CHF) (n = 9) who were maximally treated with conventional regimens: increase in mean velocity of circumferential fiber shortening (healthy volunteers: 1.29 ± 0.05 to 1.60 ± 0.11 circ/s [p <0.05]; patients with CHF: 0.69 ± 0.08 to 0.93 ± 0.09 circ/s [p <0.01]), ejection fraction (healthy volunteers: 68 ± 2 to 75 ± 2% [p <0.05], patients with CHF: 37 ± 4 to 45 ± 5% [p <0.01]) without change in heart rate. The cardiac index was increased only in the CHF group (2.71 ± 0.22 to 3.21 ± 0.24 liters/min/$m^2$) (p <0.05). No significant untoward effects were observed. Thus TA-064 is a potent inotropic agent and can be used either parenterally or orally. Salutary effects can be expected in patients with congestive heart failure who are treated with digitalis and diuretic agents.**

The goal of medical management of the patient with severe heart failure refractory to the conventional regimen of digitalis and diuretic agents is to improve the quality of life and prolong it. Intensive efforts have been directed toward development of efficacious and safe drugs for ambulatory use to minimize disabling symptoms of dyspnea and fatigue. To attain this goal, various combination therapies of digitalis and afterload or preload-reducing agents have been used to increase cardiac pump function with some success.[1–5] However, the clinical use of digitalis is limited because of its narrow therapeutic range and serious arrhythmogenic effects in patients with severe heart failure; only a limited number of inotropic agents are available for ambulatory therapy.[6–10] The catecholamines dopamine and dobutamine, which have a strong positive inotropic effect, cannot be used because of their lack of oral effectiveness. Thus, an orally effective new class of inotropic agent is necessary. To this end, various inotropic agents have been developed and are currently under investigation.[6–14]

TA-064 was synthesized recently at Tanabe Seiyaku, Osaka, Japan (Fig. 1). It has been shown to have a strong

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positive inotropic effect. In the experimental animal, when given orally, TA-064 is quickly absorbed from the gastrointestinal tract and its inotropic effect lasts for 7 hours.[15-17] Its oral effectiveness and lack of significant toxicity in the experimental animal makes it potentially important for clinical use as a cardiotonic agent in the therapy of human heart failure.

In this report we describe the acute cardiovascular effects of the new cardiotonic agent TA-064 on normal and diseased human hearts.

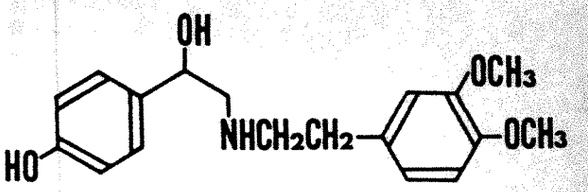
## Methods

This study comprises 3 parts: (1) the dose response effects of intravenous TA-064 on hemodynamic variables (n = 6), and (2) the echocardiographic effects of TA-064 given orally to healthy volunteers (n = 8), and (3) to patients with congestive heart failure (CHF) (n = 9).

### Dose Response of Intravenous TA-064

The purpose of this part of the study is to examine the hemodynamic effects of intravenous TA-064 precisely and the dose response of positive inotropic and chronotropic effects, if any. Six patients were selected and agreed to participate in this study on the basis of mild valvular disease or a normal heart confirmed by routine diagnostic cardiac catheterization; 1 had mitral regurgitation, 1 had mitral and aortic regurgitation, and 4 other patients had undergone routine diagnostic catheterization for angina pectoris and were proven to have normal coronaries. All patients were placed in class I to II, according to the New York Heart Association functional classification scheme. The ages of the patients ranged from 32 to 65 years, with a mean of 47.3. The catheterization was performed using the brachial approach with the patient in the fasting state after oral premedication with 5 mg of diazepam; all medications except digitalis were withheld for 10 to 16 hours before the procedure. Left ventricular pressure was recorded in each patient with a high-fidelity micromanometer-tipped angiocatheter (Mikrotip, model PC-471 or 481, Millar Instruments) at high and low gains; left ventricular dP/dt (mm Hg/s) was recorded simultaneously. Zero level was calibrated electronically by a transducer control unit (model TCB-100, Millar Instruments) before the insertion of the catheter, and the zero shift was adjusted to the level of mid-chest position by way of the water-filled system using a Statham P23Db pressure transducer. Right ventricular, pulmonary arterial, and pulmonary capillary wedge pressure were recorded with use of a water-filled system (Swan-Ganz thermodilution catheter, Edwards Laboratories). Cardiac output was measured by the thermodilution technique (model 9510-A, Cardiac Output Computer, Edwards Laboratories). Photographic recordings were obtained at paper speed of 25, 50, and 100 mm/s in each patient, using an 8-channel optical recording system (model 4588D, Hewlett-Packard). Five consecutive complexes in cases of normal sinus rhythm and 10 consecutive complexes in patients with atrial fibrillation were averaged for determination of the pressure, peak rate of left ventricular pressure increase (dP/dt), and the ratio of left ventricular dP/dt at a developed pressure of 40 mm Hg (dP/dt/DP40) ($s^{-1}$).[18] Premature complexes and immediate postpremature complexes were discarded.

Upon completion of baseline measurements, TA-064 was administered intravenously, starting at 1 μg/kg/min with graded increments to 2 and 4 μg/kg/min for a 10-minute infusion period, respectively. At each period, hemodynamic measurements were repeated. Electrocardiogram and the patients' clinical condition were monitored continuously throughout this study.




(—) -α- (3,4 - dimethoxy phenethylamino methyl) - 4 - hydroxybenzylalcohol

**FIGURE 1.** Chemical structure and name of TA-064.

### Effects of Oral TA-064: Echocardiographic Study

**Effects on the normal heart:** After informed consent was obtained, 8 healthy male medical students participated in this study (age range from 18 to 28 years, mean 23.3). After 30 minutes of bed rest, an echocardiographic study was performed in the standard method with the patient in the supine position, with a 78° phased electronic sector scanner with 32 elements (Toshiba SSH-11A), using a 2.4 MHz transducer placed in the third or fourth intercostal space. While cardiac motion was observed in 2-dimensional long- and short-axis images, the M-mode echocardiogram was displayed on a fiberoptic recorder (Honeywell model 1218A) at a paper speed of 100 mm/s with simultaneous electrocardiographic, carotid pulse, and phonocardiographic recordings. Echocardiographic measurements were made according to the recommendation by the committee on M-mode standardization of the American Society of Echocardiography.[19] Left ventricular ejection time was obtained from the carotid pulse tracing. After the baseline echocardiogram was obtained, 1 single dose (10 mg) of TA-064 was given orally and echocardiographic study was repeated 30, 45, 60, 90, and 120 minutes after its administration. Blood pressure was automatically measured by cuff method (sphygmomanometer BP-203X, Nihon Kohrin, Tokyo) throughout this study. Fractional shortening (FS) was calculated as FS = (Dd − Ds)/Dd, where Dd = internal dimension of the left ventricle at end-diastole, and Ds = internal dimension of the left ventricle at end-systole. Left ventricular volume at end-diastole and end-systole was calculated according to the method of Teichholz et al[20] as V = (7.0/2.4 + D)($D^3$), where V = volume and D = the internal dimension of the left ventricle at end-diastole and end-systole. Ejection fraction, mean velocity of circumferential fiber shortening,[21] cardiac output, and systemic vascular resistance were also calculated by the standard formulas. Five consecutive beats in normal sinus rhythm were averaged for the echocardiographic measurements.

**Effects on diseased hearts with CHF:** This part of the study was conducted to determine whether positive inotropic effects demonstrated in normal hearts can be elicited in diseased hearts as well by a single oral dose (10 mg) of TA-064. It is not our intention to demonstrate the maximal effect of TA-064. Since we chose to use M-mode echocardiograms to assess left ventricular function, 9 patients with diseased hearts were selected on the basis of uniform hypocontraction of the left ventricle without any segmental dyskinetic area. All had CHF (New York Heart Association functional class II to IV) after full medical treatment with bed rest, low sodium diet, digitalis, diuretics, and other preload- and afterload-reducing agents. The causes of CHF were peripartum cardiomyopathy, terminal stage of syphilitic aortic regurgitation, and ischemic cardiomyopathy, 1 case each; the other 6 patients had con-

**TABLE I Dose Response Effects of Intravenous TA-064 on Hemodynamic Variables**

| | HR | LVS | LVED | PAM | CI | TPR | Peak (+)dP/dt | dP/dt/ DP40 | SI | SWI | LVMWI | TA-064 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 73.1 ±5.1 | 133 ±7 | 11.7 ±1.9 | 15.3 ±0.9 | 3.29 ±0.43 | 233 ±21 | 1450 ±63 | 25.0 ±2.9 | 44.5 ±3.2 | 51.0 ±3.8 | 3.77 ±0.50 | 0 |
| 1 μg/kg/min | 74.0 ±4.2 | 133 ±6 | 8.3 ±1.3* | 13.2 ±0.5* | 3.28 ±0.37 | 201 ±19* | 1690 ±128 | 29.2 ±3.3 | 44.0 ±3.2 | 50.8 ±3.7 | 3.78 ±0.41 | 14.7 |
| 2 μg/kg/min | 79.7 ±3.4 | 135 ±6 | 5.7 ±0.7† | 11.7 ±0.3† | 3.42 ±0.35 | 169 ±14† | 2153 ±121† | 32.0 ±1.5* | 43.3 ±3.4 | 52.9 ±4.2 | 4.22 ±0.41 | 34.9 |
| 4 μg/kg/min | 94.3 ±4.2† | 133 ±4 | 4.2 ±0.5† | 10.7 ±0.3† | 3.55 ±0.53 | 157 ±21† | 3042 ±349† | 38.9 ±1.7† | 38.5 ±5.2 | 46.9 ±6.6 | 4.38 ±0.64 | 81.7 |

Mean ± SEM (n = 6).
* $p < 0.05$.
† $p < 0.01$.
CI = cardiac index (liters/min/m$^2$); HR = heart rate (beats/min); LVED = left ventricular end-diastolic pressure (mm Hg); LVMWI = left ventricular minute work index (kg·m/min/m$^2$); LVS = left ventricular systolic pressure (mm Hg); PAM = mean pulmonary artery pressure (mm Hg); SI = stroke index (ml/m$^2$); SWI = stroke work index (g·m/min/m$^2$).

gestive cardiomyopathy. All cases except 1 with congestive cardiomyopathy (Patient 4, Table III) were studied by cardiac catheterization, including left ventriculography and coronary cineangiography. The diagnosis was based not only on the findings of cardiac catheterization but also on the typical clinical presentation and echocardiographic findings, according to the criteria of the National Study Group of Idiopathic Cardiomyopathies of Japan[22] after modification of the criteria of Goodwin and Oakley.[23] The method of this part of the study is almost identical to that described in the previous section on the normal heart. In summary, after informed consent was obtained, the patients were evaluated in the postabsorptive state, 3 to 5 hours after receiving their daily oral dose of digitalis, diuretics, or other conventional regimens. Bed rest of at least 30 minutes stabilized blood pressure and heart rate. After baseline echocardiographic measurements were obtained, the patient was given 1 single dose (10 mg) of TA-064 orally. Echocardiographic examination was repeated 30, 45, 60, 90, 120, and 180 minutes later. Five consecutive beats in cases of normal sinus rhythm and 7 consecutive beats in cases of atrial fibrillation were averaged for the determination of echocardiographic variables. Premature and postpremature beats were discarded.

In each study period, peripheral venous blood samples were obtained for the determination of plasma catecholamine levels and TA-064 concentrations. Plasma catecholamine levels were measured fluorimetrically by high performance liquid chromatography using the trihydroxyindole (THI) method.[24] TA-064 was measured using selected ion monitoring technique by gas chromatography mass spectrometry. We used Student's

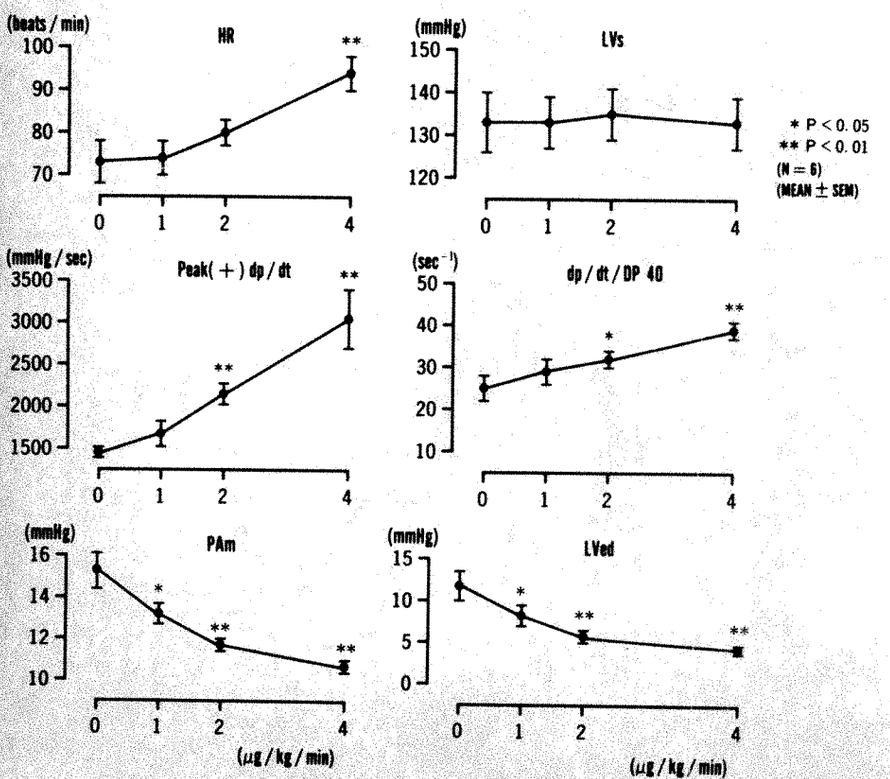



**FIGURE 2.** Dose response effects of intravenous TA-064 upon hemodynamic variables. Peak (+) dP/dt and dP/dt/DP40 were significantly increased even at the dose of 2 μg/kg/min, where the heart rate (HR) and left ventricular systolic pressure (LVs) remained unchanged, and continued to increase at higher doses of TA-064. Mean pulmonary arterial (PAm) and left ventricular end-diastolic pressure (LVed) decreased. Only at a high dose of TA-064 (4 μg/kg/min) did the heart rate increase significantly.

$t$ test for paired data for the comparison of measurements before and after TA-064 administration. All group data in this report are presented as mean ± SEM.

## Results

**Dose response effects of intravenous TA-064 on hemodynamic variables (Table I):** Intravenous infusion of TA-064 with increments to 1, 2, and 4 μg/kg/min increased the mean plasma concentration of TA-064 to 14.7, 34.9, and 81.7 ng/ml, respectively. Left ventricular systolic pressure was not altered. Only with a high dose of TA-064 (4 μg/kg/min) was the heart rate increased significantly. Peak (+) dP/dt and dP/dt/DP40 were significantly increased even at the dose of 2 μg/kg/min, at which heart rate and left ventricular systolic pressure remained unchanged, and continued to increase at higher doses of TA-064 (Table I, Fig. 2). Mean pulmonary and left ventricular end-diastolic pressures were decreased significantly, depending on the dose of TA-064. The cardiac index was not increased. Total pulmonary vascular resistance was significantly reduced. The positive inotropic effect of TA-064 becomes more apparent when the left ventricular end-diastolic pressure-left ventricular work index relation is studied (Fig. 3). In all patients the pressure-work relation was shifted upward toward the left, suggesting an increased inotropic effect of TA-064.

**Effects of oral TA-064 on the normal heart:** After oral administration, TA-064 appeared in the blood at 30 minutes, reached its peak (12.6 ± 2.2 ng/ml) at 90 minutes, and remained in the plasma over 120 minutes. Baseline echocardiographic data and their response to oral TA-064 are presented in Table II. With oral TA-064, the heart rate was increased slightly (11%, 61.1 ± 1.9 to 67.7 ± 2.5 beats/min, $p < 0.01$). Systolic blood pressure increased (14%, 118 ± 4 to 135 ± 4 mm Hg, $p < 0.01$) and diastolic pressure showed a trend toward a decrease, resulting in unchanged mean blood pressure. Left ventricular end-diastolic volume remained unaltered, whereas left ventricular end-systolic volume was significantly reduced (23%, 31 ± 3 to 24 ± 2 ml, $p < 0.05$).

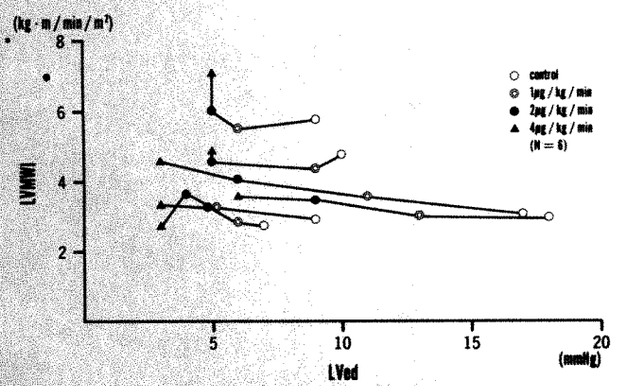
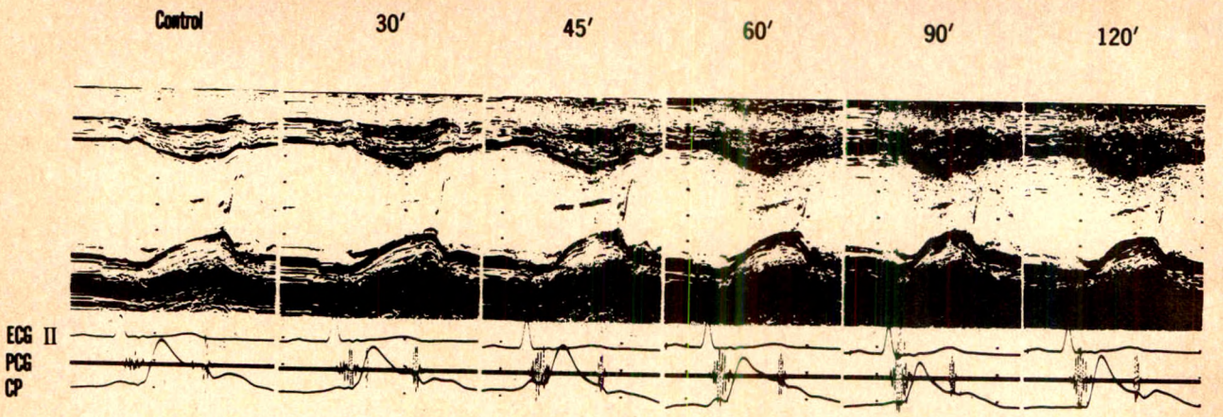



**FIGURE 3.** Dose response effects of intravenous TA-064 and the left ventricular end-diastolic pressure (LVed) left ventricular minute work index (LVMWI) relation. With increasing doses of intravenous TA-064, the pressure-work relation was shifted upward toward the left, suggesting an increased inotropic effect of TA-064.

**TABLE II Echocardiographic Variables and Their Responses to Oral TA-064 in Healthy Volunteers (Body Surface Area 1.70 ± 0.60 m²)**

| | HR | SBP | DBP | Dd | Ds | FS | LVEDV | LVESV | SV | CI | TSR | EF | Mean Vcf | TA-064 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 61.1 ±1.9 | 118 ±4 | 60 ±3 | 4.6 ±0.1 | 2.8 ±0.1 | 0.38 ±0.01 | 96 ±6 | 31 ±3 | 65 ±4 | 2.31 ±0.13 | 1,654 ±81 | 67.7 ±1.8 | 1.29 ±0.05 | 0 |
| 30 minutes | 62.1 ±2.3 | 122 ±4 | 62 ±4 | 4.5 ±0.1 | 2.8 ±0.1 | 0.38 ±0.02 | 95 ±7 | 31 ±3 | 64 ±5 | 2.29 ±0.13 | 1,706 ±99 | 67.5 ±2.6 | 1.38 ±0.07* | 5.6 ±1.3 |
| 45 minutes | 63.0 ±2.0 | 126 ±4* | 60 ±4 | 4.5 ±0.1 | 2.7 ±0.1† | 0.41 ±0.02 | 94 ±6 | 27 ±3† | 67 ±5 | 2.48 ±0.19 | 1,617 ±125 | 71.6 ±2.5 | 1.49 ±0.09† | 9.2 ±0.9 |
| 60 minutes | 64.4 ±1.9* | 131 ±4* | 58 ±5 | 4.6 ±0.1 | 2.7 ±0.1* | 0.42 ±0.02† | 96 ±7 | 27 ±3* | 70 ±5 | 2.65 ±0.24 | 1,521 ±124 | 72.4 ±2.3* | 1.51 ±0.10† | 12.4 ±1.4 |
| 90 minutes | 66.2 ±2.5* | 135 ±4† | 56 ±4 | 4.5 ±0.2 | 2.5 ±0.1* | 0.44 ±0.02* | 95 ±9 | 24 ±2* | 71 ±8 | 2.76 ±0.31 | 1,508 ±133 | 74.6 ±2.2* | 1.60 ±0.11* | 12.6 ±2.2 |
| 120 minutes | 67.7 ±2.5†. | 133 ±4† | 65 ±4 | 4.5 ±0.2 | 2.6 ±0.1† | 0.42 ±0.02 | 92 ± 6 | 25 ± 3† | 67 ±5 | 2.67 ±0.22 | 1,576 ±106 | 72.9 ±1.9* | 1.56 ±0.09† | 9.6 ±1.1 |

Mean ± SEM ($n = 8$).
* $p < 0.05$.
† $p < 0.01$.
CI = cardiac index (liters/min/m²); DBP = diastolic blood pressure (mm Hg); Dd = internal dimension of the left ventricle at end-diastole (cm); Ds = internal dimension of the left ventricle at end-systole (cm); EF = ejection fraction (%); FS = fractional shortening; HR = heart rate (beats/min); LVEDV = left ventricular end-diastolic volume (ml); LVESV = left ventricular end-systolic volume (ml); SBP = systolic blood pressure (mm Hg); SV = stroke volume (ml); TSR = total systemic vascular resistance (dynes s cm⁻⁵); Vcf = velocity of circumferential fiber shortening (circ/s).




| Blood level (ng/ml) | 0 | 5.1 | 9.6 | 11.9 | 25.4 | 15.0 |
|---|---|---|---|---|---|---|
| HR (BP) | 58 (120/63) | 57 (118/60) | 59 (128/53) | 64 (129/53) | 71 (141/63) | 71 (132/55) |
| Dd (cm) | 4.6 | 4.5 | 4.5 | 4.7 | 4.4 | 4.5 |
| Ds (cm) | 2.9 | 2.8 | 2.8 | 2.5 | 2.5 | 2.7 |
| EF (%) | 67 | 68 | 68 | 78 | 75 | 71 |
| meanVcf (circ/sec) | 1.37 | 1.44 | 1.56 | 1.84 | 1.92 | 1.70 |

**FIGURE 4.** Echocardiographic response of oral TA-064 in normal volunteers. A representative case is shown. TA-064 appeared in the plasma 30 minutes after oral administration and reached its peak at 90 minutes. With increasing plasma concentration of TA-064, augmented left ventricular contraction is evident in the echocardiographic tracing. CP = carotid pulse tracing; Dd = end-diastolic diameter; Ds = end-systolic diameter; ECG = electrocardiogram; EF = ejection fraction; HR = heart rate; PCG = phonocardiogram; Vcf = velocity of circumferential fiber shortening.

Cardiac index showed a trend toward an increase, and total systemic vascular resistance a trend toward a decrease. The ejection fraction was significantly increased (10%, 67.7 ± 1.8 to 74.6 ± 2.2%, $p < 0.05$) and mean velocity of circumferential fiber shortening was significantly increased 30 minutes after oral administration of TA-064 and continued to increase (24%, 1.29 ± 0.05 to 1.60 ± 0.11 circ/s, $p < 0.05$). These inotropic effects continued over 120 minutes. A representative case is shown in Figure 4. With increasing plasma concentration of TA-064, augmented left ventricular contraction is evident in the echocardiographic tracings.

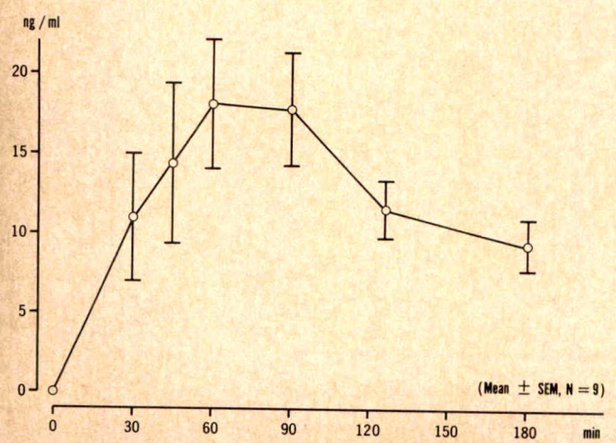



**FIGURE 5.** Plasma concentration of TA-064 in patients with CHF after oral administration of TA-064. TA-064 appeared in the plasma at 30 minutes and reached its peak at 60 to 90 minutes.

**Effects of oral TA-064 on diseased hearts with CHF:** Clinical characteristics and echocardiographic responses are presented in Table III. The plasma concentration of TA-064 is shown in Figure 5. After a single oral dose, plasma TA-064 appeared at 30 minutes and reached its peak at 60 as well as 90 minutes (17.7 ± 3.8 ng/ml); it remained until 180 minutes. In patients with CHF, heart rate and mean blood pressure were not changed, while systolic blood pressure increased only at 180 minutes (107 ± 9 to 117 ± 10 mm Hg, $p < 0.05$) with 10 mg of oral TA-064. Left ventricular end-systolic volume was significantly reduced while left ventricular end-diastolic volume was unchanged, resulting in increased stroke volume (21%, 57 ± 6 to 69 ± 7 ml, $p < 0.01$). The cardiac index increased significantly (18%, 2.71 ± 0.22 to 3.21 ± 0.24 liters/min/$m^2$, $p < 0.05$). Total systemic vascular resistance showed a trend toward a decrease. Ejection fraction increased significantly (21%, 37.1 ± 4.3 to 45.0 ± 4.6%, $p < 0.01$). Mean velocity of circumferential fiber shortening also increased significantly (35%, 0.69 ± 0.08 to 0.93 ± 0.09 circ/s, $p < 0.01$) (Fig. 6).

Findings from individual case examinations indicated the plasma level of TA-064 at 90 minutes did not reach

**TABLE III Clinical Characteristics and Echocardiographic Responses to Oral TA-064 in Patients With CHF (Body Surface Area 1.53 ± 0.51 $m^2$)**

| Patient | Age (yr) & Sex | Dx | NYHA | | HR | SBP | DBP | Dd | Ds | FS | LVEDV | LVESV | SV | CI | TSR | EF | Mean Vcf | TA-064 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 57F | CCM | III | Before | 63.8 | 107 | 64 | 4.8 | 3.8 | 0.21 | 108 | 62 | 46 | 2.03 | 2,156 | 42.3 | 0.87 | 0 |
| | | | | After* | 75.0 | 129 | 74 | 5.0 | 3.7 | 0.26 | 118 | 58 | 60 | 3.15 | 1,637 | 50.9 | 1.24 | 27.4 |
| 2 | 45F | CCM | III | Before | 73.2 | 95 | 52 | 5.2 | 4.3 | 0.17 | 130 | 83 | 46 | 2.50 | 1,560 | 35.8 | 0.60 | 0 |
| | | | | After* | 70.6 | 96 | 60 | 4.8 | 3.8 | 0.21 | 108 | 62 | 45 | 2.34 | 1,811 | 41.9 | 0.74 | 9.3 |
| 3 | 31F | PPCM | II | Before | 76.9 | 101 | 78 | 5.2 | 3.6 | 0.31 | 130 | 54 | 75 | 3.38 | 1,186 | 58.0 | 1.14 | 0 |
| | | | | After* | 70.6 | 107 | 80 | 5.2 | 3.4 | 0.35 | 130 | 47 | 82 | 3.39 | 1,227 | 63.4 | 1.33 | 5.2 |
| 4 | 44F | CCM | II | Before | 64.8 | 108 | 68 | 6.0 | 4.6 | 0.23 | 180 | 97 | 83 | 3.29 | 1,212 | 45.9 | 0.76 | 0 |
| | | | | After* | 61.8 | 126 | 62 | 5.8 | 3.8 | 0.34 | 167 | 62 | 105 | 3.96 | 1,030 | 62.8 | 1.13 | 23.6 |
| 5 | 49M | CCM | III | Before | 81.7 | 93 | 58 | 5.0 | 4.5 | 0.10 | 119 | 92 | 27 | 1.53 | 2,532 | 22.5 | 0.47 | 0 |
| | | | | After* | 76.7 | 102 | 62 | 5.1 | 4.3 | 0.16 | 123 | 81 | 41 | 2.21 | 1,896 | 33.7 | 0.72 | 22.5 |
| 6 | 70M | AR | IV | Before | 57.1 | 175 | 19 | 5.6 | 4.1 | 0.27 | 154 | 74 | 80 | 3.09 | 1,251 | 51.7 | . . . | 0 |
| | | | | After* | 58.8 | 168 | 27 | 5.8 | 4.1 | 0.29 | 167 | 74 | 92 | 3.69 | 1,090 | 55.5 | . . . | 16.8 |
| 7 | 51F | CCM | III | Before | 92.9 | 105 | 70 | 6.5 | 5.8 | 0.11 | 216 | 167 | 49 | 3.35 | 1,424 | 22.9 | 0.50 | 0 |
| | | | | After* | 93.3 | 76 | 57 | 6.6 | 5.7 | 0.14 | 224 | 160 | 64 | 4.33 | 853 | 28.4 | 0.69 | 6.4 |
| 8 | 53M | CCM | III | Before | 85.2 | 98 | 64 | 6.5 | 5.6 | 0.14 | 214 | 156 | 58 | 2.92 | 1,230 | 26.9 | 0.56 | 0 |
| | | | | After* | 79.9 | 91 | 67 | 6.4 | 5.5 | 0.14 | 206 | 149 | 56 | 2.68 | 1,334 | 27.4 | 0.67 | 9.6 |
| 9 | 56M | ICM | IV | Before | 76.9 | 82 | 59 | 6.0 | 5.2 | 0.13 | 180 | 130 | 51 | 2.28 | 1,374 | 28.1 | 0.63 | 0 |
| | | | | After* | 74.3 | 94 | 63 | 6.0 | 4.8 | 0.20 | 180 | 108 | 73 | 3.16 | 1,091 | 40.3 | 0.94 | 38.8 |
| | Mean ± SEM | | | Before | 74.7 ±3.8 | 107 ±9 | 59 ±6 | 5.6 ±0.2 | 4.6 ±0.3 | 0.19 ±0.02 | 159 ±14 | 102 ±13 | 57 ±6 | 2.71 ±0.22 | 1,547 ±159 | 37.1 ±4.3 | 0.69 ±0.08 | 0 |
| | | | | After* | 73.4 ±3.4 NS | 110 ±9 NS | 61 ±5 NS | 5.6 ±0.2 NS | 4.3 ±0.3 p <0.01 | 0.23 ±0.03 p <0.01 | 158 ±14 NS | 89 ±14 p <0.01 | 69 ±7 p <0.01 | 3.21 ±0.24 p <0.05 | 1,330 ±123 NS | 45.0 ±4.6 p <0.01 | 0.93 ±0.09 p <0.01 | 17.7 ±3.8 |

* 90 minutes after oral TA-064.

AR = aortic regurgitation; CCM = congestive cardiomyopathy; CI = cardiac index (liters/min/$m^2$); DBP = diastolic blood pressure (mm Hg); Dd = internal dimension of the left ventricle at end-diastole (cm); Ds = internal dimension of the left ventricle at end-systole (cm); Dx = diagnosis; EF = ejection fraction (%); FS = fractional shortening; HR = heart rate (beats/min); ICM = ischemic cardiomyopathy; LVEDV = left ventricular end-diastolic volume (ml); LVESV = left ventricular end-systolic volume (ml); mean Vcf = (circ/s); PPCM = peripartum cardiomyopathy; SBP = systolic blood pressure (mm Hg); SV = stroke volume (ml); TSR = total systemic vascular resistance (dynes s $cm^{-5}$).

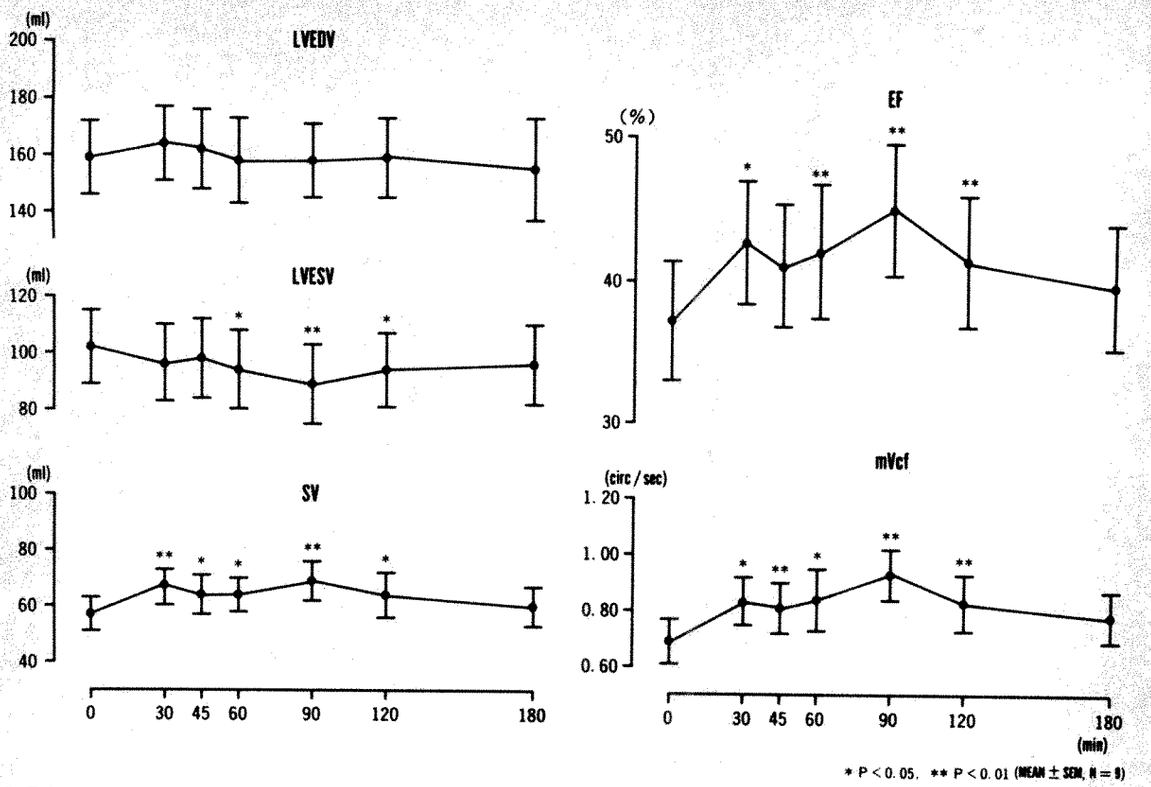



**FIGURE 6.** Echocardiographic response after oral TA-064 in patients with CHF. Left ventricular end-systolic volume (LVESV) was significantly reduced while left ventricular end-diastolic volume (LVEDV) was unchanged, resulting in increased stroke volume (SV). Ejection fraction (EF) and mean velocity of circumferential fiber shortening (mVcf) increased significantly with oral TA-064.

sufficient concentration in 4 patients (Patients 2, 3, 7, and 8, Table III) (<10 ng/ml). However, in these 4 patients the peak plasma level of TA-064 reached was 30 (Patient 2), 60 (Patient 3), 180 (Patient 7), and 120 (Patient 8) minutes, respectively. Moreover, the dose response of TA-064 is evident. The plasma level of TA-064 correlated well with the degree of improvement of mean velocity of circumferential fiber shortening ($r = 0.746$, $p < 0.05$) and ejection fraction ($r = 0.657$, $0.05 < p < 0.1$).

In 2 of 9 patients, 200 to 300 ml of diuresis was obtained 120 to 180 minutes after TA-064 administration. None had noticeable adverse effects. In 1 patient (Patient 7, in Table III), frequent premature ventricular contractions observed at control period were completely abolished during TA-064 administration.

The control value of plasma norepinephrine concentration was increased in 2 patients, both of whom were in New York Heart Association functional class IV (Patient 6, 0.49 ng/ml; Patient 9, 0.80 ng/ml) before study. At 180 minutes after oral administration of TA-064, the plasma concentration of epinephrine was lowered ($0.06 \pm 0.02$ to $0.04 \pm 0.01$ ng/ml, $p < 0.05$), while that of norepinephrine remained unaltered ($0.33 \pm 0.07$ to $0.32 \pm 0.09$ ng/ml).

## Discussion

Although it is well-known that both isovolumic and ejection phase indexes employed in this study are influenced by preload, afterload, and heart rate,[18,25–28] the increase in heart rate and systolic blood pressure were minimal and left ventricular end-diastolic pressure was reduced with TA-064 administration. Therefore, it can be concluded that the marked increase in both isovolumic and ejection phase indexes of contractility seen here were solely due to the inotropic effect of this drug. The inotropic effect of TA-064 is also evident from the cardiac function curve; the left ventricle performs the same or more work at a reduced filling pressure (Fig. 3).

The peak plasma concentration of TA-064 after a single oral administration (normal 12.6 ng/ml; CHF 17.7 ng/ml) corresponds with that of 1 μg/kg/min during intravenous infusion (14.7 ng/ml). Even with this small dose, TA-064 was shown to have a strong positive inotropic effect in patients already on a maximal medical regimen with digitalis and a diuretic agent, resulting in an increased cardiac index.

TA-064 increased contractile function at a dose that did not affect heart rate and blood pressure. Moreover, this inotropic effect of TA-064 is dose-dependent. Thus, a stronger cardiotonic effect can be expected at a higher oral dose of TA-064.

During intravenous infusion study, all 6 patients had a significant reduction in left ventricular filling pressure. Although these reductions could be mediated by improvement in contractility with enhanced systolic emptying of the left ventricle, the marked decrease in left ventricular filling pressure may limit the ability of the drug to further increase cardiac output. This fact

may explain the lack of significant increase in cardiac index in healthy subjects.

TA-064 did not alter plasma norepinephrine concentration. Only the plasma epinephrine level was reduced significantly with TA-064, although this is considered biologically insignificant. We can comment on this only by stating that TA-064 may influence adrenal metabolism directly and its inotropic effect is not mediated by the release of intrinsic catecholamines.

Although the exact mechanism remains to be determined, TA-064 is thought to act on the beta-1 adrenergic receptor. In the experimental animal, increased left ventricular contractile force was inhibited by practolol.[15,17] However, TA-064 was found to have unique but important cardiovascular effects.

The direct effect of TA-064 on cardiac muscle was investigated using isolated guinea pig papillary muscle and right atrium preparation. The effect of TA-064 appeared more rapidly than that of ouabain without inducing any arrhythmia, as usually observed with the latter. Moreover, TA-064 augmented the increase in contractile force induced by ouabain, and vice versa.[17]

Thus, the potentially synergistic effect of TA-064 is to be expected when it is used with digitalis.

In conscious instrumented dogs, after oral administration TA-064 is quickly absorbed from the gastrointestinal tract, metabolized mainly in the liver, and excreted in the urine as glucuronide form. After a single oral dose, TA-064 remained in the plasma >7 hours,[15,17] which is suitable for 3 to 4 times daily administration in ambulatory patients.

While the protocol of this study was not designed to compare the effectiveness of TA-064 with other new classes of inotropic agents, particular comment on amrinone should be made. Amrinone, recently discovered by the investigators at the Sterling-Winthrop Laboratories, was also found to have potent positive inotropic effects on diseased as well as normal hearts. Its effects are not inhibited by beta blockade or in the heart where catecholamine stores are depleted. $Na^+$-$K^+$ adenosine triphosphatase activity is not inhibited as it is by digitalis.[10–14,29] Using various experimental models, positive isotropic and chronotropic effects of TA-064 were compared with those of isoproterenol and amrinone. The positive inotropic effect of TA-064 was 1/50th to 1/100th that of isoproterenol and 100 to 1,500 times stronger than that of amrinone. The positive chronotropic effect of TA-064 was 1/200th to 1/300th that of isoproterenol and 100 to 1,000 times stronger than that of amrinone.[17] The separation of positive inotropic and chronotropic effects was almost identical to that of amrinone.[15,17] These observations showed that TA-064 is a potent inotropic agent, comparable to amrinone.

Since TA-064 exerts its inotropic action by way of beta 1-adrenergic receptor, this drug should be used with great caution in patients with a normal heart size, especially in those with ischemic heart disease. Any inotropic agent such as this one would be expected to increase myocardial oxygen consumption of the nonfailing heart. However, in the failing heart with dilated left ventricular cavity, the overall effect on the cardiac metabolism depends on the interplay of several factors. The increase in myocardial oxygen consumption induced by any inotropic agent may be offset somewhat by the reduction in left ventricular chamber size and therefore systolic-wall tension (the law of LaPlace). Since wall tension during systole and the duration of systole are major determinants of myocardial oxygen consumption,[30] any reduction in these values lessens the effect of augmented myocardial contractility on myocardial oxygen consumption. A potent inotropic agent is thus said to reduce myocardial oxygen consumption in patients with heart failure.[14] The present study does not answer whether this fact may also play a part in the action of TA-064. TA-064, however, was well tolerated and was without noteworthy adverse effects in this study. Indeed, no subject had chest pain or palpitations without development of any change in the electrocardiogram or dysrhythmia. Frequent premature ventricular contractions were completely abolished during this study in 1 patient, and significant diuresis was obtained in 2 of 9 patients. Thus, it may be stated that TA-064 can be safely administered and a potentially beneficial effect can be expected in patients with CHF. However, our study population was small and administration of the drug was short-term; these observations must therefore be considered preliminary. Documentation of a lack of chronic toxicity in human subjects will be necessary before the drug can be considered for long-term administration.

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## References

1. **Abrams J.** Usefulness of long-acting nitrates in cardiovascular disease. Am J Med 1978;64:183–186.
2. **Chatterjee K, Massie B, Rubin S, Gelberg H, Brundage BH, Ports TA.** Long-term outpatient vasodilator therapy of congestive heart failure. Consideration of agents at rest and during exercise. Am J Med 1978;65: 134–145.
3. **Davis R, Ribner HS, Keung E, Sonnenblick EH, LeJemtel TH.** Treatment of chronic congestive heart failure with captopril, an oral inhibitor of angiotensin-converting enzyme. N Engl J Med 1979;301:117–121.
4. **Colucci WS, Wynne J, Holman BL, Braunwald E.** Long-term therapy of heart failure with prazosin: a randomized double blind trial. Am J Cardiol 1980; 45:337–344.
5. **Weber KT, Kinasewitz GT, West JS, Janicki JS, Reichek N, Fishman AP.** Long-term vasodilator therapy with trimazosin in chronic cardiac failure. N Engl J Med 1980;303:242–250.
6. **Hutton I, Murray RG, Boyes RN, Rae AP, Hillis WS.** Hemodynamic effect of prenalterol in patients with coronary heart disease. Br Heart J 1980; 43:134–137.
7. **Bourdillon PDV, Dawson JR, Foale RA, Timmis AD, Poole-Wilson PA, Sutton GC.** Salbutamol in treatment of heart failure. Br Heart J 1980;43: 206–210.
8. **Awan NA, Evenson MK, Needham KE, Evans TO, Hermanovich J, Taylor CR, Amsterdam E, Mason DT.** Hemodynamic effects of oral pirbuterol in chronic severe congestive heart failure. Circulation 1981;63:96–101.
9. **Rude RE, Turi Z, Brown EJ, Lorell BH, Colucci WS, Mudge GH Jr, Taylor CR, Grossman W.** Acute effects of oral pirbuterol on myocardial oxygen metabolism and systemic hemodynamics in chronic congestive heart failure. Circulation 1981;64:139–145.
10. **Wynne J, Malacoff RF, Benotti JR, Curfman GD, Grossman W, Holman BL, Smith TW, Braunwald E.** Oral amrinone in refractory congestive heart failure. Am J Cardiol 1980;45:1245–1249.
11. **Benotti JR, Grossman W, Braunwald E, Davolos DD, Alousi AA.** Hemodynamic assessment of amrinone. A new inotropic agent. N Engl J Med 1978;299:1373–1377.
12. **LeJemtel TH, Keung E, Sonnenblick EH, Ribner HS, Matsumoto M, Davis R, Schwartz W, Alousi AA, Davolos D.** Amrinone: a new non-glycosidic, non-adrenergic cardiotonic agent effective in the treatment of intractable myocardial failure in man. Circulation 1979;59:1098–1104.
13. **Weber KT, Andrews V, Janicki JS, Wilson JR, Fishman AP.** Amrinone and exercise performance in patients with chronic heart failure. Am J Cardiol 1981;48:164–169.
14. **Benotti JR, Grossman W, Braunwald E, Carabello BA.** Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. Circulation

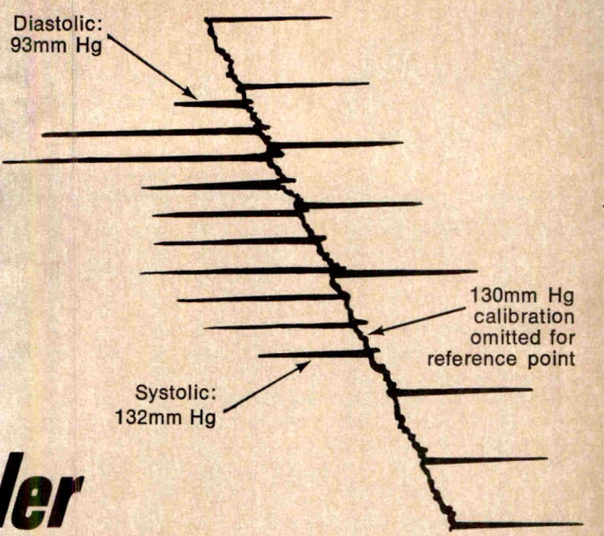
1980;62:28–34.
15. **Nagao T, Ikeo T, Sato M, Nakajima H, Kiyomoto A.** Positive inotropic effect of (−)-α-(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzyl-alcohol (TA-064) in the dog (abstr). Tokyo: Proceedings of the Eighth International Congress of Pharmacology, 1981:921.
16. **Ikeo T, Nagao T, Suzuki T, Yabana H, Nakajima H.** Effect of TA-064, a new positive inotropic agent, on left ventricular function in conscious instrumented dogs (abstr). Tokyo: Proceedings of the 55th General Meeting of Japan Pharmacological Society, 1982:20.
17. New Product Information TA-064. Osaka, Japan: Tanabe Seiyaku, 1982.
18. **Davidson DM, Covell JW, Mailoch CI, Ross J Jr.** Factors influencing indices of left ventricle contractility in the conscious dog. Cardiovasc Res 1974; 8:299–312.
19. **Sahn DJ, DeMaria A, Kisslo J, Weiman A.** The Committee on M-Mode Standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58: 1072–1083.
20. **Teichholz LV, Kreulen T, Herman MV, Gorlin R.** Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence or absence of asynergy. Am J Cardiol 1976;37:7–11.
21. **Cooper RH, O'Rourke RA, Karliner JS, Peterson KL, Leopol CR.** Comparison of ultrasound and cineangiographic measurements of the mean rate of circumferential fiber shortening in man. Circulation 1972;46:914–923.
22. Study Group for Idiopathic Cardiomyopathies of Japan. The criteria for the diagnosis of idiopathic cardiomyopathies. In: The Committee for Diseases of Unknown Etiology, ed. A guide for the diagnosis of the Diseases of Unknown Etiology. Kyoto, Japan: Ministry of Health and Welfare of the Japanese Government, 1975:45.
23. **Goodwin JF, Oakley CM.** The cardiomyopathies. Br Heart J 1972;34: 545–552.
24. **Hamaji M.** Estimation of catecholamines in human plasma by ion-exchange chromatography coupled with fluorometry. J Chromatogr 1979;163: 329–336.
25. **Mason DT, Braunwald E, Covell JW, Sonnenblick EH, Ross J Jr.** Assessment of cardiac contractility. The relation between the rate of pressure rise and ventricular pressure during isovolumic systole. Circulation 1971;44: 47–58.
26. **Quinones MA, Gaasch WH, Alexander JK.** Influence of acute changes in preload, afterload, contractile state and heart rate on ejection and isovolumic indices of myocardial contractility in man. Circulation 1976;53:293–302.
27. **Rankin LS, Moos S, Grossman W.** Alterations in preload and ejection phase indices of left ventricular performance. Circulation 1975;51:910–915.
28. **Hirshleifer J, Crawford M, O'Rourke RA, Karliner JS.** Influence of acute alterations in heart rate and systemic arterial pressure on echocardiographic measures of left ventricular performance in normal human subjects. Circulation 1975;52:835–841.
29. **Alousi AA, Farah AE, Lesher GY, Opalka CJ Jr.** Cardiotonic activity of amrinone-Win 40680(5-amino-3,4′-bipyridin-6(1H)-one). Circ Res 1979; 45:666–677.
30. **Braunwald E.** Thirteenth Bowditch Lecture: The determinants of myocardial oxygen consumption. Physiologist 1969;12:65–93.

Because of a printing error, 2 table headings were transposed in the article by Hirota et al (Hypertrophic Nonobstructive Cardiomyopathy: A Precise Assessment of Hemodynamic Characteristics and Clinical Implications) in our November 1982 issue. The error appears in Table IV, on page 994. The correct placement of the 2 headings is as follows:

| $(dP/dt)/DP_{40}$ ($s_{-1}$) | Peak (−)dP/dt (−mm Hg/s) |
|---|---|
| 32.9 ±7.0 | 1,079* ±329 |
| 31.4 ±5.3 | 1,923 ±440 |



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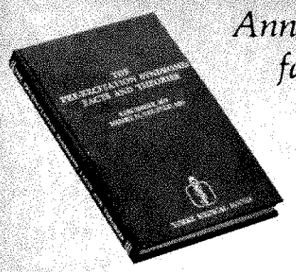
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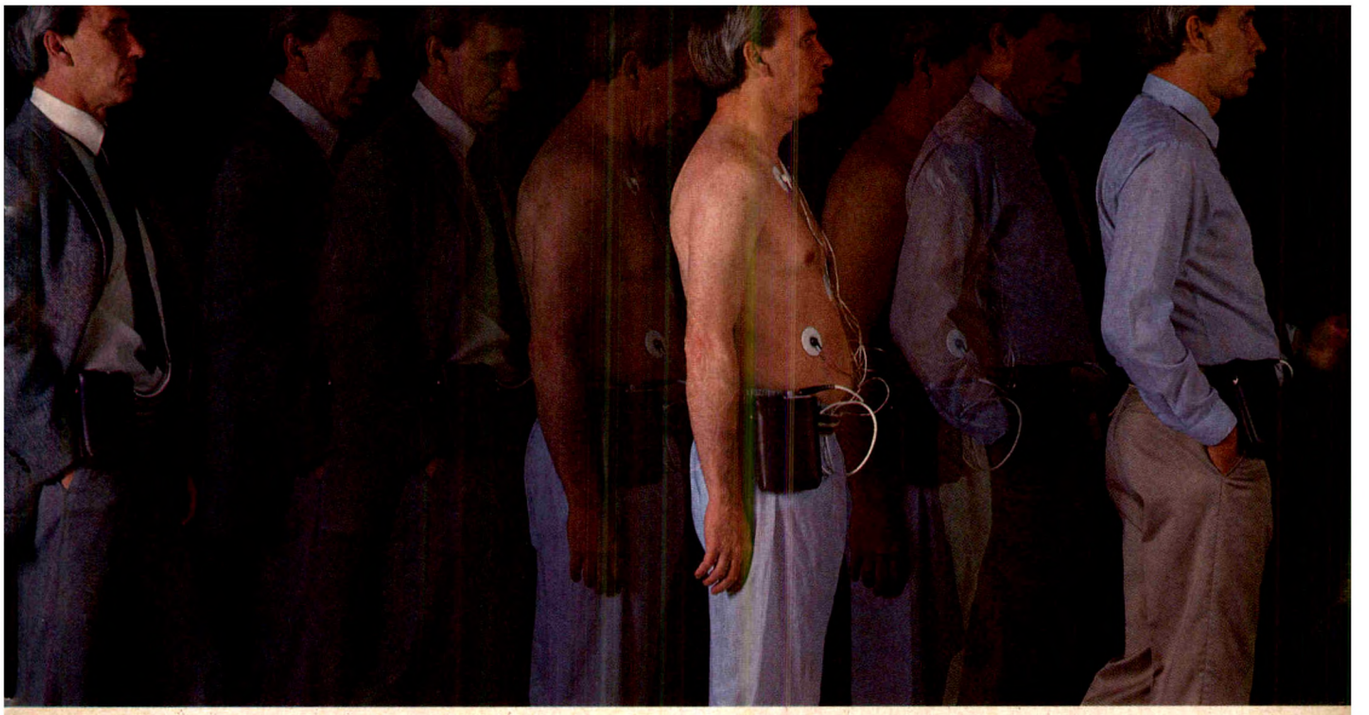
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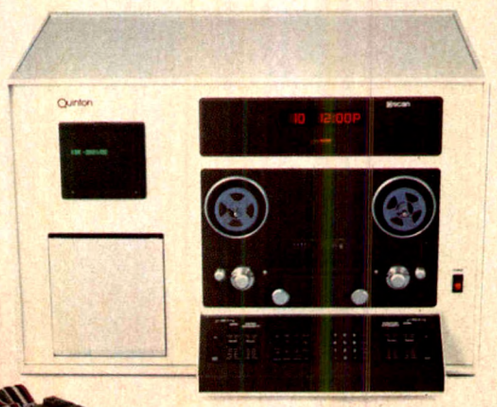
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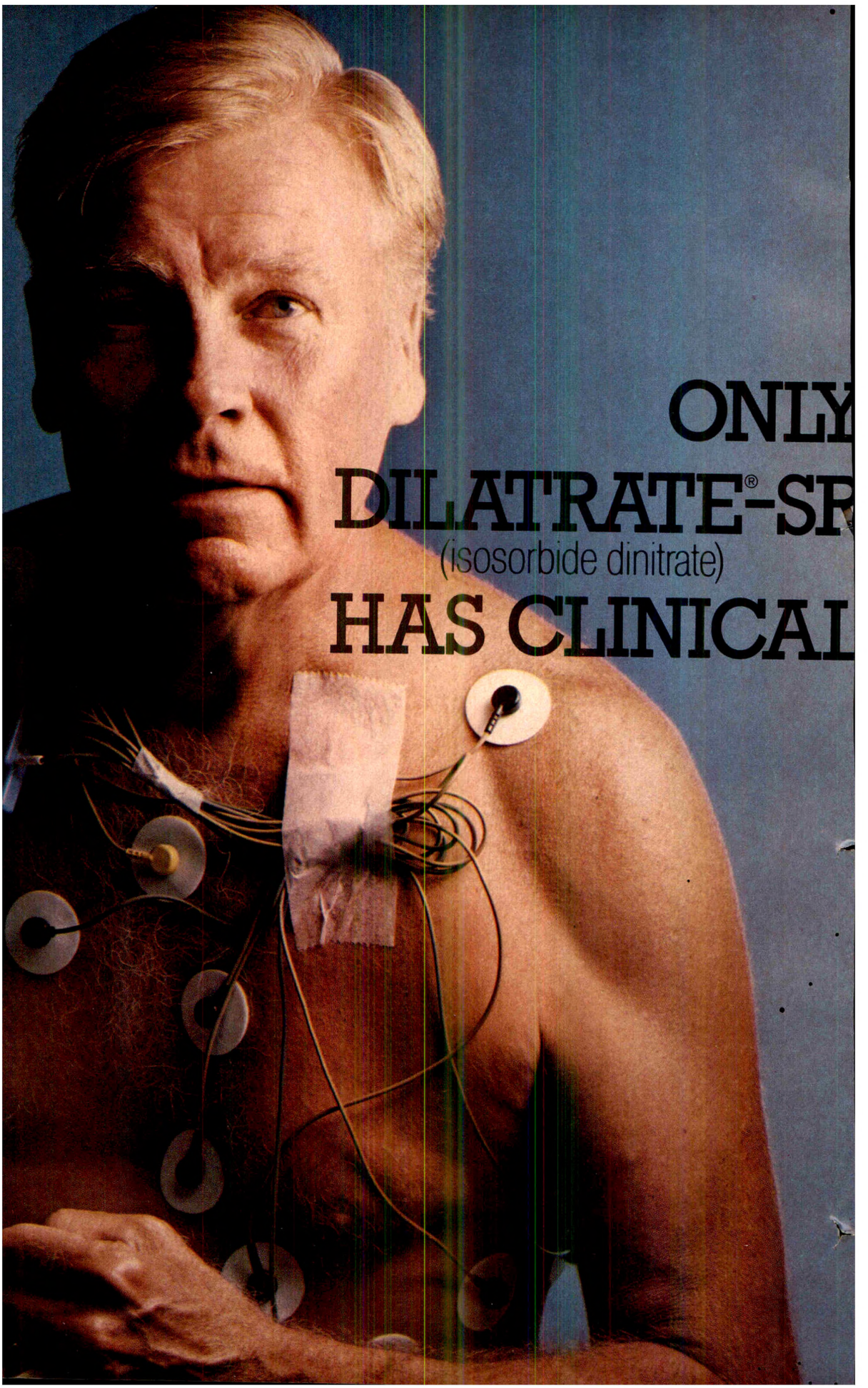
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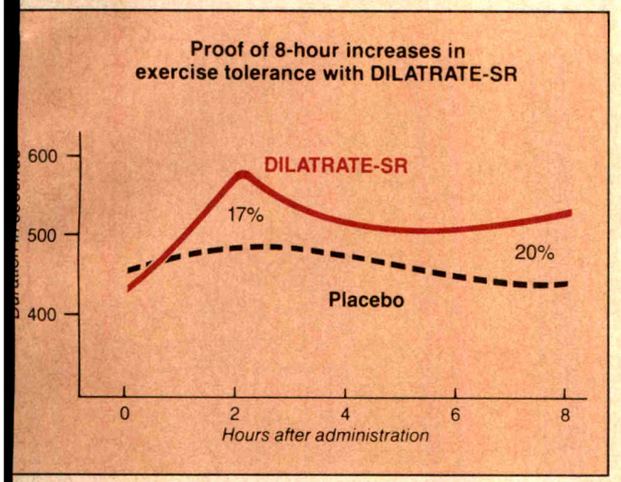
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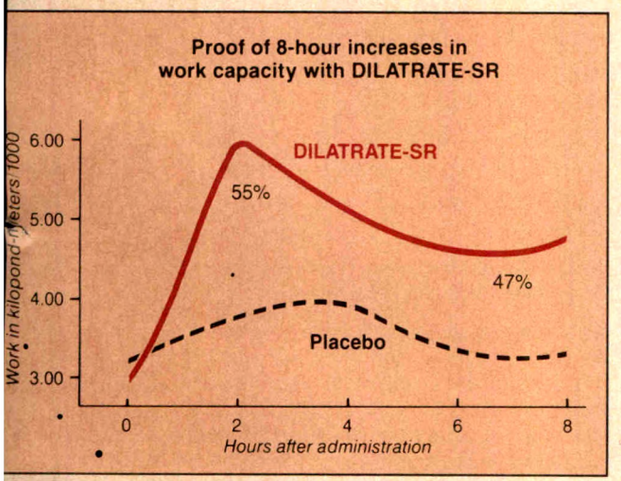
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The proven sustained activity of DILATRATE-SR offers anginal patients convenient b.i.d. dosage and can reduce the need for sublingual nitroglycerin.

*Please see brief summary of full prescribing information on following page. For full prescribing information, consult package insert.

**References:**

1. DiBianco R et al: Effects of a new oral slow release form of isosorbide dinitrate on the hemodynamics and exercise capacity of patients with angina — a placebo controlled and double blind study. *Circulation* (Supp II) 66:381, Oct 1982.
2. Dinsdale J, Allen J: Data on file, Medical Department, Reed & Carnrick.

# Dilatrate®-SR
## (isosorbide dinitrate) 40 mg

Reed & Carnrick / Piscataway, New Jersey 08854

# Dilatrate®-SR
## (isosorbide dinitrate) 40 mg

**BRIEF SUMMARY**

Indications: Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: When taken by the oral route, is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indication requires further investigation.

**CONTRAINDICATION:** Idiosyncrasy to this drug.

**WARNINGS:** Data supporting the use of nitrates and nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

**PRECAUTIONS:** Tolerance to this drug, and cross-tolerance to other nitrates or nitrites may occur.

In patients with functional or organic gastrointestinal hypermotility or malabsorption syndrome it is suggested that either the 5 mg. or 10 mg. oral tablets or 2.5 mg. or 5 mg. sublingual tablets be the preferred therapy.

**ADVERSE REACTIONS:** Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

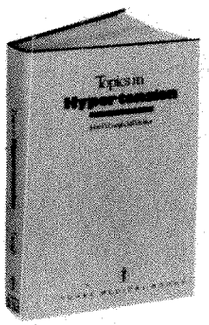
An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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A123

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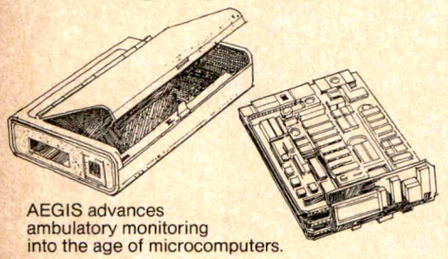
# ...with none of the drawbacks.

Although scanning services are well established, they do have their drawbacks. The first is turnaround time. It's not unusual for two, three or even four days to pass before you receive a report on your Holter patient. Then you'll pay a hefty charge for this time consuming service.

What's even more critical, some physicians question the consistency of the reports they receive from scanning services... with good reason. The high speed at which scanners operate has made it difficult to incorporate sensitive enough computer recognition criteria at an affordable cost.

Compounding the problem is technician fatigue. Since a technician normally scans a number of Holter tapes at one sitting, significant data may be missed. And since technician capabilities vary from person to person, the doctor receiving a report has no way of knowing just how reliable the report is or is not.

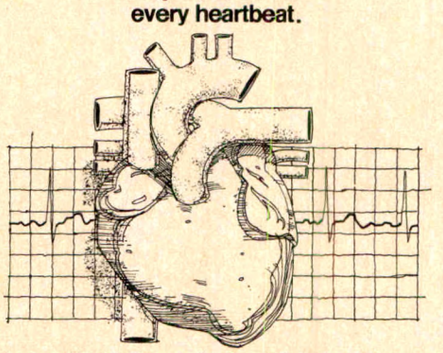
### Now the new technology of microcomputers does the work of the technician and scanner right in your office.



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After more than six years of development and rigorous clinical evaluation, AEGIS advances ambulatory monitoring and reporting into the age of microcircuity and sophisticated computers. Now both the recording and analyzing activities are combined into one compact unit that analyzes, counts and categorizes arrhythmias as they occur. Because analysis occurs in real time, the inefficient high-speed scanner and the fatigue-prone technician can now be replaced by a real time analyzer and an automatic, consistently reliable playback unit that prints out rhythm strips as well as summation and categorization reports...in your office...within minutes after your Holter patient returns. AEGIS does all this without a specially trained operator.

### Analyzes each and every heartbeat.



Real time analysis of each heartbeat.

Unlike traditional Holter monitoring equipment, AEGIS *does not analyze a recording* of your patient's heartbeat, nor does it rely upon visual identification of condensed rhythm strips. Rather, AEGIS analyzes each heartbeat as it occurs. No scanning service or human eye can practically match AEGIS in consistency and speed.

Here's how it works. AEGIS automatically establishes a "normal" reference for each patient, then compares each heartbeat to the normal pattern, looks for deviations in rate, rhythm and morphology, distinguishes each arrhythmia, and performs highly refined classification decisions. All of this data, analyzed in real time, is stored on an integral digital tape.

Because the microcomputer works in real time, it is able to apply many more computer cycles in its decision making than those computers used with high-speed Holter scanners.

### Compares against what's abnormal for each individual patient...not against some "universal norm."

AEGIS recognizes that no two patients are exactly alike. In order to analyze deviations more accurately, the AEGIS microprocessor automatically establishes the "normal" reference for each patient. The sophisticated computer program used for this function can find and reference a patient's "normal" beat in less than two minutes. Furthermore, it has been proven that AEGIS can establish a "normal" reference under a variety of difficult conditions such as chronic bigeminy, atrial fibrillation and bundle branch block.

In addition, the "normal" reference is continually updated throughout the analysis period to account for changes in the position of the heart due to body movement and changes in the patient's position.

### Puts the control of evaluating Holter studies directly into your hands.

AEGIS gives you *both* a rhythm strip along with a summary report for your confirmation. The rhythm strip is a two-channel electrocardiogram with the time and classification of the recording and the specific lead processed printed right

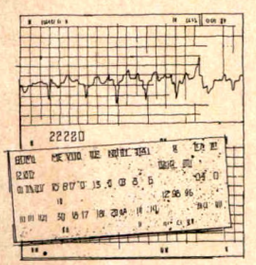


on the rhythm strip for easy reference.

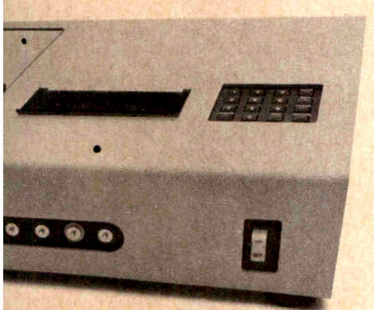
The printed report summarizes the frequency and classification of arrhythmias, as well as heart rate information for each one hour or quarter hour increment of the 24-hour monitoring period. It also calls out specific morphologies that require your review.

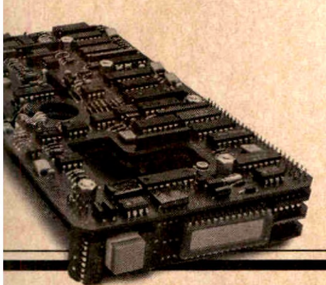
Since rhythm strip and summary report are both time-stamped, it's easy for you to compare both documents and verify the data. Together, the strip chart and summary report provide you with all the visual and quantitative data you need to make an in-depth diagnosis.

In addition, the rhythm strip record and summary report can be used as a basis for comparison with follow-up rhythm strips and reports in order to determine patient progress and to evaluate methods of treatment.



Rhythm strip and summary report for your confirmation. Highlights morphologies requiring your review.





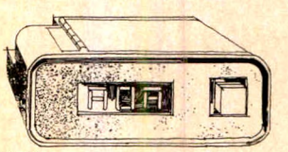
**Review results at your convenience or begin treatment immediately when it's called for.**



No need to wait days for Holter results.

The AEGIS System gives you all the data you need to make a sound diagnosis right in your office. Instead of waiting a day or more for results, you get them when you need them—a most important plus when dealing with patients for whom further diagnostic testing is suspected or must be scheduled. In short, you fit the AEGIS System to your schedule.

**The system validates itself—no need for repeat studies due to "lost" data or faulty equipment.**



LED display alerts you to system or procedure problems.

AEGIS overcomes the problems of interference or artifacts overcoming accurate analysis. AEGIS automatically senses when artifacts are overwhelming the usefulness of information, and switches to the other lead signal for processing. Thus, there's no need for retakes due to artifacts.

In addition, self-diagnostic checks are built into the Real Time Analyzer and the Report Generator so you can verify all system operations from patient hook-up to report generation. No more invalid studies due to malfunctioning recorders, weak batteries or over-used tapes. AEGIS is the only completely self-validating system.

**No need to hire specially trained operators.**

The AEGIS System is totally self-contained and so easy to use, it requires no dependence on specially trained personnel in or out of your office.

Patient hook-up to the Real Time Analyzer is identical to that of traditional Holter ECG monitoring systems. And the Report Generator is so automatic that once the cassette tape is inserted and the printout process is started, it requires no operator attendance.

**Takes up no more space than a desk-top copier.**

The AEGIS System fits easily into any office practice. The Real Time Analyzer is approximately the same size as other ambulatory monitoring units and the compact Report Generator requires only about four square feet of counter space.

AEGIS is protected against obsolescence, too. As new software developments and technological advances are made, the AEGIS System can be inexpensively updated.



Fits compactly into any office.

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- Provides the same clinical information as a scanning service—with none of the drawbacks.
- Replaces the high-speed scanner and technician—brings those activities into your office. More convenient. More efficient.
- Analyzes each heartbeat as it occurs; counts and categorizes arrhythmias in real time.




- Puts the control of evaluating Holter studies directly into your hands. Provides time-stamped rhythm strip and summary report for your confirmation.
- System validates itself—no need for repeat studies due to "lost" data or faulty equipment.
- Fits easily into any office.

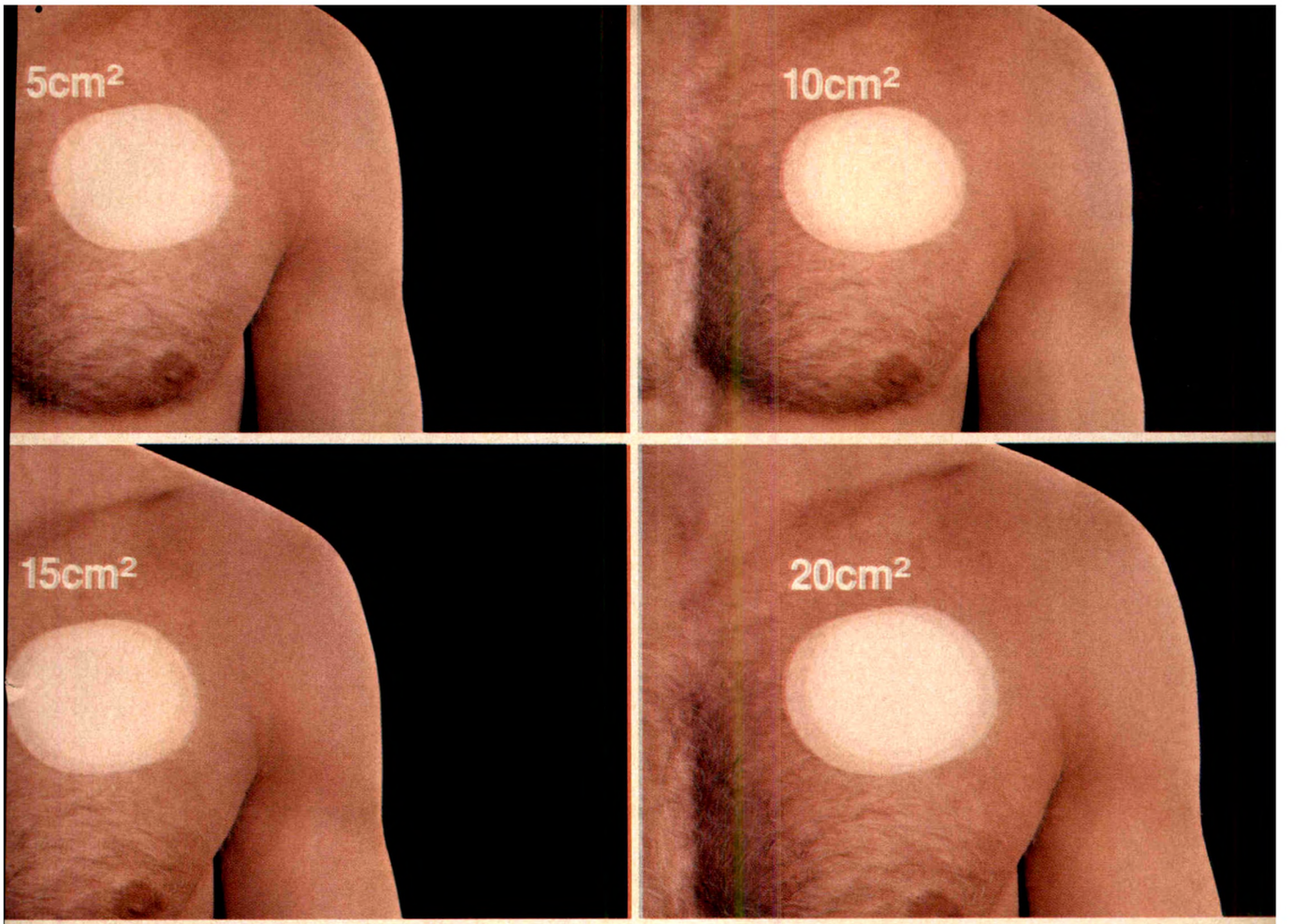
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Nitro-Dur™ (nitroglycerin) is the only transdermal nitroglycerin with four dosage strengths—5, 10, 15 and 20 cm² (approximately 2.5 mg, 5 mg, 7.5 mg and 10 mg released in 24 hours), permitting titration in increments of 5 cm². This gives Nitro-Dur greater dosage flexibility than any other form of transdermal nitroglycerin.

Nitro-Dur also has a sophisticated product design which includes a wide, microporous adhesive strip. The strip insures firm matrix-to-skin contact and helps keep the system sealed and in place.

Greater dosage flexibility and better adhesion. Two reasons why Nitro-Dur is the most widely prescribed transdermal nitroglycerin system.

# Nitro-Dur™
(nitroglycerin)
Transdermal Infusion System

## The most widely prescribed transdermal nitroglycerin system.

Please see next page for a summary of prescribing information.

# Nitro-Dur™
(nitroglycerin)
Transdermal Infusion System



## The most widely prescribed transdermal nitroglycerin system.

**DESCRIPTION:** The Nitro-Dur Transdermal Infusion System contains nitroglycerin in a gel-like matrix composed of glycerin, water (purified), lactose, polyvinyl alcohol, povidone and sodium citrate to provide a continuous source of the active ingredient. Nitro-Dur is available in dosage sizes 5cm², 10cm², 15cm² and 20cm², containing 26 mg, 51 mg, 77 mg and 104 mg of nitroglycerin, respectively, thereby providing precise dosing levels of nitroglycerin. Nitro-Dur has a rated release *in vivo* of approximately 0.5mg/cm²/24 hours. Each unit is sealed in a polyester-foil-polyethylene laminate. The bandage portion consists of a medical grade non-woven, heat sealable, microporous tape.

**CLINICAL PHARMACOLOGY:** When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies,[1] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

**INDICATIONS AND USAGE:** Prevention and treatment of angina pectoris due to coronary artery disease.

**CONTRAINDICATIONS:** Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

**WARNINGS:** The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

**PRECAUTIONS:** Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

**ADVERSE REACTIONS:** Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

**HOW SUPPLIED:** Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28.

**CAUTION:** Federal law prohibits dispensing without a prescription.

**PATIENT INSTRUCTIONS FOR APPLICATION:** Patient instructions are furnished with each unit dose package.

*For complete prescribing information, please see package insert.*

[1]Data on file: Key Pharmaceuticals, Inc. 1082

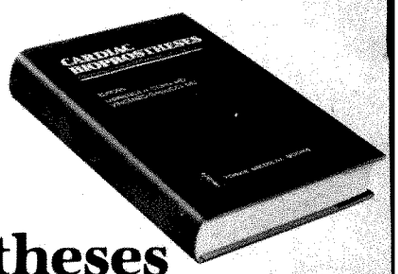
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# Cardiac Bioprostheses

**Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982**

**edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD**
**ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $65.00**

An international program committee organized this symposium on a strictly competitive abstract basis. It was held less than six months ago. One-hundred-eighty abstracts were submitted and 45 in 8 categories were accepted. Virtually every major cardiovascular center in the world that has any meaningful experience with cardiac bioprosthetic valves was represented. Nowhere will you find between two covers as much *current* information on the field of cardiac valves.

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If your interests include the clinical, pathological and bioengineering aspects of cardiac bioprostheses then this book is a *must buy!* It should not be missing from your own professional library.

## Who are the editors?

**Lawrence H. Cohn, MD,** is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

**Vincenzo Gallucci, MD,** is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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# Vulnerability of Patients With Obstructive Hypertrophic Cardiomyopathy to Ventricular Arrhythmia Induction In the Operating Room

## Analysis of 17 Patients

KELLEY P. ANDERSON, MD, EDWARD B. STINSON, MD, GERALDINE C. DERBY, RN, PHILIP E. OYER, MD, and JAY W. MASON, MD

**To evaluate vulnerability to ventricular arrhythmia induction, programmed electrical stimulation was performed in the operating room in 17 consecutive patients undergoing myotomy-myectomy for obstructive hypertrophic cardiomyopathy (HC). A control group of 5 patients undergoing coronary artery bypass grafting with normal left ventricular function and no previous myocardial infarction also was tested. Of the 17 patients with HC, 14 had inducible sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), 1 had inducible unsustained VT and the remaining 2 had <6 ventricular beats. In contrast, none of the 5 control patients had an inducible sustained ventricular arrhythmia, 1 had inducible unsustained VT, and the remaining 4 had <3 ventricular beats. The difference between the 2 groups with respect to induction of a sustained ventricular arrhythmia, unsustained VT or <6 ventricular beats was significant ($p < 0.001$). It is concluded that patients with severe obstructive HC are unusually vulnerable to ventricular arrhythmia induction. This suggests that spontaneous ventricular tachyarrhythmias may be an important cause of sudden death in patients with HC.**

Death in patients with hypertrophic cardiomyopathy (HC) is usually sudden,[1,2] but the mechanism is uncertain in most cases. Ventricular tachyarrhythmias are a prominent etiologic possibility; unsustained ventricular tachycardia (VT) detected on ambulatory electrocardiography has been associated with subsequent sudden death or cardiac arrest.[3–6] Programmed electrical stimulation of the heart has been used to diagnose and treat arrhythmias in patients with syncope or cardiac arrest of unknown cause.[7–9] No systematic study of arrhythmia induction in patients with HC has been reported. We performed programmed electrical stimulation in the operating room in patients undergoing myotomy-myectomy for obstructive HC in order to safely evaluate their vulnerability to ventricular arrhythmia induction. We compared findings in these patients with those in a control group without HC.

From the Cardiac Arrhythmia Study Unit and the Department of Cardiovascular Surgery, Stanford University School of Medicine, Stanford, California. Dr. Anderson is Research Fellow of the American Heart Association, California Affiliate, Burlingame, California. Dr. Mason is an Established Investigator of American Heart Association, Dallas, Texas. Manuscript received September 23, 1982; revised manuscript received and accepted November 12, 1982.

Address for reprints: Jay W. Mason, MD, Cardiac Arrhythmia Study Unit, Stanford University School of Medicine, Stanford, California 94305.

### Methods

The study group consisted of 17 consecutive patients who underwent myotomy-myectomy for obstructive HC at Stanford University Hospital between January 1, 1981 and June 1, 1982. The diagnosis was based on typical clinical characteristics[10] and on at least 2 of the following echocardiographic and hemodynamic features: a ventricular septal to left ventricular posterior free wall thickness ratio ≥1.3, systolic anterior motion of the anterior leaflet of the mitral valve, a pressure gradient at rest across the left ventricular outflow tract ≥30 mm Hg, and a provocable left ventricular outflow tract gradient ≥60 mm Hg. The diagnosis was supported at the time of operation by the presence of a hypertrophic septal ridge and a septal endocardial plaque in all patients. The presence or absence of myocardial fiber disarray was noted during pathologic examination of the resected septal tissue. Other causes of myocardial hyertrophy and left ventricular outflow obstruction were excluded by preoperative evaluation and intraoperative inspection.

The control group consisted of 5 patients who underwent coronary artery bypass grafting during the same time period. Those patients fulfilled the following criteria: normal elec-

trocardiogram at rest, normal left ventricular angiogram, no history of myocardial infarction or ventricular arrhythmias, no family history of sudden death or hypertrophic cardiomyopathy, and no evidence of valvular disease. The protocol was approved by the Standard University Medical Committee for Human Subjects in Research and informed written consent was obtained.

The patients were maintained on their chronically prescribed medications until operation. The patients were premedicated with scopolamine and diazepam or morphine sulfate, or all 3. Pancuronium bromide was the muscle relaxant used in all cases. Fentanyl or hydromorphone hydrochloride was used for general anesthesia. When necessary, a volatile agent (enflurane, halothane, or isoflurane) was added. The heart was exposed using a midline sternotomy and the formation of a pericardial cradle. After systemic heparinization the superior and inferior venae cavae were cannulated through the lateral right atrium. The distal ascending aorta was cannulated and appropriate connections to the pump oxygenator were made. A quadripolar electrode plaque was sutured to the anterior right ventricular epicardium. An Electronics for Medicine VR16 and an Ampex PR2200 were used for continuous display and recording of the epicardial electrograms and 6 surface electrocardiograms. A WPI programable stimulator was used to deliver rectangular pulses with a duration of 2 ms and current 2 to 4 times diastolic threshold. Stimulation was performed before the initiation of cardiopulmonary bypass.

An identical stimulation protocol was used for all patients. The steps described were followed until a tachyarrhythmia was induced. A single ventricular extrastimulus ($V_2$) was placed in late diastole after every eighth spontaneous beat and brought closer by 20 ms decrements until the refractory period of the spontaneous beat was reached. With $V_2$ just outside the refractory period of the spontaneous beat, a second ventricular extrastimulus ($V_3$) was applied 360 ms after $V_2$ and brought progressively closer until the refractory period of $V_2$ was reached. Ventricular pacing was then begun at 100 beats/min and a ventricular extrastimulus ($V_2$) placed 360 ms after every eighth ventricular paced beat ($V_1$). The $V_1$-$V_2$ interval was progressively reduced by 20 ms until the $V_2$ stimulus no longer captured the ventricles. The $V_1$-$V_2$ interval was then increased by 10 ms intervals until ventricular capture was obtained to define the right ventricular refractory period during ventricular pacing. The pacing rate was increased to 120, 140, and 150 beats/min. At each rate the $V_1$-$V_2$ interval was decreased until ventricular capture no longer occurred. The pacing rate was then decreased to 100 beats/min, $V_2$ placed just outside the refractory period of $V_1$, and $V_3$ added at about 360 ms after and brought progressively closer to $V_2$. The pacing rate was again increased to 120, 140, and 150 beats/min, and at each rate $V_1$-$V_2$-$V_3$ stimulation was carried out to the minimal obtainable $V_1$-$V_2$ and $V_2$-$V_3$ intervals. The same process was performed with a third ventricular extrastimulus ($V_4$) so that $V_1$-$V_2$-$V_3$-$V_4$ stimulation was carried out at the minimal intervals at each pacing rate. Interstimulus intervals <200 ms were not used. If a ventricular arrhythmia lasting at least 5 seconds was not induced with the foregoing measures, 10 to 20 beat bursts of rapid ventricular pacing were performed beginning at a rate of 200 beats/min, which was progressively increased until 1 to 1 capture of the ventricles was no longer obtained. If a ventricular tachyarrhythmia was not induced the experiment was terminated. In the first 6 study patients the stimulation protocol differed slightly in that a third extrastimulus was applied during the patient's spontaneous rhythm.

When a ventricular arrhythmia lasting at least 5 seconds was induced, normothermic cardiopulmonary bypass was immediately instituted. If the arrhythmia terminated spontaneously during this period (5 patients), reinduction was attempted during circulatory support using the same stimulation program. In 4 additional cases the arrhythmia was terminated by a single countershock and reinduction attempted using the same stimulation program during bypass.

VT was defined as ≥6 consecutive ventricular beats. VT was unsustained if it terminated spontaneously in <15 seconds. Sustained VT lasted >15 seconds. Pleomorphic VT was de-

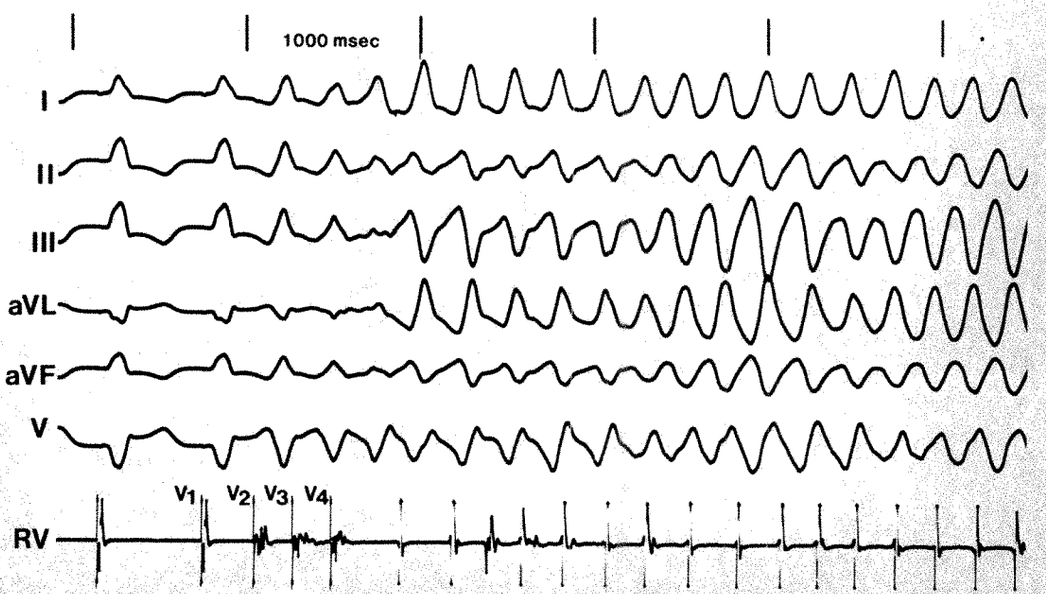



**FIGURE 1.** Pleomorphic ventricular tachycardia. A right ventricular epicardial electrogram (RV) is recorded with 6 surface electrocardiograms, leads I, II, III, aVL, and aVF, and a posterior chest lead (V). Three ventricular extrastimuli ($V_2$, $V_3$, and $V_4$) applied during ventricular pacing ($V_1$) induce ventricular tachycardia with a changing QRS morphology and discrete right ventricular electrograms. The rate averages 250 beats/min.

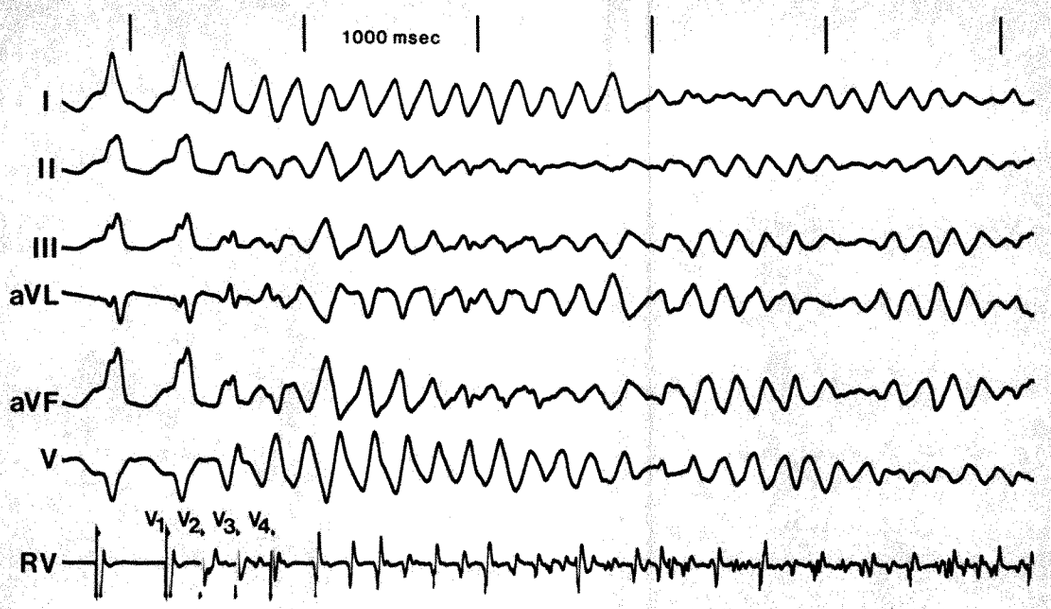



**FIGURE 2.** Ventricular fibrillation. Same leads as in Figure 1. Three ventricular extrastimuli ($V_2$, $V_3$, and $V_4$) applied during ventricular pacing ($V_1$) induced ventricular fibrillation with continuously changing QRS morphology and fragmentation of the right ventricular electrograms. The rate is >300 beats/min. Abbreviations as in Figure 1.

fined as VT with continuously changing QRS morphology, a rate less than 300 beats/min, and discrete right ventricular electrograms (Fig. 1). Ventricular fibrillation (VF) was defined as a ventricular rhythm with continuously changing QRS morphology, a rate ≥300 beats/min, and fragmentation of the right ventricular electrograms (Fig. 2).

Statistical analysis was performed by Mann-Whitney U test and unpaired *t* test.

## Results

Several clinical, echocardiographic, hemodynamic, and pathologic characteristics of the patients with HC are listed in Table I. The group consisted of 6 men and 11 women with a mean age of 46 years. Dyspnea was the most common presenting complaint, followed by chest pain. One patient had suffered a cardiac arrest and 5 others had a history of syncope. All but 2 patients demonstrated systolic anterior motion of the anterior leaflet of the mitral valve. Five of 6 patients who had septal to posterior left ventricular free wall thickness ratios <1.3, had diastolic ventricular septal wall thicknesses >20 mm. A hypertrophic ridge with endocardial fibrosis was noted at operation in all patients. Myocyte

**TABLE I Clinical Features of Patients With Hypertrophic Cardiomyopathy**

| Patient | Age (yr) & Sex | Chief Complaint | Septal Thickness (mm) | Septal/Free Wall Ratio | SAM | LVOT Gradient (mm Hg) | | Fiber Disarray |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Rest | Provoked | |
| 1 | 15M | Cardiac arrest | 40 | 2.0 | + | 70 | ND | + |
| 2 | 74F | Chest pain | ND | ND | − | 18 | ND | + |
| 3 | 26F | Dyspnea | 14 | 1.9 | + | 66 | ND | ND |
| 4 | 49M | Syncope | 30 | 1.0 | + | 60 | 138 | ND |
| 5 | 25M | Dyspnea | 24 | 1.2 | + | 119 | ND | + |
| 6 | 49F | Dyspnea | 27 | 1.1 | + | 90 | 140 | + |
| 7 | 33F | Dyspnea | 26 | 1.4 | + | 90 | 250 | + |
| 8 | 70F | Chest pain | ND | ND | + | 157 | ND | + |
| 9 | 64F | Dyspnea | 23 | 1.2 | + | 70 | 110 | + |
| 10 | 63F | Syncope | 23 | 1.4 | + | 80 | 150 | + |
| 11 | 33M | Hemoptysis | 20 | 2.3 | + | 80 | 100 | + |
| 12 | 51M | Dyspnea | 16 | 1.0 | + | 16 | 75 | − |
| 13 | 46M | Chest pain | 20 | 1.7 | + | 80 | 100 | − |
| 14 | 47F | Fatigue | 32 | 1.0 | + | 98 | ND | + |
| 15 | 36F | Chest pain | 22 | 1.3 | + | 154 | ND | − |
| 16 | 39F | Dyspnea | 26 | 1.3 | + | 12 | 65 | ND |
| 17 | 55M | Syncope | 20 | 1.1 | − | 51 | 122 | − |

LVOT = left ventricular outflow tract; ND = not done or not measurable; SAM = systolic anterior motion of the anterior mitral valve leaflet. + = present; − = absent.

**TABLE II Ventricular Arrhythmia Induction**

| Induced Ventricular Arrhythmia | Patients (n) With Hypertrophic Cardiomyopathy | Patients (n) With Coronary Disease |
|---|---|---|
| Sustained VT or VF | 14 | 0 |
| Unsustained VT | 2 | 1 |
| Less than 6 VB | 1 | 4 |

VB = ventricular beats; VF = ventricular fibrillation; VT = ventricular tachycardia.

disarray was noted in the resected tissue of 10 of 14 patients. Histologic examination was not performed in 3 patients.

The 5 control patients consisted of 4 men and 1 woman with a mean age of 56 years. The chief complaint was chest pain in all. All had >70% stenoses of the left anterior descending and right coronary arteries, and all but 1 had >70% stenosis of the left circumflex artery or 1 of its major branches.

In 14 of the 17 patients with hypertrophic cardiomyopathy sustained, rapid, pleomorphic VT (9 patients) or VF (5 patients) was induced (Table II). In 3 of these 14 patients a sustained ventricular arrhythmia was induced with 2 ventricular extrastimuli during ventricular pacing. In the remaining 11 patients VT or VF was induced with 3 ventricular extrastimuli during sinus rhythm or ventricular pacing. VF never terminated spontaneously. The rates of pleomorphic VT varied between 210 and 300 beats/min and there was often beat-to-beat cycle length variation. Pleomorphic VT degenerated into VF within 2 to 15 seconds in 5 patients. It lasted 6 to 14 seconds in the other 4 patients but terminated during the initiation of cardiopulmonary bypass. In each case the same stimulation program reapplied during circulatory support produced pleomorphic VT which degenerated into VF.

A sustained ventricular arrhythmia could not be induced in 3 of 17 patients with HC. In 1 of these patients VT lasting 4 seconds was induced. In the other 2 patients <5 consecutive ventricular beats were induced. These 2 patients (Cases 6 and 17, Table I) did not have any clinical, electrocardiographic, echocardiographic, or hemodynamic characteristics that distinguished them from the other patients with HC.

The stimulation protocol failed to induce a sustained ventricular arrhythmia in all of the control patients. A 15 beat run of unsustained VT was induced in 1 patient with a burst of rapid ventricular pacing at a rate of 250 beats/min. No more than 2 ventricular beats were induced in the remaining 4 control patients. The difference in inducibility between the study and control groups was analyzed with respect to the arrhythmia categories as shown in Table II: sustained ventricular tachyarrhythmia, unsustained VT, and <6 ventricular beats. The difference was highly significant ($p < 0.001$) using the Mann-Whitney U test. If the 6 patients with a history of syncope or cardiac arrest are excluded from the study group, the difference is still significant ($p < 0.005$). If the 4 study patients in whom VT terminated during the initiation of bypass are included in the group with unsustained VT the difference is still significant ($p < 0.005$).

There was no significant difference between the right ventricular refractory periods obtained during ventricular pacing at 100 beats/min in 14 patients with HC (mean ± standard deviation 284 ± 25) and the 5 control patients (274 ± 15 ms). There was no significant difference between the refractory periods of 13 patients (12 study and 1 control) with inducible sustained or unsustained VT or VF (280 ± 23 ms) and 6 patients (2 study and 4 control) without inducible VT or VF (283 ± 25 ms). The mean minimal $V_2$-$V_3$ interval obtained in the control patients with no inducible arrhythmia (207 ± 4 ms) was lower than that obtained in the patients with HC who had inducible sustained VT or VF (224 ± 29 ms), but the difference was not significant. The minimal $V_3$-$V_4$ intervals obtained in the control patients (202 ± 4 ms) were significantly lower than those obtained in the study group (218 ± 18 ms, $p < 0.025$) because arrhythmia induction occurred before refractoriness in the study group.

Medications taken within 24 hours before operation in the patients with HC included beta-adrenergic blocking agents in 12, calcium antagonists in 2, a beta-adrenergic blocking agent plus a calcium antagonist in 1, and no medications in 2. One of the patients with coronary artery disease was receiving a calcium antagonist plus a beta-adrenergic blocking agent, and the other 4 were receiving beta-adrenergic blocking agents. There was no association between arrhythmia induction and preoperative medications. Fentanyl was the primary anesthetic agent in 12 patients with HC and 3 patients with coronary artery disease. Hydromorphone hydrochloride was the primary agent in 5 study patients and 2 control patients. Nine patients with HC received supplemental anesthesia with enflurane and 5 with halothane, and 3 received no additional agents. Three of the patients with coronary artery disease received enflurane, 1 received halothane, and 1 received isoflurane. There was no association between anesthetic agents and arrhythmia inducibility.

To evaluate the effect of left ventricular outflow obstruction on arrhythmia inducibility, defibrillation was accomplished in 4 study patients in whom a sustained arrhythmia had been induced and the stimulation program was reapplied during cardiopulmonary bypass, which obviates the hemodynamic effects of obstruction. The arrhythmia was reinduced in each case.

## Discussion

The incidence of sudden death is high in patients with HC, roughly 2%/year.[1,2] It appears to be even higher in younger patients.[1] Sudden death may be the first manifestation of HC in some patients.[11] The mechanism of sudden death is unknown in most cases. Several investigators have suggested that ventricular tachyarrhythmias are the primary cause of sudden death,[1,3] although other potential mechanisms include acutely exacerbated outflow obstruction, reflex vasodilation,[12] acute myocardial infarction,[13] bradyarrhythmias,[14] heart block,[15,16] and supraventricular arrhythmias.[17,18]

VF has been documented in several patients at the time of attempted resuscitation,[2,3,11,19,20] but it has rarely been possible to determine whether VF was the initial event or a terminal phenomenon. In 2 patients with HC and accessory pathways VT, which rapidly degenerated into VF, was the cause of death.[17,21] Longitudinal studies of patients with HC have demonstrated an association between VT (≥3 consecutive ventricular beats) detected on ambulatory monitoring and subsequent sudden death or cardiac arrest.[3,6] The significance of this relation is tempered by the large number of patients with complex ventricular arrhythmias who did not have a catastrophic event. Maron et al[3] and McKenna and Goodwin[22] suggest that VT detected during monitoring may only be a marker of severe disease and that other coexisting variables may be necessary for a short run of consecutive ventricular beats to evolve into a terminal arrhythmia.

The purpose of this investigation was to determine the vulnerability of patients with HC to ventricular arrhythmia induction. The methods were similar to those routinely employed in the management of recurrent VT in our hospital.[23] The study group consisted of patients referred for surgical management of obstructive HC, and all patients were included whether or not previous arrhythmias were suspected. In selecting the control group an effort was made to reduce the potential for inducible arrhythmias by selecting patients with no evidence of myocardial damage.

A ventricular tachyarrhythmia was induced in 88% of the patients with HC and was sustained in all but 1 patient. In 4 study patients the induced arrhythmia terminated within 15 seconds during the initiation of cardiopulmonary bypass. The sudden change in milieu that occurs when the pump prime perfuses the heart and left ventricular afterload and coronary perfusion pressure decrease may have been responsible for the termination of these arrhythmias. Nevertheless, in each case a sustained tachyarrhythmia was induced with the same stimulation program during bypass. None of the control patients had a sustained arrhythmia despite vigorous stimulation. The difference in tachyarrhythmia inducibility between the study and control patients was highly significant despite the small number of control patients. The difference in vulnerability could not be explained on the basis of preoperative medications, which may still have been present in physiologically active concentrations in some patients, or on the basis of differences in anesthetic agents used in the 2 groups.

Several possible explanations for the different responses in the 2 groups exist. It is possible that the patients with HC had myocardial ischemia as a result of ventricular pacing. However, the control patients had critical lesions of at least 2 coronary vessels and could also be expected to have myocardial ischemia. Eight of 9 patients with HC had a sustained arrhythmia induced when the effects of left ventricular outflow obstruction were circumvented by cardiopulmonary bypass. This suggests that the vulnerability to arrhythmia induction is not due to ischemia or an acute effect of outflow obstruction.

A myocardial electrophysiologic abnormality in the patients with HC seems the most likely explanation for their vulnerability to ventricular tachyarrhythmia induction. Other investigators have demonstrated abnormal myocardial electrophysiologic properties in patients with HC.[24,25] Koyanagi et al[26] recently showed an increased incidence of sudden cardiac death in dogs with left ventricular hypertrophy subjected to coronary artery occlusion. Aronson[27] demonstrated triggered automaticity in rat hypertrophic tissue.

The unusual susceptibility to malignant ventricular tachyarrhythmia induction we observed suggests that electrophysiologic testing in some patients with HC may be hazardous. Reports of VF resulting in death during the electrophysiologic evaluation of accessory pathways in 2 patients with HC support this contention.[17,21]

Our patients with HC had symptoms and obstruction severe enough to warrant surgery. Therefore our results may not be applicable to patients with less severe symptoms.

The extension of findings obtained in the operating room to the "normal" awake state requires caution. Also, the significance of inducible ventricular tachyarrhythmias in subjects without previous spontaneous tachyarrhythmias is not fully known. However, tachyarrhythmia inducibility and noninducibility in anesthetized patients has correlated well with previous and subsequent spontaneous ventricular tachyarrhythmias.[28] Furthermore, the inducibility of ventricular tachyarrhythmias has been found to predict future sudden death in patients after infarction without previous tachyarrhythmias.[29,30] Thus, our findings suggest that patients with severe, symptomatic obstructive HC may be unusually vulnerable to spontaneous ventricular tachyarrhythmias.

## References


1. **McKenna W, Deanfield J, Faruqui A, England D, Oakley C, Goodwin J.** Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. Am J Cardiol 1981;47: 532–538.
2. **Shah PM, Adelman AG, Wigle ED, Gobel FL, Burchell HB, Hardarson T, Curiel R, de la Calzada C, Oakley CM, Goodwin JF.** The natural (and unnatural) history of hypertrophic cardiomyopathy. Circ Res 1974;34,35:(Suppl II):179–195.
3. **Maron BJ, Savage DD, Wolfson JK, Epstein SE.** The prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. Am J Cardiol 1981; 48:252–257.
4. **McKenna W, England D, Oakley C, Goodwin J.** Detection of arrhythmia in hypertrophic cardiomyopathy: prospective study (abstr). Circulation 1980;62:Suppl III:III-708.
5. **McKenna WJ, Chetty S, Oakley CM, Goodwin JF.** Arrhythmia in hypertrophic cardiomyopathy: exercise and 48 hour ambulatory electocardiographic assessment with and without beta adrenergic blocking therapy. Am J Cardiol 1980;45:1–5.
6. **McKenna WJ, England D, Doi YL, Deanfield JE, Oakley C, Goodwin JF.** Arrhythmia in hypertrophic cardiomyopathy. I. Influence on prognosis. Br Heart J 1981;46:168–172.
7. **Mason JW, Winkle RA.** Accuracy of the ventricular tachycardia-induction study for predicting long-term efficacy and inefficacy of antiarrhythmic drugs. N Engl J Med 1980;303:1073–1077.
8. **Ruskin JN, DiMarco JP, Garan H.** Out of hospital cardiac arrest: electrophysiologic observations and selection of long-term antiarrhythmic therapy. N Engl J Med 1980;303:607–613.
9. **DiMarco JP, Garan H, Harthorne JW, Ruskin JN.** Intracardiac electrophysiologic techniques in recurrent syncope of unknown cause. Ann Intern Med 1981;95:542–548.
10. **Braunwald E, Lamrew CT, Rockoff SD, Ross J Jr, Morrow AC.** Idiopathic hypertrophic subaortic stenosis. 1. A description of the disease based upon an analysis of 64 patients. Circulation 1964;30:Suppl IV:IV-3–IV-119.
11. **Maron BJ, Roberts WC, Edwards JE, McAllister HA, Foley DD, Epstein SE.** Sudden death in patients with hypertrophic cardiomyopathy: characterization of 26 patients without functional limitation. Am J Cardiol 1978; 41:803–810.
12. **McKenna W, Harris L, Deanfield J.** Syncope in hypertrophic cardiomyop-

athy. Br Heart J 1982;47:177–179.
13. **Maron BJ, Epstein SE, Roberts WC.** Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. Am J Cardiol 1979;43:1086–1102.
14. **Joseph S, Balcon R, McDonald L.** Syncope in hypertrophic obstructive cardiomyopathy due to asystole. Br Heart J 1972;34:974–977.
15. **Chielewzki CA, Riley RS, Mahendran A, Most AS.** Complete heart block as a cause of syncope in asymmetric septal hypertrophy. Am Heart J 1977;93:91–95.
16. **Ingham RE, Mason JW, Rossen RM, Goodman DJ, Harrison DC.** Electrophysiologic findings in patients with idiopathic hypertrophic subaortic stenosis. Am J Cardiol 1978;41:811–816.
17. **Krikler DM, Davies MJ, Rowland E, Goodwin JF, Evans RC, Shaw DB.** Sudden death in hypertrophic cardiomyopathy: associated accessory atrioventricular pathways. Br Heart J 1980;43:245–251.
18. **Bouhour JB, Bory M, Bourmayan C, Chiffoleau S, Favereau X, Foussard C, Komajda M, Lassabe G, Morand Ph, Nelman JL.** Tachycardies supraventriculaires au cours des myocardiopathies obstructives. Arch Mal Coeur 1981;74:993–1000.
19. **Krelhaus W, Kuhn H, Loogen F.** Analysis of deaths in the course of hypertrophic obstructive cardiomyopathy. In: Kaltenbach M, Loogen F, Olsen EGJ, eds. Cardiomyopathy and Myocardial Biopsy. New York: Springer-Verlag, 1978:300–307.
20. **James TN, Marshall TK.** De subitaneis mortibus: XII. Asymmetrical hypertrophy of the heart. Circulation 1975;51:1149–1166.
21. **Wellens HJJ, Bar FW, Vanagt EJ.** Death after ajmaline administration [letter]. Am. J Cardiol 1980;45:905.
22. **McKenna WJ, Goodwin JF.** The natural history of hypertrophic cardiomyopathy. Curr Prob Cardiol 1981;6:1–26.
23. **Mason JW, Stinson EB, Winkle RA, Griffin JC, Oyer PE, Ros DL, Derby G.** Surgery for ventricular tachycardia: efficacy of left ventricular aneurysm resection compared with operation guided by electrical activation mapping. Circulation 1982;65:1148–1155.
24. **Coltart DJ, Meldrum SJ.** Hypertrophic cardiomyopathy: an electrophysiologic study. Br Med J 1970;4:217–218.
25. **Cosio FG, Moro C, Alonso M, De La Calzada CS, Llovet A.** The Q waves of hypertrophic cardiomyopathy: an electrophysiologic study. N Engl J Med 1980;302:96–99.
26. **Koyanagi S, Eastham C, Marcus ML.** Effects of chronic hypertension and left ventricular hypertrophy on the incidence of sudden cardiac death after coronary artery occlusion in conscious dogs. Circulation 1982;65: 1192–1197.
27. **Aronson RS.** Afterpotentials and triggered activity in hypertrophied myocardium from rats with renal hypertension. Circ Res 1981;48:720–727.
28. **Josephson ME, Harken AH, Horowitz LN.** Long-term results of endocardial resection for sustained ventricular tachycardia in coronary disease patients. Am Heart J 1982;104:51–57.
29. **Uther JB, Cody DV, Denniss AR, Richards DA, Russell PA, Young AA.** Ventricular programmed stimulation and exercise ST segment depression as predictors of post-infarction mortality (abstr). Am J Cardiol 1982;49: 902.
30. **Richards DA, Cody DV, Denniss AR, Russell PA, Uther JB.** Ventricular electrical instability during the first year following myocardial infarction (abstr). Am J Cardiol 1982;49:929.

# Myocardial Texture Characterization by Two-Dimensional Echocardiography

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**Twenty-four normal subjects and 181 patients with various cardiac disorders (36 autopsies) were studied by 2-dimensional echocardiography. In vitro echocardiographic studies were performed on 26 of 36 autopsied hearts utilizing an ultrasonically visible metallic probe to correlate myocardial echo patterns with histopathologic features. All normal subjects and the majority of patients with ventricular hypertrophy due to valvular or hypertensive lesions showed a uniformly speckled or an echolucent appearance of the myocardium (type I texture). No autopsied heart with this texture had gross fibrosis (visible to the naked eye) or infiltrative disease. All patients with infiltrative disorders (amyloidosis, 7 of 7; Pompe's disease, 4 of 4) had multiple, discrete, and small (3 to 5 mm) highly refractile echoes (HREs) in the myocardium involving the ventricle or ventricles completely (type IIA texture) or partly (type IIB texture). However, this finding was nonspecific and was observed in many other conditions such as left heart hypoplastic syndrome (10 of 10), hypertrophic cardiomyopathy (19 of 26), and chronic renal failure (4 of 9). In the noninfiltrative group, HREs in the autopsied cases were shown to result from gross fibrosis or endocardiofibroelastosis utilizing in vitro echocardiographic studies and metallic probe-guided biopsies, while HREs in the autopsied cases with cardiac amyloidosis could be correlated only with amyloid deposits since fibrosis was absent. Larger HREs (>5 mm) presenting as broad patches or long linear echoes in the myocardium (type IIC texture) was seen in old myocardial infarctions (9 of 21) and congestive cardiomyopathy (4 of 26) and were correlated with large areas of myocardial fibrosis. Two-dimensional echocardiographic studies of myocardial texture help identify various infiltrative and degenerative processes in the heart.**

Real-time 2-dimensional echocardiography has assumed an important role in the identification and evaluation of patients with various cardiac disorders.[1,2] Its clinical value has depended to a large extent on changes in the cardiac chamber size, wall thickness, cardiac contractility, and structural alterations in the cardiac valves. Little emphasis has been placed on the echocardiographic evaluation of myocardial texture until recently, when attention was drawn to altered myocardial echo patterns in cardiac amyloidosis[3,4] and idiopathic hypertrophic subaortic stenosis.[5] However, a detailed and systematic 2-dimensional echocardiographic analysis of alterations in the myocardial texture in various myocardial disorders has not been reported so far.

With the use of 2-dimensional echocardiography, we report our findings on the echocardiographic analysis of myocardial texture in 24 normal subjects and 181 patients (36 autopsies) with various cardiac disorders.[6] In addition, in vitro 2-dimensional echocardiographic studies were performed on 26 of 36 autopsied hearts in an attempt to precisely correlate echo patterns with local histopathologic changes.[7]

## Methods

The study population was comprised of 205 randomly selected patients (41 children, 164 adults), all of whom were seen at Strong Memorial Hospital from 1980 to 1982. The clinical and diagnostic profiles of these patients are summarized in Table I. Twenty-four normal subjects had no known disease and had normal findings on physical examination, electrocardiography, and echocardiography. One hundred eighty-one patients had various cardiac disorders which met standard diagnostic criteria. Based on echocardiographic criteria reported previously,[8,9] 55 patients had single or biventricular

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**TABLE I Clinical Profile of 205 Patients**

| Disease Category: Patients (n) | Mean Age (yr) | Comments | Autopsy |
|---|---|---|---|
| 1. Normal 24 (19A, 5P) | 28 | No known disease | 2 |
| 2. UVH 55 (40A, 15P) | 43 | 5 BVH (moderate) 44 LVH, 5 RVH (mild 20, moderate 11, severe 18) | 12 |
| 3. CRF 9 (8A, 1P) | 50 | 9 LVH (3 moderate, 6 severe) all on maintenance dialysis | 3 |
| 4. CCM 26 (24A, 2P) | 52 | No valvular or coronary disease | 3 |
| 5. HCM 26 (23A, 3P) | 52 | Resting SAMs and ASH in all | 2 |
| 6. AMI 14 (14A) | 58 | History, cardiac enzymes and electrocardiographic changes in all | ... |
| 7. CMI 21 (20A, 1P) | 60 | | 2 |
| 8. Amyloidosis 7 (7A) | 63 | CHF in all, 5 had systemic biopsy positive for amyloid | 2 |
| 9. Pompe's disease 4 (4P) | 0.5 | CHF and skeletal muscle biopsy in all | ... |
| 10. Hemochromatosis 9 (9A) | 55 | CHF in 1, liver biopsy in all | ... |
| 11. LHH 10 (10P) | Newborn | Systemic hypoperfusion in all | 10 |

A = adult; AMI = acute myocardial infarction; BVH = biventricular hypertrophy; CCM = congestive cardiomyopathy; CHF = congestive heart failure; CMI = chronic myocardial infarction; CRF = chronic renal failure; HCM = hypertrophic cardiomyopathy; LHH = left heart hypoplastic syndrome; P = pediatric; SAM = systolic anterior motion; UVH = uncomplicated single/biventricular hypertrophy.

hypertrophy due to rheumatic heart disease (14 patients), bicuspid or degenerative aortic stenosis (17 patients), hypertensive heart disease (7 patients), and congenital heart disease (17 patients) (uncomplicated ventricular hypertrophy group).

Two-dimensional echocardiography was performed using a commercially available real-time wide angle (90°) mechanical sector scanner and a 3.0 or 5.0 mHz transducer (Advanced Technology Laboratories). Images were recorded on videotapes (Sanyo or Panasonic half-inch tapes) for later analysis in real time or slow motion. Polaroid photographs were made of stop action frame images for illustrations.

Standard echocardiographic examinations were performed with the patient in the supine and/or left lateral decubitus positions.[1,10] The instrumental gain settings were adjusted to obtain optimal images of the myocardial and valvular structures. All patient examinations were done using a 45 dB logarithmic gray scale curve (GSC) which is recommended by the manufacturer for routine echocardiographic studies. This GSC assigns most of the available 8 gray shades to the low

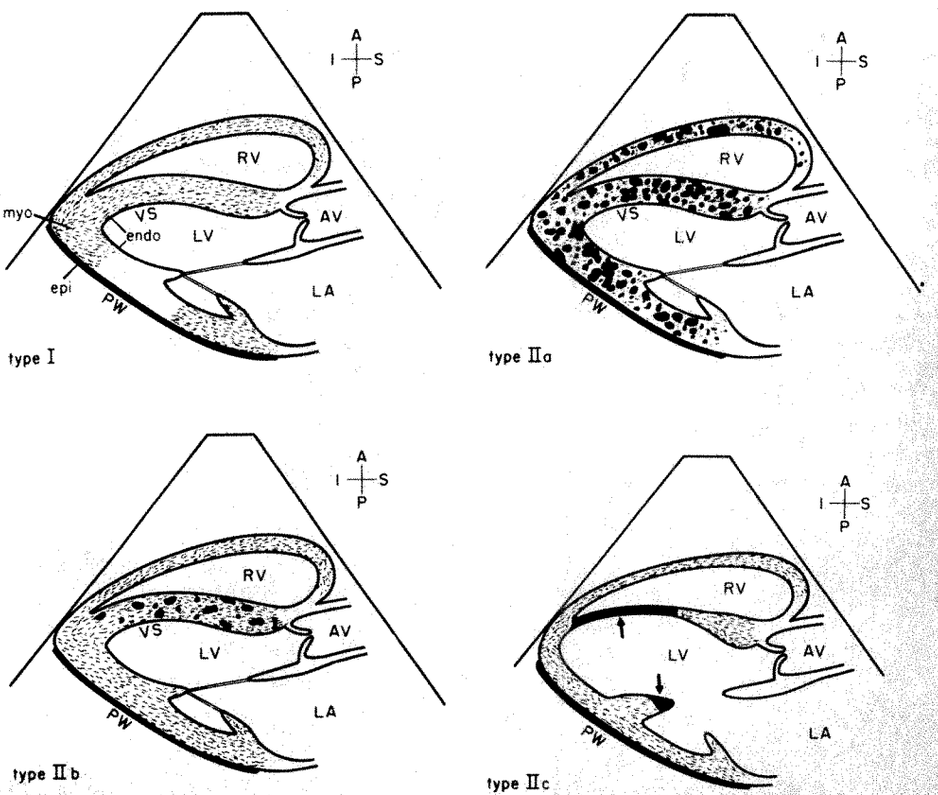



**FIGURE 1.** Schematic representation of the types of myocardial texture. Type I texture is characterized by a fine, speckled, and homogeneous or an echolucent appearance of the myocardium. In both types IIA and IIB texture, multiple, small, and discrete HREs shown as dark areas are seen in the myocardium and are separated from one another by lower-amplitude fine speckled echoes. In type IIA, HREs involve all walls of 1 or both ventricles while only some but not all walls are involved in type IIB texture. Larger HREs presenting as long linear or broad patches (**dark areas**) in the myocardium characterize type IIC texture.

amplitude echosignals for their better differentiation. Additionally, echocardiographic images were also studied using a linear GSC (available in ATL model 850A), which assigns gray shades in a uniform manner regardless of range of echo signal amplitudes. An attempt was made to visualize all walls of both ventricles in each patient by obtaining parasternal long- and short-axis views, apical 4-chamber and 2-chamber views, and subcostal views.

Thirty-six hearts available for postmortem studies were examined in a standard manner. Histopathologic studies were performed on multiple sections obtained routinely from both the ventricular septal and left ventricular posterior walls at the level of the papillary muscles and just below the mitral anulus and on those taken from the areas of discernible disease. Special stains were employed whenever endofibroelastosis and infiltration with amyloid, mucopolysaccharide, or iron were suspected. The cut surfaces of the ventricles were closely inspected for areas of gross fibrosis (visible to the naked eye); these were subsequently confirmed by histologic study. Additionally, histologic sections from multiple sites were carefully examined for the presence of interstitial or perivascular fibrosis.

In vitro 2-dimensional echocardiography was performed by suspending the heart specimens or isolated slices of the ventricular walls to a depth of 4 to 5 cm in a water bath at 22°C.[7] Keeping the transducer at the water surface, multiple echocardiographic views of the suspended hearts—some simulating in vivo long- and short-axis views of the left ventricle, were obtained using 45 dB logarithmic and linear GSCs. A long thin metallic probe which could be ultrasonically imaged was advanced under echo control to identify and penetrate areas of the myocardium giving rise to different echo patterns; biopsies were taken along the probe to precisely correlate echo patterns with histopathology. The contact between the tip of the metallic probe and the myocardium was echocardiographically recognized by "dimpling" and motion of myocardial surface as the probe touched it.

For the purposes of our study, left ventricular hypertrophy was graded based on diastolic left ventricular posterior wall thickness as mild (12 to 15 mm), moderate (16 to 18 mm), or severe (>18 mm). Right ventricular hypertrophy was graded based on diastolic right ventricular diaphragmatic wall thickness as mild (6 to 8 mm), moderate (9 to 10 mm), or severe (>10 mm). Myocardial texture was evaluated in a qualitative fashion by analyzing visual appearances of the amplitude and spatial distribution of echo signals reflected by the myocardium. Particular attention was paid to areas of very bright or highly refractile echoes in the myocardium. Highly refractile echoes were defined as echoes which persisted at gain settings low enough to completely eliminate the adjacent left ventricular/right ventricular endo- or myocardial echoes. Their size, shape, and distribution in the myocardium were studied in multiple echocardiographic planes obtained by different transducer positions and angulations. All echocardiograms were independently reviewed by 2 observers for the presence or absence of HREs and their size and spatial distribution in the myocardium. All histopathologic sections were reviewed by 2 members of the pathology department.

## Results

There was no disagreement in the interpretation of myocardial echo patterns of all patients as studied by 2 independent observers; echo patterns could be classified in 2 broad categories (Fig. 1).

**Type I myocardial texture** was characterized by a fine, speckled, and uniform appearance of the myocardium bordered by a thin linear echo from the endocardium and a bright thick echo from the epicardial-lung interface. The echo signals reflected from the myocardium were of low amplitude and the myocardium often appeared echolucent, especially at low gain settings or when linear GSC was used.

Type I myocardial texture was observed in 133 patients (as shown in Fig. 2) and included all normal subjects, all patients with acute myocardial infarctions, the majority of patients with uncomplicated ventricular hypertrophy (Fig. 3) as well as congestive cardiomyopathy, and some patients with chronic renal failure, systemic hemochromatosis, chronic myocardial infarction, and hypertrophic cardiomyopathy. Postmortem studies available in 15 patients with this texture (2 normal, 9 uncomplicated ventricular hypertrophy, 2 chronic renal failure, 2 congestive cardiomyopathy) demonstrated no gross fibrosis, endocardiofibroelastosis, calcification, or infiltrative pathology involving the ventricular myocardium (Fig. 4). Some patients, however, had microscopic fibrosis in the myocardium.

**Type II myocardial texture** was characterized by the presence of very bright or highly refractile echoes in the myocardium. The visual differences between HREs and the surrounding low amplitude echoes became more prominent when linear rather than 45 dB logarithmic GSC was utilized. Based upon the size, shape, and distribution of HREs in the myocardium, 3 subtypes were recognized as follows (Fig. 1): *Type IIA:* All walls of 1 or both ventricles were involved with multiple, small (3 to 5 mm), and discrete HREs. The

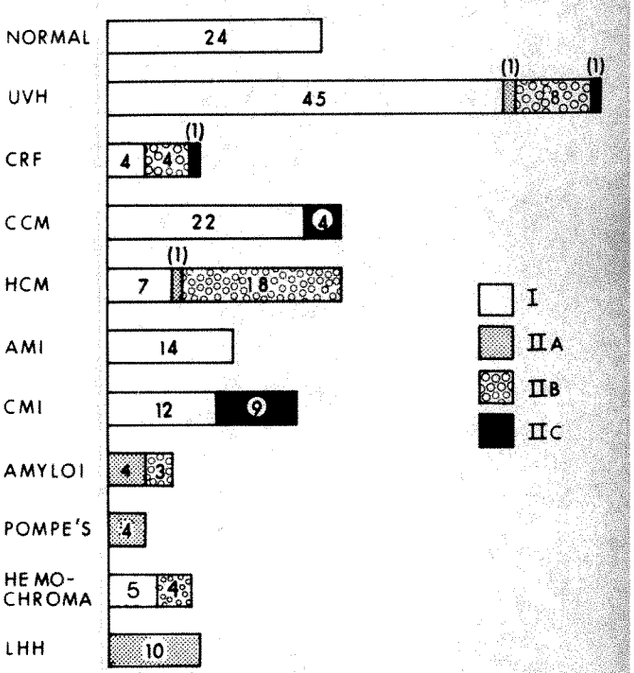



**FIGURE 2.** Types of myocardial texture observed in various disease categories. AMI = acute myocardial infarction; AMYLOI = amyloidosis; CCM = congestive cardiomyopathy; CMI = chronic myocardial infarction; CRF = chronic renal failure; HCM = hypertrophic cardiomyopathy; Hemochroma = hemachromatosis; LHH = left heart hypoplastic syndrome; UVH = uncomplicated ventricular hypertrophy.

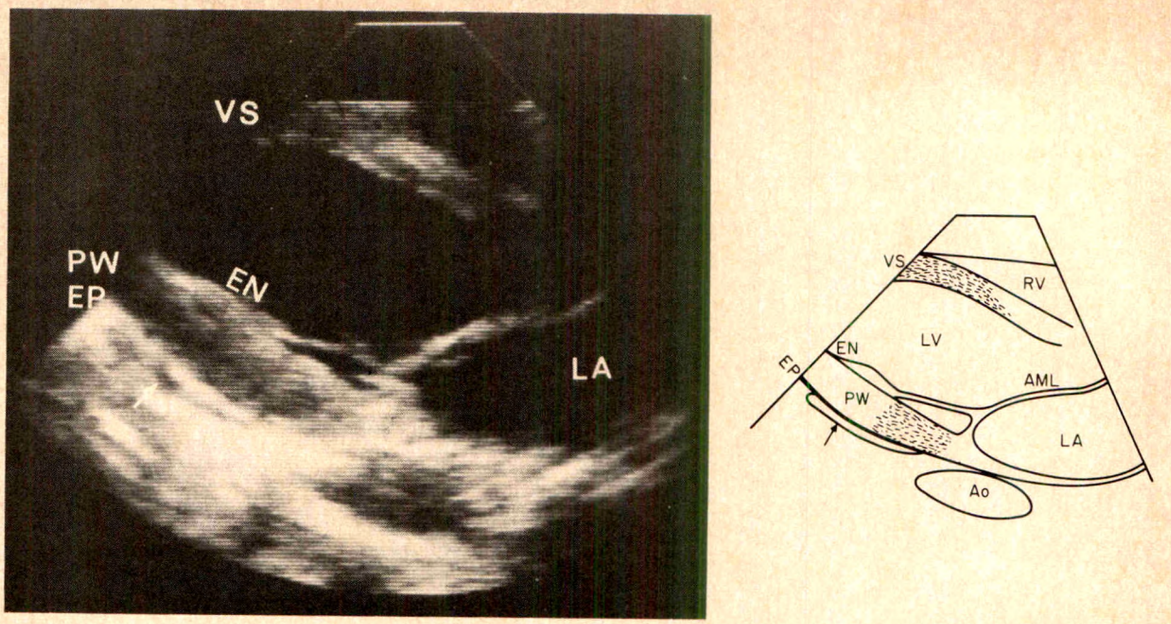



**FIGURE 3.** Type I myocardial texture. Long-axis view of the left ventricle (LV) in a patient with left ventricular hypertrophy demonstrates a fine, speckled, and homogeneous appearance of the septal and posterior wall (PW) myocardium. Bright echoes are absent in the myocardium. The left ventricular posterior wall epicardium (EP) appears thicker and brighter than the endocardium (EN). The **arrow** represents a small posterior pericardial effusion space. AML = anterior mitral leaflet; AO = aorta; LA = left atrium; RV = right ventricle; VS = ventricular septum.

latter were round or irregular in shape and were separated from one another by low amplitude echoes. *Type IIB:* One or more but not all walls of a ventricle or ventricles were involved with multiple HREs of characteristics similar to those in type IIA. *Type IIC:* The whole ventricular wall or a large localized segment (>5 mm) of a ventricular wall presented a very bright or highly refractile appearance. Small and discrete HREs seen in types IIA and IIB were absent.

**Type IIA texture** was observed in 20 patients as shown in Figure 2 and included all patients with

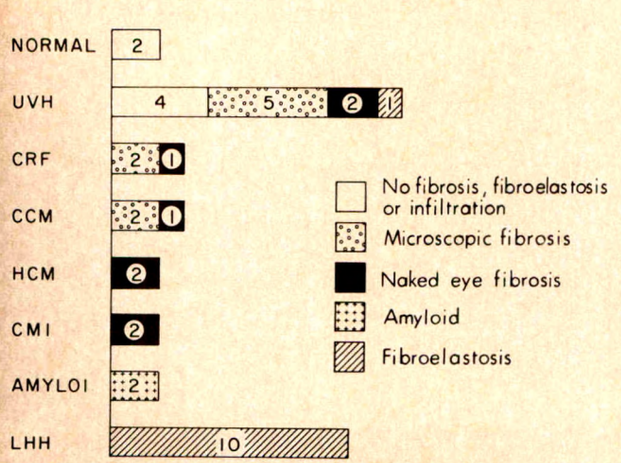



**FIGURE 4.** Histopathologic findings in 36 autopsied patients. AMYLOI = amyloidosis; CCM = congestive cardiomyopathy; CMI = chronic myocardial infarction; CRF = chronic renal failure; HCM = hypertrophic cardiomyopathy; LHH = left heart hypoplastic syndrome; UVH = uncomplicated ventricular hypertrophy.

Pompe's disease, all with left heart hypoplastic syndrome, the majority of patients with cardiac amyloidosis, 1 adult with hypertrophic cardiomyopathy, and an infant with left ventricular hypertrophy secondary to aortic stenosis. In patients with cardiac amyloidosis and Pompe's disease, HREs diffusely involved all walls of both ventricles which were markedly thickened (Fig. 5); all of them had severe congestive heart failure. In other patients with this type of texture, HREs selectively involved left ventricular walls only. Postmortem studies demonstrated severe endofibroelastosis in the left ventricle of all 10 newborns with left heart hypoplastic syndrome and in the infant with left ventricular hypertrophy. Both autopsied patients with amyloidosis had extensive myocardial deposits of amyloid in both ventricles with no associated fibrosis or calcification (Fig. 4.)

**Type IIB texture** was seen in 37 patients as shown in Figure 2 and included the majority of patients with hypertrophic cardiomyopathy and some patients with cardiac amyloidosis, chronic renal failure, systemic hemochromatosis, and uncomplicated ventricular hypertrophy. In patients with hypertrophic cardiomyopathy, HREs were seen in the ventricular septum alone in 15 (Fig. 6) and both ventricular septal and left ventricular posterior walls in 3. In patients with amyloidosis and type IIB texture, HREs were predominantly seen in the ventricular septum or posterior wall, or both, and all of them had moderate ventricular "hypertrophy" and well-compensated congestive heart failure. Postmortem studies available in 3 patients with this texture (2 hypertrophic cardiomyopathy and 1 uncomplicated ventricular hypertrophy) demonstrated discrete areas of gross fibrosis without calcification in the left ven-

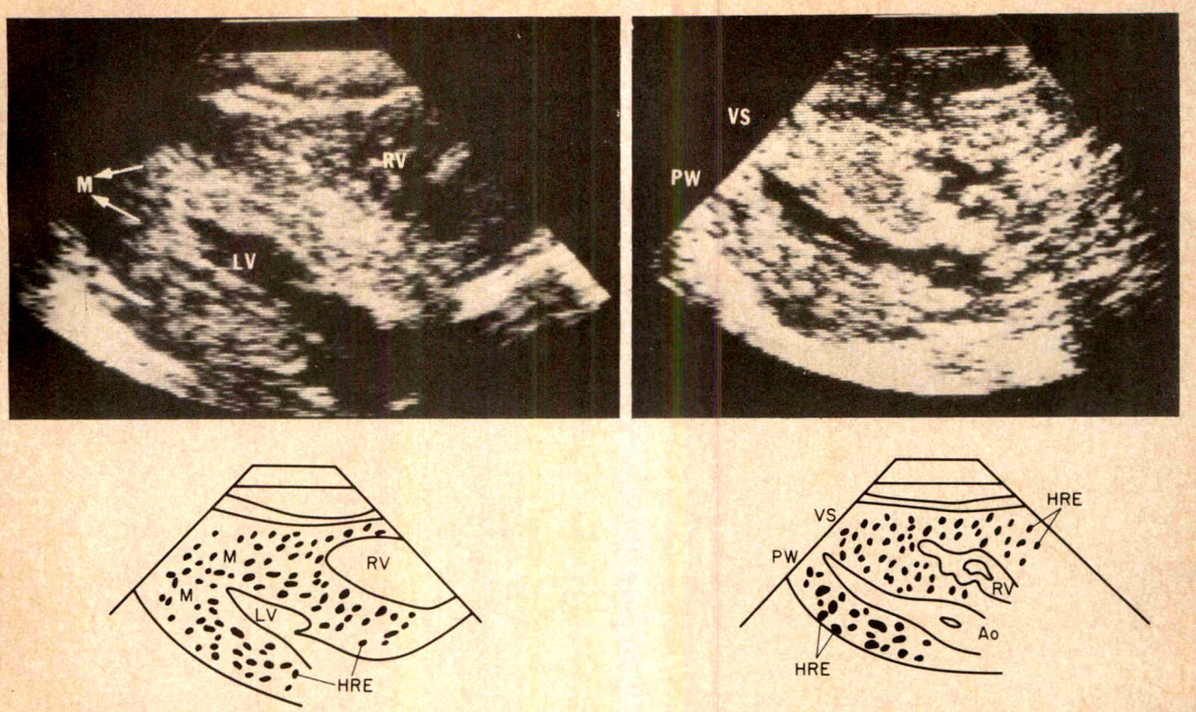



**FIGURE 5.** Type IIA myocardial texture. Subcostal views. Multiple, discrete, and small HREs involve all walls of both ventricles in a patient with cardiac amyloidosis (**left**) and in another patient with Pompe's disease (**right**). The ventricular walls are markedly thickened in both. Ao = aorta; LV = left ventricle; M = myocardium; PW = posterior wall; RV = right ventricle; VS = ventricular septum.

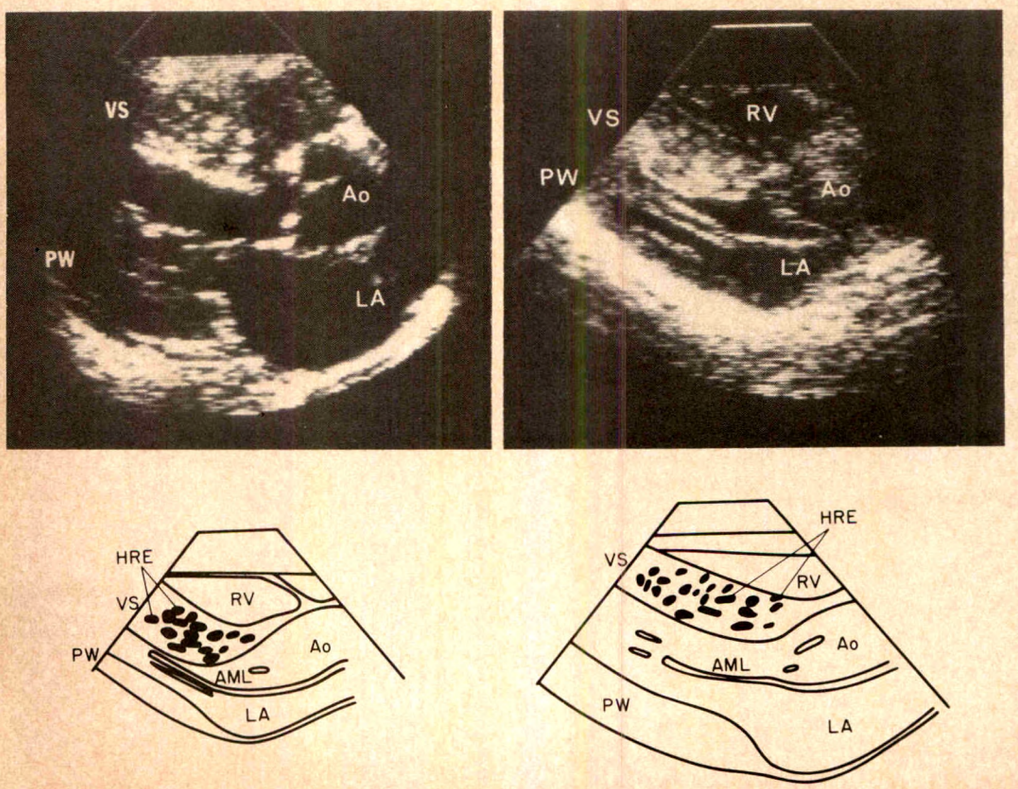



**FIGURE 6.** Type IIB myocardial texture. Long-axis view. Multiple, discrete, and small HREs are seen in the ventricular septum (VS) of a patient with chronic renal failure and concentric left ventricular hypertrophy (**left**) and in another patient with hypertrophic cardiomyopathy and asymmetrical septal hypertrophy (**right**). The left ventricular posterior wall (PW) is uninvolved in both and presents an echolucent (**left**) and fine speckled appearance (**right**). AML = anterior mitral leaflet; Ao = aorta; LA = = left atrium, RV = right ventricle.

tricular myocardium, corresponding in location to those of HREs seen in in vivo echocardiographic studies (Fig. 4).

**Type IIC texture** was observed in 15 patients as shown in Figure 2 and included about half of the patients with chronic myocardial infarction, some patients with congestive cardiomyopathy, an adult patient with chronic-renal failure and an infant with uncomplicated ventricular hypertrophy. Bright long linear echoes (25 to 42 mm long, 4 to 8 mm broad) were visualized in the mid and distal ventricular septum virtually replacing the normal myocardium in 4 of 7 patients with anteroseptal infarcts (Fig. 7). Similar echoes were also noted in the posterior wall in 2 of 6 patients with posteroinferior infarcts and in the anterior wall of 1 of 8 patients with anterolateral infarcts. In 1 patient with congestive cardiomyopathy, bright long linear echoes were seen involving the ventricular septum (44 mm × 5 mm) as well as the left ventricular posterior wall (33 mm × 6 mm) (Fig. 7). The inner third of the papillary muscles as visualized in the left ventricular long-axis view presented a uniformly bright or hyperrefractile appearance in 2 patients with prior myocardial infarction and 3 patients with congestive cardiomyopathy. All of them had systolic mitral regurgitant murmurs suggestive of papillary muscle dysfunction. Another infant with biventricular hypertrophy secondary to double-outlet right ventricle also demonstrated a similar appearance of the papillary muscle. In 1 patient with chronic renal failure, the whole ventricular septum presented a uniformly hyperrefractile appearance which persisted in all echocardiographic views. Postmortem studies available in 5 cases with this type of texture demonstrated areas of large macroscopic fibrosis without calcification involving the myocardium (1 congestive cardiomyopathy, 1 chronic renal failure) or papillary muscles (2 chronic myocardial infarction, 1 double-outlet right ventricle) (Fig. 4).

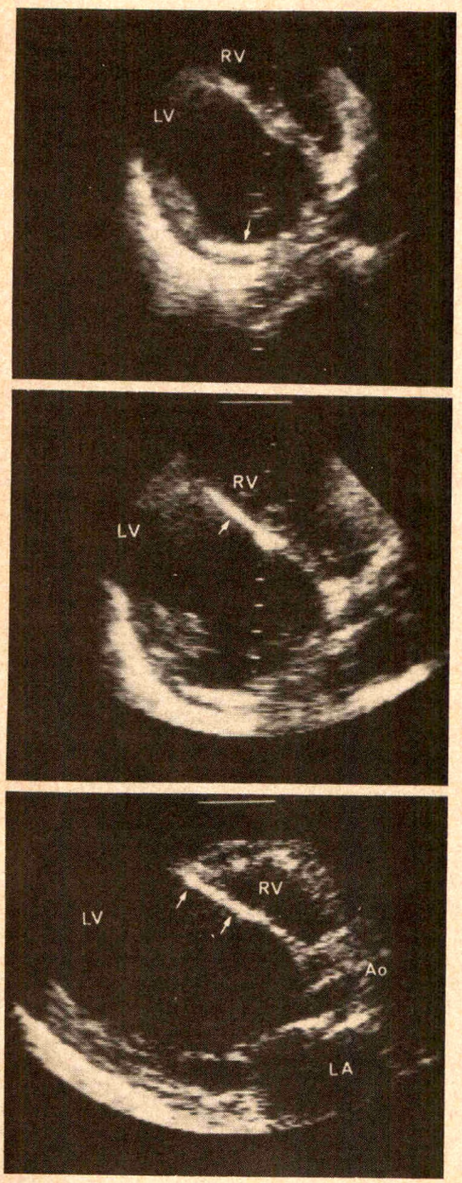



**FIGURE 7.** Type IIC myocardial texture. **Top and middle,** the oblique short-axis views of the left ventricle (LV) in a patient with congestive cardiomyopathy demonstrate very bright, long, linear thick echoes **(single arrows)** in the posterior wall (PW) myocardium and in the ventricular septum (VS), which were shown to be due to gross fibrosis without any calcification at subsequent autopsy. **Bottom,** the distal ventricular septum seen in long-axis view in this patient with old anteroseptal myocardial infarct is virtually replaced by a bright long linear thick echo **(double arrows)** consistent with scar tissue. Other abbreviations as before.

Myocardial echo patterns obtained from in vitro echocardiographic studies performed on 26 hearts were found similar in appearance to in vivo echo patterns in all cases. In vitro 2-dimensional echocardiographic studies were used to correlate areas of ultrasonic hyperreflectivity in the myocardium with histopathologic features by means of metallic probe-guided tissue biopsies. Areas of hyperreflectivity were shown to correlate with amyloid deposits (2 hearts with amyloidosis), endofibroelastosis (2 hearts with left heart hypoplastic syndrome, 1 with aortic stenosis), and naked eye fibrosis (2 hypertrophic cardiomyopathy, 1 chronic renal failure, 1 congestive cardiomyopathy, 1 double-outlet right ventricle, 2 chronic myocardial infarction) (Fig. 8). The remaining 14 hearts (2 normal, 9 uncomplicated ventricular hypertrophy, 2 chronic renal failure, 1 congestive cardiomyopathy) demonstrated a fine, speckled, and uniform appearance with no HREs; none had macroscopic fibrosis, calcification, endofibroelastosis, or infiltrative pathology.

## Discussion

Previous 2-dimensional echocardiographic studies have demonstrated altered myocardial echo patterns in patients with idiopathic hypertrophic subaortic stenosis,[5] cardiac amyloidosis,[3,4] and coronary artery disease.[11,12] Martin et al[5] reported a "ground glass texture" of the proximal ventricular septum in patients with idiopathic hypertrophic subaortic stenosis,[5] but the specificity or etiology of this finding was not determined. Chiaramida et al[4] found "bright patchy echoes" in the myocardium of a patient with cardiac

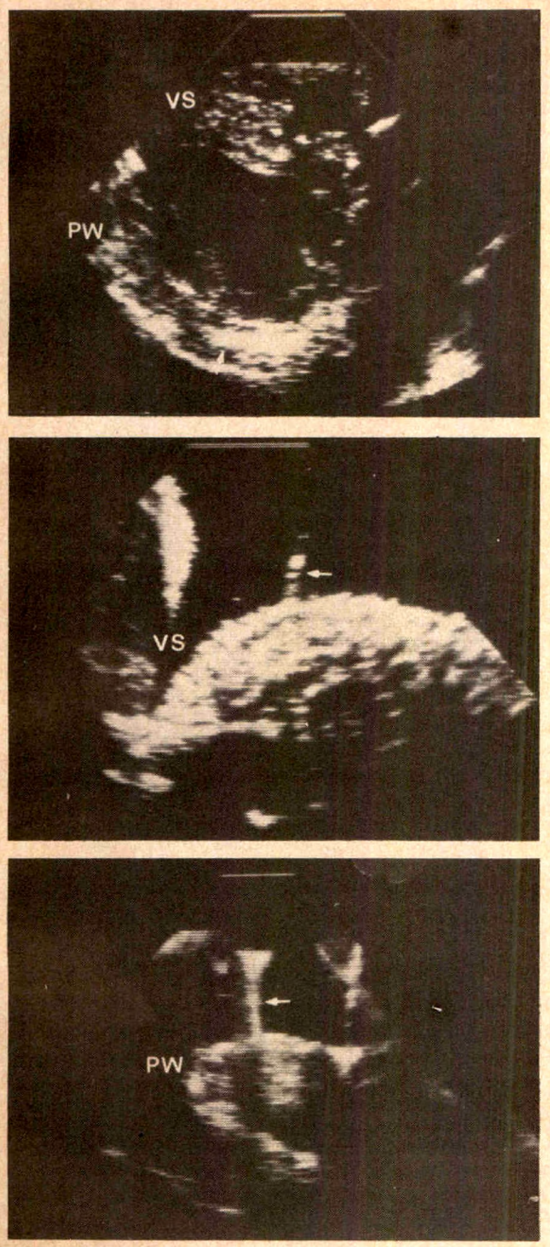



**FIGURE 8.** In vitro echocardiographic studies obtained by immersing parts of or whole heart specimens in a waterbath. **Top,** oblique short-axis examination of a heart specimen from an autopsied patient with congestive cardiomyopathy. The bright, long, linear thick echo (**arrow**) seen in the posterior wall (PW) myocardium (type IIC texture) was shown by a metallic probe-guided biopsy to be due to gross fibrosis. Note the similarities in shape and location of this finding to in vivo studies in this patient (Figure 7, top). **Middle,** in vitro echocardiographic examination of the ventricular septum (VS) obtained from an autopsied patient with cardiac amyloidosis. Note the presence of multiple, small, and discrete HREs within the ventricular septum. The **arrow** demonstrates the ultrasonically visible-probe in contact with the ventricular septal surface. Biopsy samples taken along the probe revealed extensive amyloid deposits without fibrosis or calcification. **Bottom,** In vitro echocardiographic study of the hypertrophied left ventricular posterior wall obtained from an autopsied patient with chronic renal failure. An ultrasonically visible metallic probe (which was advanced under echomonitoring) is seen (**arrow**) at the junction between the relatively bright and the echolucent myocardial areas. Subsequent biopsies showed normal myocardium in the echolucent portion and extensive fibrosis in the bright area.

amyloidosis and considered this finding to be specific for this entity since such a pattern had not been detected by them previously in any other cardiac disorder. Siqueira-Filho et al[3] also described a similar echo pattern in 12 of 13 patients with cardiac amyloidosis. Other workers have described increased echogenicity of the myocardium associated with chronic myocardial infarction[11] and discrete echolucent zones in patients with acute myocardial infarction.[12] Although these preliminary findings are encouraging, their diagnostic significance and clinical applicability remain to be studied.

Our results demonstrate that myocardial texture characterization by 2-dimensional echocardiography is useful in the evaluation of various myocardial disorders. The fine, speckled, and homogeneous, or echolucent appearance of the myocardium without HREs (type I texture) characterizes normal myocardium. Simple hypertrophy of the myocardium does not result in any visually recognizable alteration in the myocardial texture unless there is a severe degree of coexistent fibrosis, endofibroelastosis, or infiltration with amyloid or glycogen. Highly refractile echoes in the myocardium (type II texture) may be observed in a wide variety of myocardial disorders (Fig. 2) and are, therefore, not specific for a single cardiac disease process. However, diffuse and extensive involvement of all walls of 1 or both ventricles with HREs (type IIA texture) was noted in a relatively small number of pediatric and adult conditions, namely left heart hypoplastic syndrome, Pompe's disease, endofibroelastosis associated with left-sided cardiac anomalies, cardiac amyloidosis, and, rarely, hypertrophic cardiomyopathy. The first 3 disorders generally manifest in the newborn or first few years of life and can be distinguished from one another by clinical and other echocardiographic features.[13–15] Patients with hypertrophic cardiomyopathy rarely present with type IIA texture and HREs characteristically involve the left ventricle only. Therefore, the presence of type IIA texture with involvement of both ventricles by HREs in an adult patient would be highly suggestive of cardiac amyloidosis. This finding enabled us to prospectively diagnose cardiac amyloidosis in 2 patients with subsequent confirmation of the diagnosis at autopsy. However, some patients with cardiac amyloidosis, especially those with mild to moderate biventricular hypertrophy and compensated congestive heart failure, demonstrated less generalized involvement of the myocardium with HREs (type IIB texture). The latter texture does not aid in the diagnosis of cardiac amyloidosis since it was observed in many other cardiac disorders such as hypertrophic cardiomyopathy, chronic renal failure, systemic hemochromatosis, and uncomplicated ventricular hypertrophy. (Fig. 2) Bright long linear or broad patch-like echoes (type IIC texture) observed in the myocardium of patients with chronic myocardial infarction and congestive cardiomyopathy represented large areas of gross fibrosis on anatomical correlation. However, all areas of gross fibrosis may not always be identified echocardiographically. Unlike in the ventricular septum and posterior wall, many infarct scars in the anterior and inferior walls of the left ventricle were not identified, probably due to the inability

of echocardiographic tomographic planes to pass through these walls. It would be even more unlikely for standard echocardiographic planes to traverse very small areas of myocardial fibrosis, and this may explain our inability to echocardiographically detect microscopic fibrosis in any patient in this series. Myocardial calcification, though not found in any of our autopsied patients, would also be expected to produce HREs.

Myocardial texture depends on spatial distribution and amplitude of the echo signals reflected from its biologic interfaces.[16-21] Fine, speckled, and homogeneous appearance of the normal myocardium can be explained on the basis of low amplitude echo reflections from various myocardial components such as muscle fibers, capillaries, and collagen strands which present only small differences in acoustic impedances. Also, being irregular in shape and smaller in size than the wave lengths of the ultrasonic beam, they act as diffuse scatterers so that only a small percentage of the incident acoustic energy is returned to the transducer, producing low-amplitude echo signals.[16,19] The markedly bright image from the epicardium-lung interface can be attributed to the enormous acoustic impedance mismatch between heart muscle (1.65 to $1.74 \cdot 10^6$ kg $m^{-2}s^{-1}$)[22] and lung (0.26 to $0.46 \cdot 10^6$ kg $m^{-2}s^{-1}$)[22] and to the specular echo reflections from the relatively large and smooth epicardial surface. The proportional increase in the size of myocardial fibers and the capillary network in simple ventricular hypertrophy[23] would not be expected to significantly alter its acoustic impedance characteristics, and hence hypertrophied myocardium generally presents an echocardiographic appearance similar to that of normal myocardium (Fig. 3).

Fibrosis is well known to give rise to high-amplitude echoes due to marked acoustic impedance mismatch with the adjoining soft tissue.[20,21] This has been shown to be due to the high collagen content of the fibrous tissue.[21] Scar tissue also tends to act as a specular reflector of ultrasound due to its relatively smooth surface and the horizontal orientation of the collagen bundles.[11] Based on pathologic and in vitro echocardiographic studies of autopsied patients in our series, HREs were shown to correlate with areas of naked eye fibrosis in patients with congestive cardiomyopathy, chronic myocardial infarction, chronic renal failure, hypertrophic cardiomyopathy, and uncomplicated ventricular hypertrophy.[24] It is possible that myocardial fiber disarray in hypertrophic cardiomyopathy may be another important contributing factor in the genesis of HREs although neither of our 2 autopsied hearts with this disorder demonstrated fiber disarray in the regions of HREs. Iron deposition in the myocardium of patients with systemic hemochromatosis has been shown to result in reactive or degenerative fibrosis[25] which may explain the occurrence of HREs in this disorder. Endofibroelastosis seen in left heart hypoplastic syndrome and glycogen deposition Pompe's disease[14,15] are associated with considerable increase in collagen and elastin content of the myocardium and may account for the presence of HREs in these disorders. In cardiac amyloidosis, HREs appear to be directly related to amyloid deposits in the myocardium since significant fibrosis or calcification is not associated.[26] HREs may be due to specular reflections from multiple abnormal tissue interfaces produced by large sheet-like deposits of amyloid in the myocardium.

Although ultrasonic properties of myocardial tissue measured in vitro may change depending on time after excision, temperature, and mode of preservatives,[19] we observed no significant differences between in vitro and in vivo myocardial echo patterns. Therefore, it was possible for us to utilize in vitro echocardiographic technique to obtain precise histopathologic correlation of specific myocardial echo patterns. This was achieved by directing a metallic probe under echo monitoring to area of interest and taking tissue biopsies along it. For example, fibrotic areas in the myocardium could be identified as the source of HREs in contrast to the surrounding normal myocardium which gave rise to low-amplitude echoes (Fig. 8).

Certain technical considerations and other limitations need to be emphasized for myocardial texture characterization by echocardiography. Because of the many variable factors, such as the thickness of the chest wall, the depth of cardiac structures from the transducer and their orientation in relation to the ultrasonic beam direction, instrument gain as well as the time gain compensation curve require individual adjustments for examination of any given myocardial wall segment; therefore, routine echocardiographic studies cannot be performed using any fixed gain settings. In our study, instrument gain settings were adjusted in each case so as to obtain an optimal visualization of the endocardium, myocardium, and epicardium. Increases in instrument gain did not result in any significant change in the size of HREs unless gain was so high as to flood the oscilloscope images with noise signals. Since HREs were defined by us as those which persisted at gain settings low enough to completely eliminate the adjacent left ventricular/right ventricular endocardial or myocardial echo signals, echoes which appeared bright only at very high gain settings were automatically excluded from our study. Although we have no experience with other types of commercial echocardiographic instruments which may use different echo signal processing modes, investigators have been able to identify HREs in the myocardium of patients with cardiac amyloidosis[3,4] and idiopathic hypertrophic subaortic stenosis[5] using echocardiographic instruments different from ours. Visual interpretation of myocardial texture is qualitative in nature, but no differences were found in the interpretations of 2 independent observers. Though myocardial tissue characterization has also been attempted by complex quantitative measurements of acoustic properties of the normal and abnormal myocardium,[16,18,27,28] their advantage over qualitative texture characterization has not been shown yet. Since no complex computerized measurements were made in this study, our results show that clinically useful information can be obtained by carefully studying the myocardial texture during routine echocardiographic examinations. The use of multiple GSCs in the characterization of myocardial texture has not been evaluated so far in clinical settings. Although a recent study

has demonstrated the feasibility of combining luminosity modulation and color coding as an alternative to gray scale display,[29] its utility in myocardial texture characterization has not been systematically assessed. Theoretically, the complex interaction of ultrasound with the semirandomly distributed back scatterers in the myocardium can result in the erroneous production of high- or low-amplitude echoes by mechanisms of constructive or destructive interference, respectively.[18] However, this does not introduce any significant errors in qualitative tissue characterization.

In conclusion, myocardial texture characterization by 2-dimensional echocardiography is useful in the evaluation of myocardial infiltrative and degenerative processes and in their differentiation from normal myocardium. Further prospective studies using large numbers of patients and sophisticated equipment with advanced computer techniques for signal processing may permit a more accurate appreciation of tissue-specific echocardiographic patterns.

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## References

1. **Tajik AJ, Seward JB, Mair DD, Lie JT.** Two-dimensional real-time ultrasonic imaging of the heart and great vessels: technique, image orientation, structure identification and validation. Mayo Clin Proc 1978;53:271–303.
2. **Kotler MN, Mintz GS, Segal BL, Parry WR.** Clinical uses of two-dimensional echocardiography. Am J Cardiol 1980;45:1061–1082.
3. **Siqueira-Filho AG, Cunha CLP, Tajik AJ, Seward JB, Schattenberg TJ, Giuliani ER.** M-mode and two-dimensional echocardiographic features in cardiac amyloidosis. Circulation 1981;63:188–196.
4. **Chiaramida SA, Goldman MA, Zema MJ, Pizzarello RA, Goldberg HM.** Real time cross sectional echocardiographic diagnosis of infiltrative cardiomyopathy due to amyloid. J Clin Ultrasound 1980;8:58–62.
5. **Martin PR, Rakowski H, French J, Popp RL.** Idiopathic hypertrophic subaortic stenosis viewed by wide angle phased array echocardiography. Circulation 1979;59:1206–1217.
6. **Bhandari AK, Nanda NC.** Two-dimensional echocardiographic characterization of myocardial texture: nonspecificity in amyloidosis (abstr). Circulation 1981;64:Suppl V:V-313.
7. **Bhandari AK, Nanda NC.** Two-dimensional myocardial echo patterns: in vivo and in vitro correlation (abstr). Am J Cardiol 1982;49:931.
8. **Feigenbaum H.** Echocardiography. 3rd ed. Philadelphia: Lea & Febiger, 1981;156.
9. **Prakash R.** Determination of right ventricular wall thickness in systole and diastole. Echocardiographic and necropsy correlation in 32 patients. Br Heart J 1978;40:1257–1261.
10. **Nanda NC, Gramiak R.** Two-Dimensional Echocardiography. In: Clinical Echocardiography. St Louis: CV Mosby, 1978:369–431.
11. **Rasmussen S, Cohya BC, Feigenbaum H, Knoebel SB.** Detection of myocardial scar tissue by M-mode echocardiography. Circulation 1978; 57:230–237.
12. **Werner JA, Pearlman AS, Janko C.** Pathophysiological implications of a new echocardiographic finding in acute myocardial infarction (abstr). Eur Cong Cardiol 1980;VIII:76.
13. **Saied A, Folger GM.** Hypoplastic left heart syndrome—clinicopathologic and hemodynamic correlation. Am J Cardiol 1972;29:190–198.
14. **Howel RR.** Glycogen storage diseases. In: Stanbury JB, Wyngaarden JB, Frederickson DS, eds. The Metabolic Basis of Inherited Disease. New York: McGraw-Hill, 1979:149–173.
15. **Moller JJ, Lucas RV, Adams P, Anderson RC, Jorgens J, Edwards JE.** Endocardial fibroelastosis—a clinical and anatomic study of 47 patients with emphasis on its relationship to mitral insufficiency. Circulation 1964;30:759–782.
16. **Price RR, Jones TB, Goddard J, James AE.** Basic concepts of ultrasonic tissue characterization. Radiol Clin North Am 1980;18:21–30.
17. **Rosenfield AJ, Taylor KJW, Jaffe CC.** Clinical applications of ultrasound tissue characterization. Radiol Clin North Am 1980;18:31–58.
18. **Ziskin MD, Wells PND.** Tissue characterization. Clin Diag Ultrasound 1980;5:186–201.
19. **Chivers RC.** Tissue characterization. Ultrasound Med Biol 1981;7:1–20.
20. **Kossoff G, Gossett WJ, Carpenter DA, Jellins J, Dadd MJ.** Principles and classification of soft tissues by grey scale echography. Ultrasound Med Biol 1976;2:89–105.
21. **Fields S, Dunn F.** Correlation of echographic visualizability of tissue with biological composition and physiological state. J Acoust Soc Am 1973; 54:809–812.
22. **Wells PNT.** Basic physics. In: DeVlieger M, ed. Handbook of Clinical Ultrasound. New York: John Wiley & Sons, 1978:19.
23. **Olsen EGJ.** Hypertrophy, hyperplasia and dilatation. In: The Pathology of the Heart. 2nd ed. Baltimore: University Park Press, 1980:41–45.
24. **Anderson KR, Sutton MG, Lie JT.** Histopathological types of cardiac fibrosis in myocardial disease. J Pathol 1979;128:79–85.
25. **Buja LM, Roberts WC.** Iron in the heart—etiology and clinical significance. Am J Med 1971;51:209–221.
26. **Buja LM, Khoi NB, Roberts WC.** Clinically significant cardiac amyloidosis—clinicopathological findings in 15 patients. Am J Cardiol 1970;26: 394–405.
27. **Mimbs JW, O'Donnel M, Miller JG, Sobel BE.** Detection of cardiomyopathic changes induced by doxorubicin based on quantitative analysis of ultrasonic back scatter. Am J Cardiol 1981;47:1056–1060.
28. **Skorton DJ, Collins S, Nichols J, Pandian NG, Kerber RE.** Quantitive texture analysis of two-dimensional echocardiograms: application to the diagnosis of acute myocardial contusion (abstr). Am J Cardiol 1982;49:931.
29. **Sinclair RL, Wong CM, Gibson DG.** Clinical application of amplitude processing of echocardiographic images. Br Heart J 1981;45:621–627.

# Sensitivity of Technetium-99m–Pyrophosphate Scintigraphy In Diagnosing Cardiac Amyloidosis

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**To determine the value of technetium-99m–pyrophosphate myocardial scintigraphy in the diagnosis of amyloid heart disease this procedure was prospectively performed in 20 consecutive patients with biopsy-proven primary amyloidosis. Eleven patients had echocardiographic abnormalities compatible with amyloid cardiomyopathy, 9 of whom had congestive heart failure. Diffuse myocardial pyrophosphate uptake was of equal or greater intensity than that of the ribs in 9 of the 11 patients with echocardiograms suggestive of amyloidosis, but in only 2 of the 9 with normal echocardiograms, despite abnormal electrocardiograms ($p < 0.01$). Increased wall thickness measured by M-mode echocardiography correlated with myocardial pyrophosphate uptake ($r = 0.68$, $p < 0.01$). None of 10 control patients with nonamyloid, nonischemic heart disease had a strongly positive myocardial pyrophosphate uptake.**

**Thus, myocardial technetium-99m–pyrophosphate scanning is a sensitive and specific test for the diagnosis of cardiac amyloidosis in patients with congestive heart failure of obscure origin. It does not appear to be of value for the early detection of cardiac involvement in patients with known primary amyloidosis without echocardiographic abnormalities.**

Generalized amyloidosis commonly involves the heart and may present as heart failure of obscure origin,[1] sometimes with features suggestive of hypertrophic cardiomyopathy or constrictive pericarditis. Several invasive and noninvasive methods have been described for the diagnosis of cardiac amyloidosis. These include cardiac catheterization,[2,3] M-mode and 2-dimensional echocardiography,[4,5] and combined electrocardiographic and echocardiographic criteria.[6] Although these studies aid in the diagnosis of amyloidosis, the number of patients studied is generally small, some studies were retrospective, and unequivocally diagnostic findings have not been documented. Recently there have been reports of strongly positive technetium pyrophosphate scans in patients with cardiac amyloidosis.[7–9] All of these subjects had advanced cardiac involvement demonstrated by abnormal systolic time intervals, echocardiographic variables, or ejection fraction. Since patients with early or subclinical cardiac involvement were not included, it is not known how early pyrophosphate scans become positive in the course of cardiac amyloidosis. We therefore prospectively evaluated the role of technetium pyrophosphate scintigraphy in patients with primary amyloidosis[10] and varying degrees of cardiac involvement, and were able to further delineate its value in the early diagnosis of myocardial amyloid infiltration.

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## Methods

The study population consisted of 20 consecutive patients with amyloidosis (mean age 58.7 ± 8.8 years) admitted to the Thorndike Memorial Laboratory Clinical Research Center of the Boston City Hospital between July 1980 and March 1982 (Table I). All patients had amyloid associated with plasma-cell dyscrasia (AL-amyloid).[10] The diagnosis was confirmed by observing the characteristic green birefringence after Congo red staining of biopsy tissue.[11] The diagnosis of cardiac amyloidosis was made if patients had biopsy-proven amyloidosis in other tissues, cardiac symptoms, and echocardiographic and electrocardiographic features compatible with amyloidosis. These include low voltage on the electrocardiogram (QRS deflection ≤5 mm in any limb lead), cardiac wall thickening on echocardiography in the absence of hypertension, and a "granular sparkling" appearance on 2-

**TABLE I Clinical Characteristics and Test Results in Amyloid Patients**

| Case | Age (yr) & Sex | Clinical Organ Involvement | | | Electrocardiogram | | Cardio-megaly on X-ray | Echo LVPW (mm) | PYP Uptake | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Heart | Kidney | Other | Low Voltage | Conduction Defect | | | Heart | Liver |
| | | | | | Group A | | | | | |
| 1 | 52M | + | 0 | Carpal tunnel | − | RBBB LAH | + | 20 | 4+ | 0 |
| 2 | 59M | + | 0 | Nerve | − | RBBB LAH | + | 18 | 4+ | 0 |
| 3 | 63M | + | 0 | Nerve | + | RBBB LAH 1°AVB | + | 17 | 4+ | 0 |
| 4 | 58F | + | 0 | 0 | + | 1°AVB LPH | + | 12 | 3+ | 4+ |
| 5 | 86F | + | 0 | 0 | + | AF | + | 23 | 4+ | 0 |
| 6 | 63F | + | 0 | Carpal tunnel | + | 0 | + | 10 | 3+ | 3+ |
| 7 | 60M | + | + | 0 | − | LPH | + | 15 | 3+ | 3+ |
| 8 | 59M | + | 0 | 0 | + | 0 | + | 14 | 3+ | 2+ |
| 9 | 62F | + | 0 | Macroglossia | + | 0 | + | 14 | 0 | 0 |
| | | | | | Group B | | | | | |
| 10 | 67M | 0 | + | 0 | + | 0 | 0 | 11 | 3+ | 2+ |
| 11 | 52M | 0 | 0 | Liver | + | RBBB, LAH | 0 | 14 | 2+ | 0 |
| | | | | | Group C | | | | | |
| 12 | 52F | 0 | + | 0 | + | LAH | 0 | 10 | 0 | 0 |
| 13 | 51M | 0 | + | 0 | 0 | 1°AVB LPH | 0 | 10 | 1+ | 0 |
| 14 | 62M | 0 | + | 0 | + | 0 | 0 | 15* | 1+ | 0 |
| 15 | 51M | 0 | 0 | Liver | + | 0 | 0 | 11 | 0 | 0 |
| | | | | | Group D | | | | | |
| 16 | 45F | 0 | + | 0 | 0 | 0 | 0 | 10 | 3+ | 3+ |
| 17 | 48M | 0 | 0 | Nerve | + | 0 | 0 | 9 | 0 | 0 |
| 18 | 65M | 0 | + | 0 | 0 | 0 | 0 | 10 | 0 | 3+ |
| 19 | 58M | 0 | 0 | Liver | 0 | 0 | 0 | 11 | 0 | 3+ |
| 20 | 61F | 0 | 0 | Macroglossia | 0 | 0 | 0 | 10 | 3+ | 3+ |

AF = atrial fibrillation; LAH = left anterior hemiblock; LPH = left posterior hemiblock; LVPW = left ventricular posterior wall; PYP = pyrophosphate; RBBB = right bundle branch block; 1 AVB = first degree atrioventricular block.
* Patient 14 had uncontrolled hypertension.

dimensional echocardiography.[4] In 4 patients, cardiac catheterization at the referring center had established the diagnosis of a restrictive cardiomyopathy.

All patients had a complete history and physical examination by a cardiologist (RHF), and a 12-lead electrocardiogram, chest x-ray, and M-mode echocardiogram. Eighteen patients also had a 2-dimensional echocardiogram. All patients underwent a technetium-99m–pyrophosphate whole body scan. M-mode echocardiography was performed with a commercially available instrument (Irex) and recorded with a multichannel strip chart recorder at a paper speed of 50 mm/s. Echocardiographic measurements were made in accordance with the standards of the American Society of Echocardiography.[12] Two-dimensional echocardiography was performed on a Diasonics instrument using standard echocardiographic views. Recordings were made on a Sony videotape recorder. A granular sparkling appearance of left ventricular walls[4] was only diagnosed if it could be seen on a cross-sectional view of the left ventricle at the level of the papillary muscles.

Technetium-99m–pyrophosphate scanning was performed as follows: Fifteen mCi of radiopharmaceutical agent was administered by injection into a peripheral vein. Three hours later examinations were performed using either the Ohio Nuclear Sigma 410 wide field view camera or Raytheon camera II. Images were obtained of the entire skeletal system, either with multiple static scans or by a "moving camera" whole body technique. Whole body scans were obtained after the acquisition of 500,000 counts centered over the anterior chest. Using this preset imaging time, the remainder of the examination was completed. High resolution collimation was used on all studies. Scans were examined by a trained nuclear radiologist (VWL) and cardiac uptake was graded as negative, diffusely positive, or locally positive using the following grading system[13]: 0 = negative scan; 1+ = equivocal uptake by the heart; 2+ = definite uptake, intensity less than ribs; 3+ = intensity equal to ribs but less than sternum; 4+ = intensity equal to or greater than the sternum. Assessment was also made of isotope uptake by other soft tissues which do not normally take up pyrophosphate (for example, liver and spleen). The physician reading the scans was aware of the diagnosis of amyloidosis but was unaware of the clinical status of the patient with respect to specific organ involvement.

On the basis of the history, clinical examination, electrocardiogram, and echocardiogram, patients were divided into the following groups (Table I): Group A—definite symptomatic cardiac involvement (symptoms referable to the heart, abnormal electrocardiogram and echocardiographic findings compatible with amyloidosis, absence of other cardiac disorder sufficient to explain symptoms); Group B—definite asymptomatic cardiac involvement (abnormal electrocardiogram, thickened ventricular walls on echocardiogram, with or without granular sparkling appearance on 2-dimensional echocardiography, with or without abnormal physical findings); Group C—possible asymptomatic cardiac involvement (low voltage electrocardiogram in the absence of echocardiographic abnormalities); and Group D—no cardiac involvement (asymptomatic with normal tests).

**Control subjects:** In order to determine the prevalence of positive pyrophosphate scans in patients with nonischemic heart disease, we reviewed the records of patients who underwent pyrophosphate scanning at the Boston City Hospital between January 1978 and December 1980. Criteria for in-

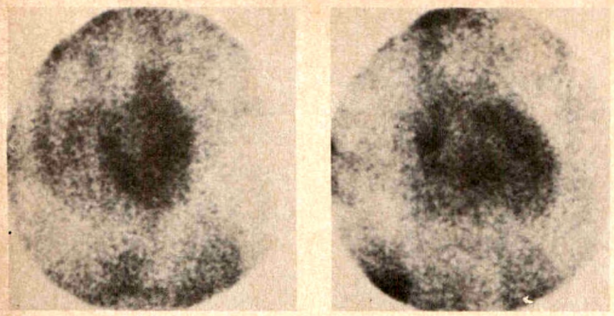


**FIGURE 1.** Technetium-99m pyrophosphate scintigram of Patient 5. Note the intense pyrophosphate uptake outlining the left ventricular cavity. **Left,** left anterior oblique 45° view. **Right,** anterior view.

clusion were absence of acute or prior myocardial infarction and a gated blood pool scan compatible with cardiomyopathy without regional wall motion abnormalities. Five such patients were identified, 4 with congestive cardiomyopathy and 1 with hypertrophic cardiomyopathy. In addition, 5 patients with nonischemic, nonamyloid heart disease prospectively underwent technetium pyrophosphate scanning. Two had congestive cardiomyopathy, 1 had noncalcific constrictive pericarditis, and 2 had hypertensive heart failure. The mean age of control subjects (56 ± 10 years) did not differ statistically from that of the amyloid patients.

All studies in control and amyloid patients were approved by the Human Studies Committee of the Boston City Hospital. Statistical analysis of data was performed using the Mann-Whitney U test for nonparametric data, Spearman's rank correlation coefficient, and Fisher's exact probability test.

## Results

Clinical data on the 20 patients are detailed in Table I. Nine of the 20 patients (Patients 1 to 9) were classified in Group A (definite, symptomatic involvement), 2 (Patients 10 and 11) in Group B, 4 in Group C (Patients 12 to 15), and 5 (Patients 16 to 20) in Group D.

Nine of the 11 patients with electrocardiographic and echocardiographic evidence of cardiac amyloidosis (Groups A and B) had strongly positive pyrophosphate scans (3+ or 4+) (Fig. 1). One patient (Case 9) had a negative pyrophosphate scan despite classical M-mode and 2-dimensional echocardiographic appearances of amyloidosis and recurrent episodes of congestive heart failure. One asymptomatic patient (Case 11) had classical echocardiographic features of amyloid and a 2+ pyrophosphate scan. Of the 9 patients in Groups C and D, only 2 (Cases 16 and 20) had positive pyrophosphate scans (3+). Neither of these patients had any other evidence of myocardial amyloid involvement. A comparison of Groups A and B with C and D revealed a significant relation between clinical and echocardiographic evidence of amyloid infiltration of the heart and a positive myocardial technetium pyrophosphate scan ($p < 0.05$ by Fisher's exact test). There was no correlation between the presence of low voltage alone and a positive scan. On the assumption that increased left ventricular wall thickness in these patients is related to amyloid infiltration, we analyzed the relation between echocardiographically measured wall thickness and scan positivity. Left ventricular posterior wall thickness was chosen as this was more accurately measured than septal thickness. No patient had asymmetric septal hypertrophy. There was a statistically significant relation between these 2 variables ($r = 0.68$, $p < 0.01$). This is illustrated graphically in Figure 2. There was also a significant relation between the presence of cardiac failure (Patients 1 to 9) and a left ventricular wall thickness >11 mm ($p < 0.02$).

**Isotope uptake in other organs:** Nine patients (Patients 4, 6, 7, 8, 10, 16, 18, 19, and 20) had isotope uptake in organs other than the heart. The liver was the most frequent site of uptake although uptake was occasionally seen in the spleen (Patients 7 and 18).

**Control subjects:** Technetium pyrophosphate scans had negative findings in 9 of the 10 control subjects with

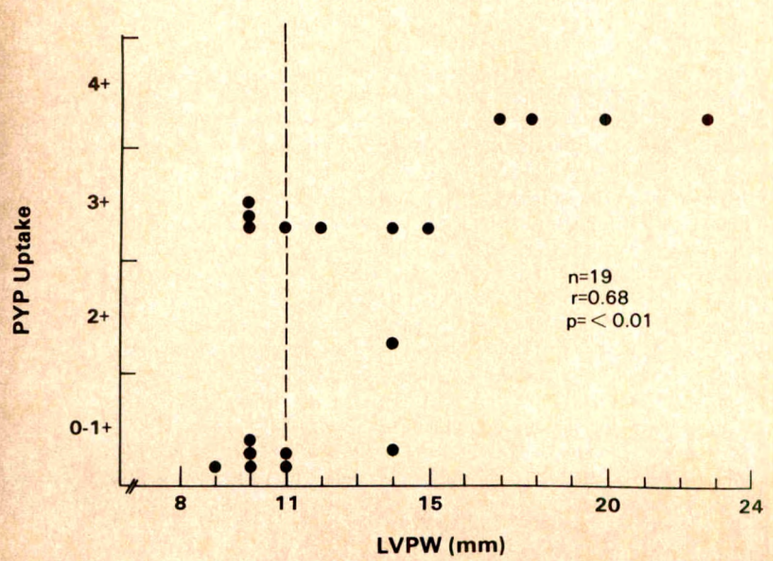



**FIGURE 2.** Pyrophosphate (PYP) uptake (0 to 4+) plotted against left ventricular posterior wall (LVPW) thickness. **Broken line** indicates upper limit of normal for LVPW thickness. For PYP grading, see text. Patient 14 (Table I) was excluded from analysis because of a history of poorly controlled hypertension. LVPW thickness was chosen because it was more accurately measured than septal thickness. No patient had asymmetric septal hypertrophy.

nonamyloid heart failure. One patient with severe congestive cardiomyopathy had a diffusely positive pyrophosphate scan of 2+ intensity. This was associated with positive linear isotope uptake in the femoral region, but no hepatic uptake. No control patient had 3+ or greater cardiac uptake compared with 8 of the 9 amyloid patients with heart failure ($p < 0.005$) and 11 of the total amyloid group ($p < 0.01$). Isotope uptake in the liver or spleen was not seen in the 6 control patients in whom scanning of these areas was performed.

In subjects with congestive heart failure, the sensitivity of a 3+ or 4+ isotope uptake for diagnosing amyloidosis was 89%, the specificity 100%, and the predictive accuracy 100%. The latter 2 figures should be interpreted with caution as they are based on a small control group.

**Follow-up:** During a mean follow-up period of 14 months there were 7 deaths. In Group A there was 1 sudden death (Patient 6) and 3 due to congestive heart failure (Patients 4, 7, and 8). The 3 remaining deaths were due to stroke (Patient 14), hepatic failure (Patient 15), and renal failure (Patient 18).

## Discussion

Since its introduction on 1974,[13] technetium pyrophosphate scanning has been shown to be a highly sensitive indicator of myocardial necrosis in acute myocardial infarction. Initial enthusiasm for this test as a specific diagnostic tool for acute infarction was tempered when other entities such as unstable angina,[14] left ventricular aneurysm,[15] acute pericarditis,[16] and myocarditis[17] were shown to produce positive scan results of either a diffuse or localized nature.

Recently, several reports have described avid myocardial pyrophosphate uptake in patients with advanced myocardial amyloidosis.[7-9] Wizenberg et al[7] described 10 patients with cardiac amyloidosis, 7 of whom had clinical evidence of congestive heart failure. Increased left ventricular wall thickness measured by echocardiography was present in all, and measurement of systolic time intervals suggested left ventricular systolic dysfunction. Technetium pyrophosphate scans were strongly positive in all 10 patients, but the investigators urged caution in the general application of pyrophosphate scanning for the diagnosis of cardiac amyloidosis until a greater number of patients representing a wider spectrum of the disease was examined.

We have deliberately limited our report to patients with primary (AL) amyloid, as this disease is associated with autopsy evidence of myocardial involvement in over 90% of cases.[1,18] Although the initial manifestations may involve 1 or more of several organ systems (such as liver, kidney, nervous system, heart), clinical cardiac involvement develops in the majority of cases and is responsible for death in approximately 50% of patients.[18] It is thus reasonable to assume that most patients will have some degree of myocardial amyloid infiltration at diagnosis, regardless of whether symptoms or signs of heart disease are present. Our results confirm the value of technetium pyrophosphate scanning in patients with congestive heart due to amyloidosis (90% sensitivity), but demonstrate that scans are rarely positive in patients presenting with amyloidosis in other organs in whom no echocardiographic abnormalities suggestive of myocardial infiltration can be demonstrated. Although 4 asymptomatic patients (Patients 12 to 15) demonstrated electrocardiographic abnormalities suggestive of myocardial amyloid involvement, pyrophosphate scans were negative in all, corresponding to their normal echocardiograms. That positive myocardial scans seem to depend in most cases on a critical mass of amyloid is demonstrated by the relation between scan positivity and left ventricular wall thickness (Fig. 1). Although occasionally asymptomatic patients with normal wall thickness may have positive pyrophosphate scans (Patients 16 and 20), most demonstrate no isotope uptake.

The exact mechanism of pyrophosphate uptake in amyloidosis remains unclear but is possibly related to increased calcium concentration in amyloid-infiltrated tissue, as studies of technetium pyrophosphate have demonstrated a strong relation between tissue uptake and calcium accumulation.[19] Amyloid fibrils in primary amyloidosis are composed of the N-terminal portion of kappa or lambda light chains (or the occasional whole light chain), and have a cross-beta tertiary structure as defined by x-ray diffraction studies, consisting of a high percentage of acidic amino acids.[20] Various serum proteins such as amyloid P-component and blood clotting factors bind to amyloid by a calcium-dependent mechanism. Yood et al[20] demonstrated an average calcium content in amyloid infiltrated livers 37 times greater than that of normal liver. Presumably, a similar high concentration of calcium is present in hearts heavily infiltrated with amyloid and is associated with the binding of pyrophosphate.

Eight patients in our series had pyrophosphate uptake by the liver. Four of these patients (Cases 4, 6, 7, and 8) had congestive heart failure and the remainder had no cardiac symptoms. Hepatic uptake of technetium isotopes is a rare finding, having been described in metastatic disease to the liver[21] and in isolated cases of amyloidosis.[20] Congestive heart failure per se does not cause hepatic pyrophosphate uptake and thus the finding of a positive hepatic and cardiac pyrophosphate scan in an individual with an obscure cardiomyopathy is suggestive of amyloidosis. However, the presence of cardiac uptake in the absence of hepatic uptake does not militate against amyloidosis as demonstrated by several patients (Cases 1, 2, 3, and 5) in whom uptake was localized to the heart.

Because of the small number of patients in our control group, the specificity of pyrophosphate scanning in the differential diagnosis of amyloid from other cardiomyopathies cannot be definitively estimated, but appears to be high. It is striking that none of the control patients had scans equal in intensity to bone. The single control patient with a 2+ positive scan also had linear femoral isotope uptake, which has been shown to correlate with falsely positive myocardial scans, probably due to persistent blood pool imaging.[22] Although few studies specifically document technetium pyrophos-

phate uptake in nonamyloid cardiomyopathy, it does appear that intense uptake is unusual. Duska et al[23] studied 5 adults with "nonobstructive" cardiomyopathy and found 2 with weakly positive scans and 1 with a 3+ diffuse scan. Scans were performed only 1 hour after injection of isotope, a period during which blood pool imaging may occur due to persistence of the isotope in the circulation.[22] It is also possible that the patient with a strongly positive scan may indeed have had cardiac amyloidosis, as no detailed clinical data are given. Berman et al[24] performed cardiac catheterization in 22 patients with chest pain, positive pyrophosphate scans and no evidence of acute myocardial infarction. Six were found to have cardiomyopathy (3 congestive and 3 nonobstructive hypertrophic). Pyrophosphate uptake was diffuse and of lesser intensity than bone in all. They suggest that the cause of this weakly positive scan in cardiomyopathy is due to persistent blood pool labelling, possibly related to the increased volume of blood in a dilated ventricular cavity. This clearly differs from amyloid cardiomyopathy, in which the intense uptake may sharply delineate the walls of the heart leaving a space in the center corresponding to the cavity (Fig. 1). Thus it appears that our finding of minimal or no pyrophosphate uptake in nonamyloid cardiomyopathy is consistent with most such cases reported in the literature.

There is a paucity of data concerning the prevalence of positive myocardial pyrophosphate scans in constrictive pericarditis—frequently clinically indistinguishable from amyloid cardiomyopathy. In the only study to examine this, 1 of 3 patients with constrictive pericarditis had a diffusely positive pyrophosphate scan of an intensity equal to that of the ribs.[16] This patient had pericardial calcification, whereas the 2 patients with negative scans had no calcification. Our single control patient with noncalcific constrictive pericarditis also had a negative pyrophosphate scan. Thus it appears that in differentiating amyloid cardiomyopathy from constrictive pericarditis, a positive technetium pyrophosphate scan would favor the former, providing no calcium is visible on x-ray examination.

*In summary*, our data indicate that avid myocardial pyrophosphate uptake is a sensitive indicator of cardiac amyloidosis. It is also highly specific, if only diffuse uptake equal to or greater than that of the ribs is considered positive. Although strongly positive scans have been described in patients with other disorders,[14–17] standard noninvasive tests can usually easily differentiate these disorders from amyloidosis. Since echocardiographic abnormalities in cardiac amyloidosis (for example, increased wall thickness) are seen in other diseases causing cardiac failure, the diagnosis may not be apparent from the echocardiogram alone. We thus believe that pyrophosphate scanning is a very useful complementary test to echocardiography. Technetium pyrophosphate myocardial scans are most valuable in the patient with congestive heart failure and suspected cardiac amyloidosis but may occasionally be positive in asymptomatic patients even when echocardiograms and electrocardiograms are normal. However, myocardial pyrophosphate scintigraphy does not appear to be a sensitive indicator of early myocardial involvement in the majority of asymptomatic patients with systemic amyloidosis. Such patients commonly have a negative scan despite an abnormal electrocardiographic finding and despite the fact that at autopsy almost all will have evidence of myocardial amyloid infiltration. It should be emphasized that these results apply only to patients with primary amyloidosis and should not be extrapolated to other forms of the disease (AA or familial amyloid polyneuropathy) as the different nature of amyloid protein in these disorders may differently affect pyrophosphate binding.[10]

## References


1. **Brandt K, Cathcart ES, Cohen AS.** A clinical analysis of the course and prognosis of forty-two patients with amyloidosis. Am J Med 1968;44: 955–969.
2. **Swanton RH, Brooksby LAB, David MJ, Coltart DJ, Jenkins BJ, Webb-Peploe MM.** Systolic and diastolic ventricular function in cardiac amyloidosis. Studies in six cases diagnosed with endomyocardial biopsy. Am J Cardiol 1977;39:658–664.
3. **Tyberg TI, Goodyer AVN, Hurst VW III, Alexander J, Langou RA.** Left ventricular filling in differentiating amyloid cardiomyopathy and constrictive pericarditis. Am J Cardiol 1981;47:791–796.
4. **Siguiera-Filho AG, Cunha CLP, Tajik AJ, Seward JB, Schottenberg TT, Guiliani ER.** M-mode and two dimensional echocardiographic features in cardiac amyloidosis. Circulation 1981;63:188–196.
5. **Child JS, Levisman JA, Abbassi AS, MacAlpin RN.** Echocardiographic manifestations of infiltrative cardiomyopathy. A report of seven cases due to amyloid. Chest 1976;70:726–731.
6. **Carroll JD, Gaasch WH, McAdam KPWJ.** Amyloid cardiomyopathy: characterization by a distinctive voltage/mass relationship. Am J Cardiol 1982;49:9–13.
7. **Wizenberg TA, Muz J, Sohn YH, Samlowski W, Weissler AM.** Value of positive myocardial technetium-99m-pyrophosphate scintigraphy in the noninvasive diagnosis of cardiac amyloidosis. Am Heart J 1982;103: 468–473.
8. **Schiff S, Bateman T, Moffatt R, Davidson R, Berman D.** Diagnostic considerations in cardiomyopathy: unique scintigraphic pattern of diffuse biventricular technetium-99m-pyrophosphate uptake in amyloid heart disease. Am Heart J 1982;103:562–563.
9. **Sobol SM, Brown JM, Bunker SR, Patel J, Lull RJ.** Noninvasive diagnosis of cardiac amyloidosis by technetium-99m-pyrophosphate scintigraphy. Am Heart J 1982;103:563–566.
10. **Cohen AS, Wegelius O.** Classification of amyloid 1979–80. Arthritis Rheum 1980;23:644–645.
11. **Libbey CA, Skinner M, Cohen AS.** Abdominal fat aspirate for diagnosis of amyloidosis (abstr). Clin Res 1981;29:159A.
12. **Sahn DJ, DeMaria A, Kisslo J, Weyman A.** Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–1083.
13. **Parkey RW, Bonte FJ, Meyer SL, Atkins JM, Curry GL, Stokley EM, Willerson JT.** A new method for radionuclide imaging of acute myocardial infarction in humans. Circulation 1974;50:540–546.
14. **Donsky MS, Curry GC, Parkey RW, Meyer SL, Bonte FJ, Platt MR, Willerson JT.** Unstable angina pectoris: clinical, angiographic and myocardial scintigraphic observations. Br Heart J 1976;38:257–263.
15. **Ahmad M, Dubiel JP, Verdon TA, Martin RH.** Technetium-99m stannous pyrophosphate myocardial imaging in patients with and without left ventricular aneurysm. Circulation 1976;53:833–838.
16. **Olson HG, Lyons KP, Aronow WS, Kuperus J, Orlando JR, Waters HJ.** Technetium-99m stannous pyrophosphate myocardial scintigrams in pericardial disease. Am Heart J 1980;99:459–467.
17. **Mitsatake A, Nakamura M, Inou T, Kikuchi Y, Takeshita A, Fujimi S.** Intense, persistent myocardial avid technetium-99m pyrophosphate scintigraphy in acute myocarditis. Am Heart J 1981;101:683–684.
18. **Wright JR, Calkins E.** Clinical-pathologic differentiation of common amyloid syndromes. Medicine 1981;60:429–447.
19. **Willerson JT, Parkey RW, Bowe TJ, Lewis SE, Corbett J, Buja LM.** Pathophysiologic considerations and clinicopathological correlates of technetium-99m stannous pyrophosphate by myocardial scintigraphy. Semin Nucl Med 1980;10:54–69.
20. **Yood RA, Skinner M, Cohen AS, Lee VW.** Soft tissue uptake of bone seeking radionuclide in amyloidosis. J Rheumatol 1981;8:760–766.
21. **Poulose KP, Reba RC, Eckelman WC, Goodyear BS.** Extraosseous localisation of 99m technetium Sn pyrophosphate. Br J Radiol 1975;48: 724–726.
22. **Prasquier R, Taradash MR, Boivinick EH, Shamas DM, Parmley WW.** The specificity of the diffuse pattern of cardiac uptake in myocardial infarction imaging with technetium-99m stannous pyrophosphate. Circulation 1977;55:61–66.
23. **Duska F, Vizda J, Kubicek J, Kafka P, Nesvadba Z, Adansky P, Bastecky J.** The sensitivity of scintigraphic myocardial imaging by the use of 99m Tc-labelled pyrophosphate in the diagnosis of cardiomyopathy of various etiology. Eur J Nucl Med 1979;4:87–90.
24. **Berman DS, Amsterdam EA, Hines HH, Salel AF, Bailey GJ, DeNardo GL, Mason DI.** New approach to interpretation of technetium-99m-pyrophosphate scintigraphy in the detection of acute myocardial infarction. Am J Cardiol 1977;39:341–346.

# Survival in Men With Severe Chronic Left Ventricular Failure Due to Either Coronary Heart Disease or Idiopathic Dilated Cardiomyopathy

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**Congestive heart failure (CHF) is known to be highly fatal, but to better assess efficacy of therapeutic interventions a greater understanding of its course is required. Previous studies of survival are limited by heterogeneity of patient populations and diverse criteria for diagnosing CHF. We followed up 182 patients with chronic left ventricular failure who were symptomatic despite therapy. The length of the follow-up period averaged 12 ± 10 (mean ± standard deviation [SD]) months (range 1 to 41). The cause of CHF was coronary artery disease in 95 patients and idiopathic dilated cardiomyopathy in 87. A total of 88 deaths occurred, of which 40 (45%) were sudden; the incidence of sudden death was similar in patients with coronary artery disease and idiopathic dilated cardiomyopathy. The overall mortality rate was 34% at 1 year, 59% at 2 years, and 76% at 3 years. The mortality rate in patients with coronary artery disease was 46 and 69% at 1 and 2 years, compared with 23 and 48% at 1 and 2 years in those with idiopathic dilated cardiomyopathy ($p < 0.01$). Comparison of all survivors and nonsurvivors showed no difference in age or duration of symptoms at entry. Clinical class was significantly worse in nonsurvivors. Nonsurvivors had higher left ventricular filling pressure (29 ± 7 versus 24 ± 9 mm Hg) and systemic vascular resistance (25 ± 10 versus 21 ± 8 units) (both $p < 0.01$); they also had lower mean arterial pressure (87 ± 13 versus 94 ± 13 mm Hg), cardiac index (2.0 ± 0.7 versus 2.5 ± 0.8 liters/min/m$^2$), and stroke work (35 ± 19 versus 56 ± 33 g-m) than did the survivors (all $p < 0.001$). However, only left ventricular filling pressure was correlated with length of survival ($r = -0.31$, $p < 0.01$). Thus, 3-year mortality is very high in patients with severe chronic left ventricular failure. The prognosis is poorer in patients with CHF due to coronary artery disease and, as expected, in those with worse symptoms and hemodynamic abnormalities.**

Congestive heart failure is a highly fatal disorder with a 5-year survival rate below 50%, which is worse than that observed for cancer in general.[1] The efficacy of therapeutic interventions in heart failure is not easily established. Demonstration of improved resting hemodynamics and left ventricular function may not suffice for this purpose because such measurements do not reliably reflect functional capacity of patients.[2,3] However, demonstration of increased exercise tolerance in the laboratory may not necessarily be related to the symptomatic status or to the long-term prognosis of patients. Thus, reductions in morbidity and mortality remain the most acceptable proof of therapeutic efficacy.

To properly assess the results of clinical therapeutic trials in heart failure, a more thorough understanding of the course of this disorder is required. Several investigators have noted relations between clinical characteristics, hemodynamics, measures of cardiac function, and prognosis in patients with congestive heart failure (CHF).[4–10] However, epidemiologists have criticized many of these earlier reports because of their lack of uniformity in diagnostic criteria of CHF and in patient populations.[11]

We have recently been evaluating new treatments in patients with chronic left ventricular failure due to myocardial dysfunction. The present report describes

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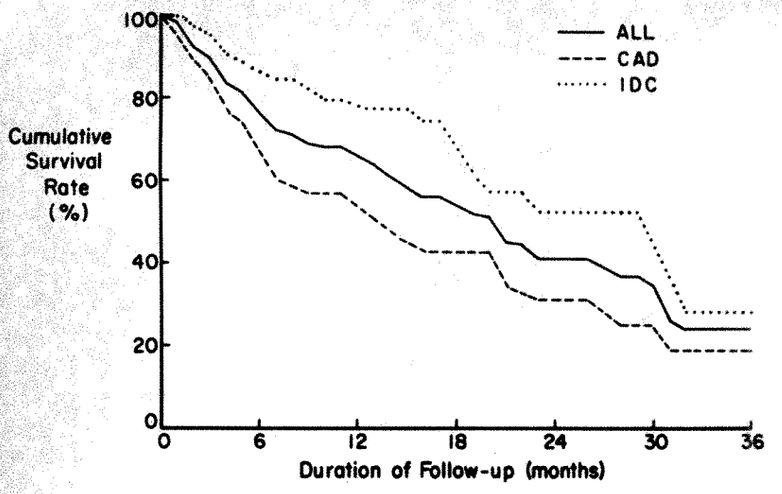



**FIGURE 1.** Survival curves in patients with severe chronic left ventricular failure due to cardiomyopathy. The curves for coronary artery disease (CAD) and idiopathic dilated cardiomyopathy (IDC) groups are significantly different ($p < 0.01$). ALL = all patients (CAD + IDC).

our experience during the long-term follow-up of these patients after a thorough clinical and hemodynamic evaluation. All patients had symptoms despite therapy and were referred to a cardiologist for further management. Thus, our study invovles a relatively homogeneous patient population in terms of the origin and severity of CHF, and they were evaluated, managed, and followed up uniformly by the same team of clinical investigators.

## Methods

The patient population consisted of men admitted to the Veterans Administration Hospital in Minneapolis, Minnesota between October 1, 1974 and January 31, 1979, and to the Veterans Administration Hospital in Philadelphia, Pennsylvania between October 1, 1979, and October 31, 1981. They were hospitalized or referred to the cardiology clinic because of decompensated chronic CHF. The cause of CHF was coronary artery disease or idiopathic dilated cardiomyopathy. Coronary artery disease was diagnosed by electrocardiographic and enzymatic documentation of previous myocardial infarction or by demonstration of significant obstructive coronary arterial disease by coronary angiography. Idiopathic dilated cardiomyopathy was diagnosed when no other cause of CHF was apparent.

An initial diagnosis of CHF required (1) a history of dyspnea or fatigue during exertion, and (2) one of the following physical signs: third heart sound, pulmonary congestion, jugular venous distention, or otherwise unexplained peripheral edema. The signs and symptoms of CHF must have been present for at least 3 months. Patients with the following were excluded: acute myocardial infarction within the previous 3 months, primary pulmonary disease, hypertrophic cardiomyopathy, primary valvular heart disease, exercise capacity limited by angina or symptoms other than dyspnea or fatigue, or any other associated disease that might limit long-term survival.

Patients satisfying the initial criteria underwent further evaluation. Symptomatic status was classified according to the criteria of the New York Heart Association. In addition, 1 of the following had to be present: (1) cardiothoracic ratio by chest X-ray of $\geq 55\%$; (2) left ventricular ejection fraction by radionuclide or contrast angiography $<46\%$; (3) left ventricular internal end-diastolic dimension by M-mode echocardiography $\geq 2.7$ cm/m$^2$; (4) left ventricular filling pressure $>15$ mm Hg; or (5) cardiac index $<2.5$ liters/min/m$^2$. Left ventricular filling pressure was obtained through right heart catheterization and taken as pulmonary arterial occluded or diastolic pressure. Cardiac output was measured by thermodilution, indicator dye dilution, or carbon dioxide rebreathing. We have previously validated the latter method in patients with CHF.[12] Blood pressure was measured by the standard cuff technique or from indwelling arterial cannula. Stroke volume, systemic vascular resistance, cardiac index, and stroke work were calculated from standard formulas.

On completion of evaluation, patients were followed up in the cardiology clinic where they were seen regularly by the same physician and nurses. No attempt was made to control therapy. However, all patients were taking at least digitalis or diuretics, or both, and many received vasodilators sometime during the follow-up period. The survival status of patients was determined from records of clinic visits or from telephone contact with the patient or his relatives. The cutoff date for determining survival status was February 28, 1979, for patients in Minneapolis and November 30, 1981, for patients in Philadelphia. All deaths that occurred were attributable to cardiovascular disease. Death was defined as sudden when it was unexpected at the time and was witnessed to occur within 24 hours of the onset of symptoms.

Probability of survival from the time of initial evaluation was analyzed by the life-table method, and survival curves were compared using the log-rank test.[13] Differences in characteristics between patient groups were compared by unpaired $t$ tests, and correlations between patient characteristics and length of survival were examined by regression analysis. A total of 194 patients was initially evaluated, and complete follow-up data were obtained in 182 patients (94%) who are the subject of this report.

## Results

Of the 182 patients with complete follow-up data, 95 had cardiomyopathy secondary to coronary artery disease and 87 had idiopathic dilated cardiomyopathy. The follow-up period averaged $12 \pm 10$ (SD) months (range 1 to 41). During this period a total of 88 deaths occurred, 58 in the coronary disease group and 30 in the idiopathic cardiomyopathy group ($p < 0.01$). Of the total number of deaths in the group with coronary artery disease, 25 (42%) were classified as sudden compared with 15 (50%) in the group with idiopathic dilated cardiomyopathy.

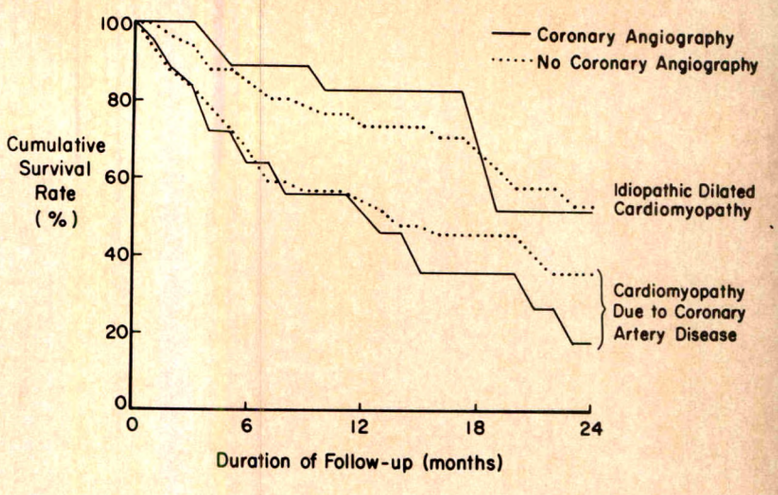



**FIGURE 2.** Survival curves in patients with severe chronic left ventricular failure due to cardiomyopathy with or without coronary angiography for diagnosis. The curves for coronary artery disease and idiopathic, dilated cardiomyopathy groups are significantly different ($p < 0.01$). Curves within diagnostic groups are not different.

The difference in incidence of sudden death was not statistically significant. Cumulative survival rates by the life-table method are shown in Figure 1. By 12 months 66% of all patients were still alive, and by 24 months only 41% were still alive. By 36 months 76% of patients had died. Survival rates for the etiologic groups were analyzed separately (Fig. 1). The survival curve of patients with idiopathic dilated cardiomyopathy indicated a 1-year survival rate of 77% compared with 54% for those with cardiomyopathy due to coronary artery disease. Differences between these groups were still present at 24 and 36 months, and the difference between the entire survival curves was statistically significant ($p < 0.01$). There were no significant differences in these 2 groups in baseline characteristics including age, duration or severity of symptoms, and hemodynamic variables.

Because only a minority of our patients (46 of 182 or 25%) underwent coronary angiography, their survival was compared with that of patients not subjected to coronary angiography within each etiologic group (Fig. 2). In the group with idiopathic dilated cardiomyopathy survival curves were not significantly different between patients with angiographically normal coronary arteries and those not subjected to coronary angiography, as their 2-year survival rates were 52 and 53%, respectively. Likewise, in the group with cardiomyopathy due to coronary artery disease, survival was not significantly different between patients with and those without angiographically proved coronary artery disease. The differing survival rates between etiologic groups were again apparent. Among the patients who underwent coronary angiography, mortality in the coronary disease group was 49% at 1 year and 82% at 2 years, compared with 17% at 1 year and 48% at 2 years in patients with idiopathic dilated cardiomyopathy ($p < 0.01$).

To further characterize differences between all survivors and nonsurvivors, symptomatic status and hemodynamic values at our initial evaluation were compared. No significant differences were noted between survivors and nonsurvivors in duration of symptoms or age at entry (Table I). However, nonsurvivors did have a significantly worse symptomatic status as judged by the criteria of the New York Heart Association. Except for heart rate, hemodynamic variables were significantly different between groups. Mean arterial blood pressure was lower in nonsurvivors, and left ventricular filling pressure and systemic vascular resistance were higher in this same group. Cardiac index, stroke volume, and stroke work were all significantly lower in nonsurvivors. Although hemodynamic variables overlapped considerably between survivors and nonsurvivors, life-table analysis also showed significantly different survival rates between hemodynamic subgroups. For this analysis the dividing point for each variable was arbitrarily taken as the point midway between the average value observed for survivors and the average value for nonsurvivors for any given variable. Figure 3 shows cumu-

**TABLE I Baseline Characteristics of Patients With Severe Chronic Left Ventricular Failure Due to Cardiomyopathy**

| | Nonsurvivors (n = 88) | Survivors (n = 94) | p |
|---|---|---|---|
| Age (yr) | 57 ± 10 | 56 ± 8 | NS |
| Duration of symptoms (mo) | 45 ± 43 | 39 ± 27 | NS |
| Clinical class (NYHA) | 3.3 ± 0.6 | 2.9 ± 0.6 | <0.001 |
| Heart rate (beats/min) | 87 ± 15 | 83 ± 16 | NS |
| Mean arterial pressure (mm Hg) | 87 ± 13 | 94 ± 13 | <0.001 |
| Left ventricular filling pressure (mm Hg) | 29 ± 7 | 24 ± 9 | <0.001 |
| Cardiac index (liters/min/m$^2$) | 2.0 ± 0.7 | 2.5 ± 0.8 | <0.001 |
| Stroke volume (ml/beat) | 45 ± 16 | 59 ± 5 | <0.001 |
| Systemic vascular resistance (units) | 25 ± 10 | 21 ± 8 | <0.01 |
| Stroke work (g-m) | 35 ± 19 | 56 ± 33 | <0.001 |

Values are listed as mean ± standard deviation.
NYHA = criteria of the New York Heart Association; NS = not significant.

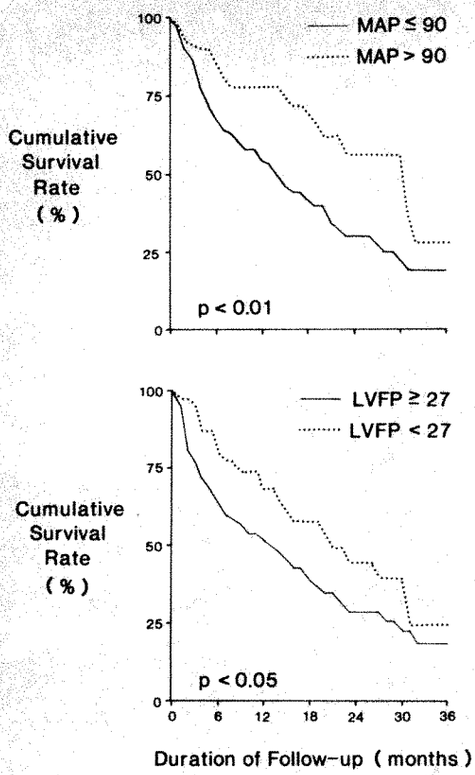



**FIGURE 3.** Survival curves in patients with severe chronic left ventricular failure due to cardiomyopathy according to blood pressure and left ventricular filling pressure at entry. LVFP = left ventricular filling pressure (mm Hg); MAP = mean arterial pressure (mm Hg).

lative survival curves according to baseline mean arterial blood pressure and baseline left ventricular filling pressure. Survival was significantly better in patients with a mean arterial pressure >90 mm Hg and with a left ventricular filling pressure <27 mm Hg. Only 52% of patients with a filling pressure of ≥27 mm Hg were alive after 1 year compared with 69% of those with lower filling pressure. Similarly, patients with a cardiac index ≥2.25 liters/min/m$^2$ had significantly better survival than did those with a lower cardiac index, with 14-month survival being exactly 1.5 times better (75 versus 50%) in those with a higher cardiac index (Fig. 4). As expected, calculated variables, which included measures of blood pressure, left ventricular filling pressure, and cardiac output, also revealed significantly different survival curves. Patients with systemic vascular resistance averaging <23 units had better survival than did those with higher systemic vascular resistance, and patients with stroke work averaging >45 g-m had better survival than did patients with lower stroke work (Fig. 5).

To determine if these same hemodynamic variables correlated with length of survival, linear regression analysis was carried out between baseline hemodynamics and time of survival until death in the nonsurviving patients. There were no significant correlations between any of the baseline hemodynamic characteristics and length of survival except for left ventricular filling pressure (Fig. 6). A slight but statistically significant inverse correlation was noted between left ventricular filling pressure and duration of survival.

## Discussion

The present results agree with those of previous reports of high fatality rates in patients with CHF. In the Framingham study 5-year survival from the time of initial diagnosis of CHF was <50%.[1] We observed higher mortality rates at 1 to 3 years, but we followed up patients from the time of appearance of refractory symptoms. A long preclinical latent period in patients with CHF has been noted.[4] The Framingham data for men from the time of the first episode of clinical CHF showed a survival rate of 79% at 1 year which is very similar to our observed 1 year survival rate of 66%. A major difference between the Framingham study and ours was the various causes of CHF included in that study which did not exclude valvular heart disease, angina pectoris, or cor pulmonale, as we did. Earlier studies of patients with cardiomyopathy tended to be retrospective reports that focused primarily on clinical features, although high total mortality was noted.[4,5,7] In a more recent report by Fuster et al[10] 104 patients with idiopathic dilated cardiomyopathy experienced a total mortality of 77% over 11 years, with two thirds of the deaths oc-

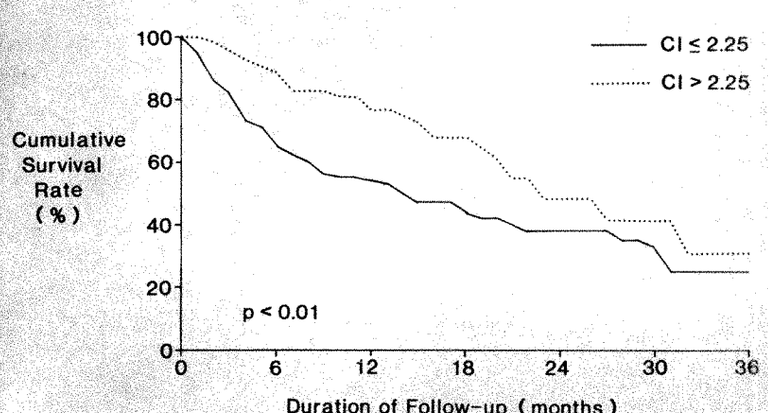



**FIGURE 4.** Survival curves in patients with severe chronic left ventricular failure due to cardiomyopathy according to cardiac index at entry. CI = cardiac index (liters/min/m$^2$).

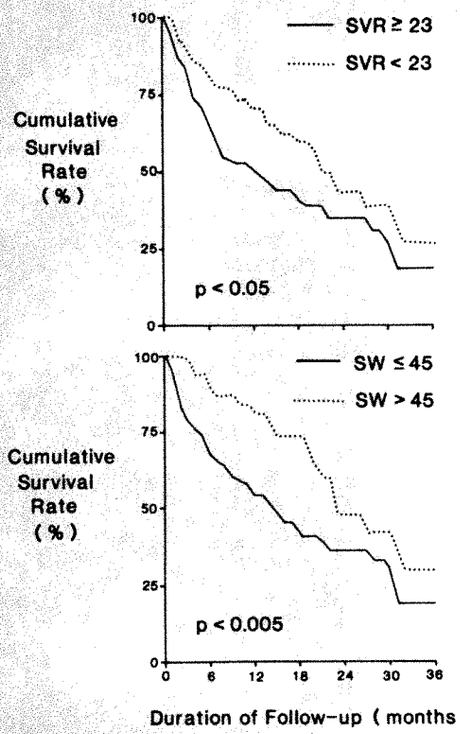



**FIGURE 5.** Survival curves in patients with severe chronic left ventricular failure due to cardiomyopathy according to systemic vascular resistance and left ventricular stroke work at entry. SVR = systemic vascular resistance (units); SW = stroke work (g-m).

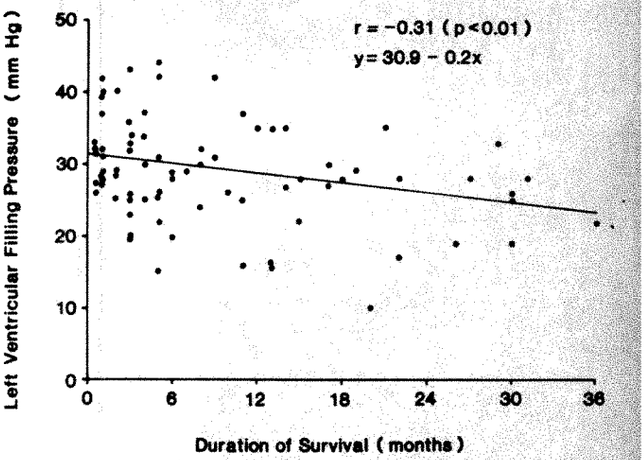



**FIGURE 6.** Relation between left ventricular filling pressure at entry and duration of survival in nonsurviving patients with severe chronic left ventricular failure due to cardiomyopathy.

curring during the first 2 years. Their survival rates of 70% at 1 year and 55% at 2 years are very similar to the 77 and 52% survival rates noted at 1 and 2 years, respectively, in our patients with idiopathic dilated cardiomyopathy. However, their study was retrospective and diagnosis of CHF was based on ventriculographic demonstration of left ventricular dysfunction. Our study differs from previous ones in that a large number of patients were followed prospectively. The study population was relatively homogeneous as all patients had chronic left ventricular failure due to cardiomyopathy and follow-up began at the time of refractory symptoms.

Our observation that survival was worse in patients with cardiomyopathy secondary to coronary artery disease has not been well appreciated. Among patients with ischemic heart disease, those with left ventricular dysfunction generally have a worse prognosis than do those without compromised ventricular function. However, most patients have clinically manifest myocardial ischemic episodes. In our series patients were limited by symptoms of CHF, and those with evidence of myocardial ischemic episodes were excluded. Yatteau et al[6] reported 50 to 69% 2-year survival in patients with ischemic cardiomyopathy which is better than the 31% survival we observed at 2 years.[6] However, although all our patients had moderately severe clinical CHF, <60% of their patients had symptomatic CHF. The worse prognosis in our patients should not be too surprising because cardiomyopathy from coronary artery disease tends to occur in patients with more severe multivessel coronary artery disease and multiple previous myocardial infarctions.[14] Clinical CHF probably represents the most extreme end of the spectrum in these patients with severe coronary artery disease.

Numerous earlier studies observed that prognosis in CHF is worse in patients with more abnormal hemodynamics.[4,6,8,10] Not surprisingly, therefore, we also observed higher mortality rates in patients with a higher left ventricular filling pressure or lower cardiac output, probably reflecting poorer left ventricular function in those patients. We also noted a worse prognosis in patients with higher systemic vascular resistance, which is consistent with a recent preliminary report that mortality is higher among patients with CHF who have high levels of circulating catecholamines.[15] Because of considerable overlap of hemodynamic values among survivors and nonsurvivors, these measurements are only of limited value in the prognosis of individual patients. The observed poor correlations between hemodynamics and duration of survival support this concept. Hemodynamic measurements are widely used to assess efficacy of therapeutic intervention, but recent demonstrations of the lack of correlation between such measurements and symptomatic status of patients with CHF have questioned the significance of such measurements.[2,3,16] The present findings that hemodynamic measurements do relate to prognosis even in patients with far advanced refractory CHF suggest that their use may still be of value because their modification might alter prognosis.

We have focused primarily on hemodynamics and prognosis because of the current popularity of hemodynamic measurements in diagnosing and managing patients with CHF. Previous studies related clinical and radiographic signs as well as left ventricular function with prognosis.[4–10] We have not emphasized these factors because our patients all had refractory symptoms of CHF at entry into the study and were required by protocol to have clinical and radiographic evidence of

CHF so that such measurements would be less likely to have significant discriminatory value. We did not quantitate left ventricular function by use of left ventricular ejection fraction because the noninvasive method required was generally unavailable in the centers involved when the study began. This measurement was obtained in a small number of patients entered later in the study and showed no significant differences between survivors and nonsurvivors, possibly because the period of risk might have been shorter in the patients who entered later.

Sudden death occurred in 22% of our patients and accounted for 45% of all deaths; the incidence was similar in idiopathic dilated cardiomyopathy and cardiomyopathy due to coronary artery disease. Others have noted the common occurrence of sudden death in patients with cardiomyopathy of either cause.[5,7,17] We did not attempt to characterize the type or frequency of arrhythmias in our patients, but others have observed that patients with CHF have a high incidence of ventricular arrhythmia, especially those who die suddenly.[8,18]

Interpretation of the present results must be qualified. Our patients entered at different points in their course. A long interval of relatively good prognosis probably exists between the initial cardiac insult and manifestations of clinical CHF. Long-standing preexisting radiographic or electrocardiographic abnormalities can be documented in a large percentage of patients who present with their first episode of clinical CHF.[4] Thus, it is difficult to ascertain the onset of CHF. Our approach was to follow up patients from the time of onset of symptoms that were refractory to treatment. Thus, our patients were far advanced in their course and are representative of patients likely to be referred to an internist or cardiologist. Another problem is that only a minority (25%) of our patients underwent left and right heart catheterization with coronary arteriography. Thus, the diagnosis, especially that of idiopathic, dilated cardiomyopathy, may not have been entirely accurate. The diagnosis of cardiomyopathy due to coronary artery disease was reasonably secure because a history of documented acute myocardial infarction or coronary arteriography was required. Some of our patients diagnosed as having idiopathic, dilated cardiomyopathy may indeed have had coronary heart disease. Finally, no attempt was made to control or account for the effects of treatment. Virtually all patients were receiving some form on therapy, and nearly all were taking at least digitalis and diuretics. The precise number taking vasodilators and the duration of such therapy are unknown. Because there is no strong evidence that any therapy affects long-term outcome in CHF, it is impossible to assess the role of treatment in affecting our results. The major advantages of our study are the relative homogeneity of the population studied, the prospective nature, and the relatively uniform management and follow-up provided by the same team of investigators.

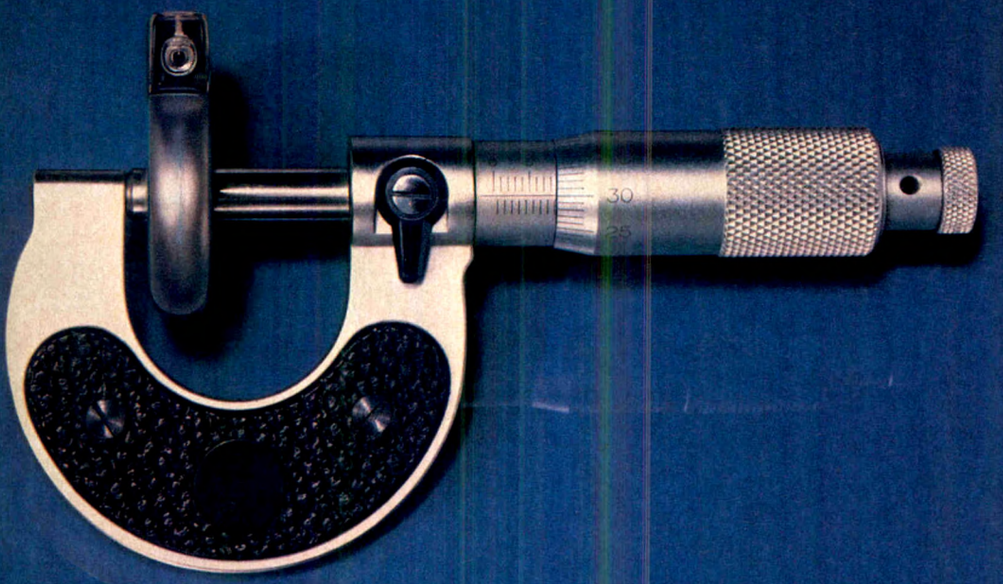
## References


1. **McKee PA, Castelli WP, McNamara PM, Kannel WB.** The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971; 285:1441–1446.
2. **Franciosa JA.** Functional capacity of patients with chronic left ventricular failure. Am J Med 1979;67:460–466.
3. **Franciosa JA, Park M, Levine TB.** Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981;47:33–39.
4. **Hamby RI.** Primary myocardial disease. A prospective clinical and hemodynamic evaluation in 100 patients. Medicine 1970;49:55–78.
5. **Shugoll GI, Bowen PJ, Moore JP, Lenkin ML.** Follow-up observations and prognosis in primary myocardial disease. Arch Intern Med 1972;129: 67–72.
6. **Yatteau RF, Peter RH, Behar VS, Bartel AG, Rosati RA, Kong Y.** Ischemic cardiomyopathy: the myopathy of coronary artery disease. Am J Cardiol 1974;34:520–525.
7. **Hatle L, Orjavik O, Stortstein O.** Chronic myocardial disease. I. Clinical picture related to long-term prognosis. Acta Med Scand 1976;199:399–405.
8. **Hatle L, Stake G, Storstein O.** Chronic myocardial disease. II. Haemodynamic findings related to long-term prognosis. Acta Med Scand 1976; 199:407–411.
9. **Walsh WF, Greenberg BH.** Results of long-term vasodilator therapy in patients with refractory congestive heart failure. Circulation 1981;64: 499–505.
10. **Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenberg RO, Frye RL.** The natural history of idiopathic dilated cardiomyopathy. Am J Cardiol 1981; 47:525–531.
11. **Klainer LM, Gibson TC, White KL.** The epidemiology of cardiac failure. J Chron Dis 1965;18:797–814.
12. **Franciosa JA, Ragan DO, Rubenstone SJ.** Validation of the $CO_2$ rebreathing method for measuring cardiac output in patients with hypertension or heart failure. J Lab Clin Med 1976;88:672–682.
13. **Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG.** Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977;35:1–39.
14. **Dash H, Johnson RA, Dinsmore RE, Harthorne JW.** Cardiomyopathic syndrome due to coronary artery disease. I. Relation to angiographic extent of coronary disease and to remote myocardial infarction. Br Heart J 1977;39:733–739.
15. **Cohn JN, Levine R, Levine TB, Gross K, Francis GS.** Prognostic significance of plasma norepinephrine in congestive heart failure (abstr). Clin Res 1981;29:562A.
16. **Franciosa JA,** Effectiveness of long-term vasodilator administration in the treatment of chronic left ventricular failure. Prog Cardiovasc Dis 1982; 24:319–330.
17. **Goodwin JF, Krikler DM.** Sudden death in cardiomyopathy. Adv Cardiol 1978;25:98–106.
18. **Follansbee WP, Michelson EI, Morganroth J.** Nonsustained ventricular tachycardia in ambulatory patients: characteristics and association with sudden cardiac death. Ann Intern Med 1980;92:741–747.

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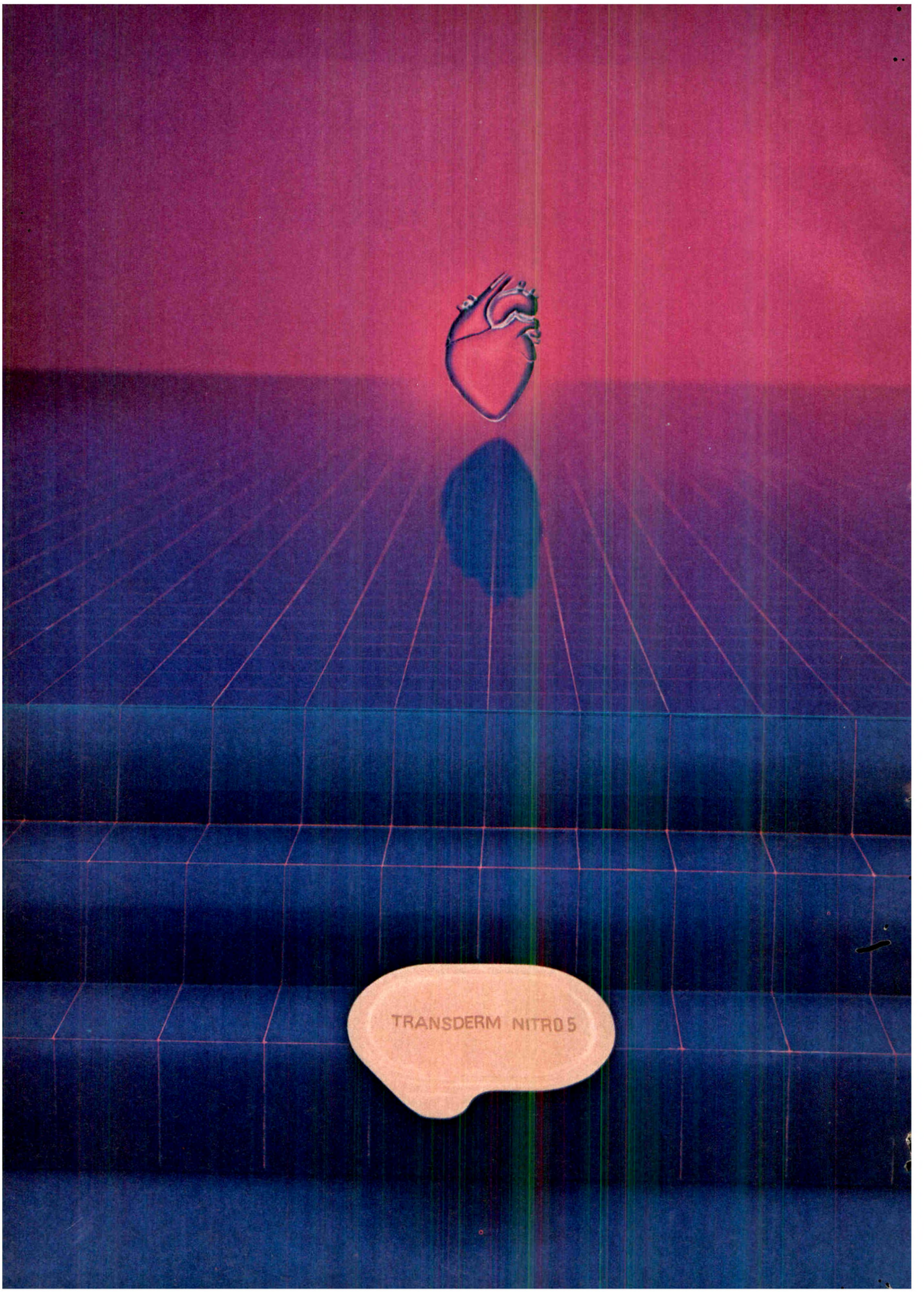

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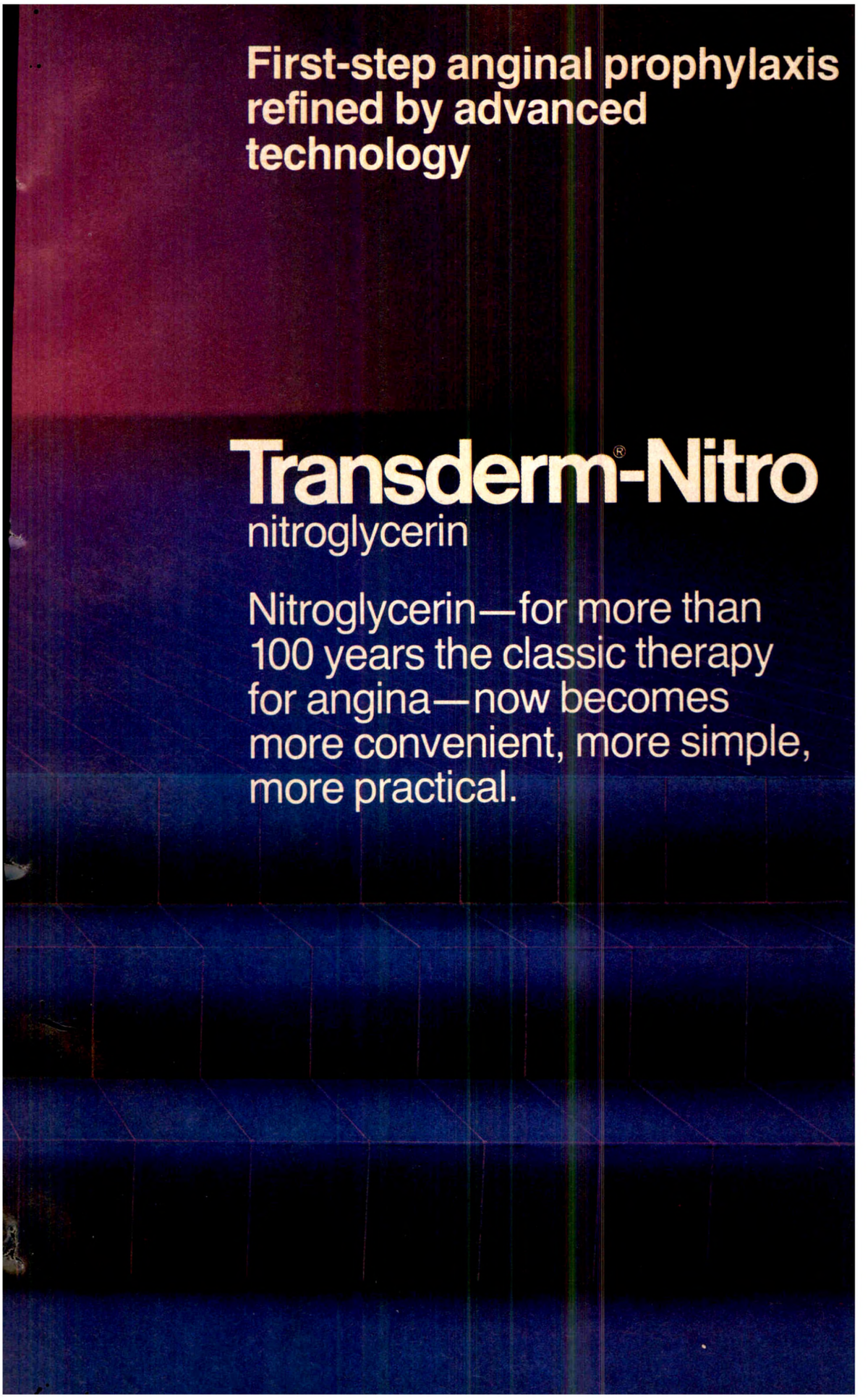
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Avoids the inconvenience of multiple dosages.

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Will not leak or stain clothing. May even be worn while bathing or swimming. Few reports of skin irritation.

Note: Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

*Black CD: Transdermal drug delivery systems. *US Pharmacist* 1982 (Nov); 7(11):49-78.

Before prescribing, please read full Prescribing Information.

C I B A

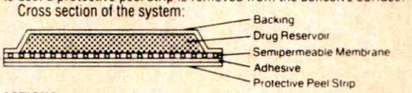
# Transderm®-Nitro
(nitroglycerin)
**Transdermal Therapeutic System**

**DESCRIPTION**
Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semi-permeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 10 and 20 $cm^2$ respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system; 0.5 mg nitroglycerin is delivered *in vivo* for every $cm^2$ of system size.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface towards the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:




**ACTIONS**
When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

**INDICATIONS AND USAGE**
Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

**CONTRAINDICATIONS**
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

**WARNINGS**
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

**PRECAUTIONS**
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

**ADVERSE REACTIONS**
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

**DOSAGE AND ADMINISTRATION**
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

**PATIENT INSTRUCTIONS FOR APPLICATIONS**
A patient leaflet is supplied with the systems.

**HOW SUPPLIED**

| Transderm-Nitro System Rated Release *in vivo* | Total Nitroglycerin in System | System Size | Carton Size |
|---|---|---|---|
| 5 mg/24 hr | 25 mg | 10 $cm^2$ | 30 Systems (NDC 0083-2105-26) |
| 5 mg/24 hr | 25 mg | 10 $cm^2$ | 7 Systems (NDC 0083-2105-07) |
| 10 mg/24 hr | 50 mg | 20 $cm^2$ | 30 Systems (NDC 0083-2110-26) |

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- drug accumulation
- hangover/daytime drowsiness
- interaction with other agents

# Some benzodiazepine hypnotics have too short a half-life

Too short a half-life may lead to:
- nocturnal awakenings
- early-morning awakenings
- anterograde amnesia



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**hours**
mean half-life
(triazolam)

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# Restful sleep, alert awakening

# RESTORIL® C IV
15 mg
30 mg
capsules

## (temazepam)

## RESTORIL®
## (temazepam)
## has an appropriate half-life




A half-life (mean of 10 hours) that parallels normal sleep time:

- patient gets 7-8 hours sleep
- most medication gone by morning
- patient awakes alert and refreshed
- minimal side effects
- insignificant accumulation

Please see brief summary of prescribing information on next page.

# Restful sleep, alert awakening

# RESTORIL®

15 mg
30 mg
capsules

(temazepam)

## A more appropriate half-life

One 30-mg capsule, h.s.—*usual adult dosage.*
One 15-mg capsule, h.s.—*recommended initial dosage for elderly and/or debilitated patients.*

**INDICATIONS AND USAGE:** Restoril® (temazepam) is indicated for the relief of insomnia associated with complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Since insomnia is often transient and intermittent, the prolonged administration of Restoril is generally not necessary or recommended. Restoril has been employed for sleep maintenance for up to 35 consecutive nights of drug administration in sleep laboratory studies.

The possibility that the insomnia may be related to a condition for which there is more specific treatment should be considered.

**CONTRAINDICATIONS:** Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Also, ingestion of therapeutic doses of benzodiazepine hypnotics during the last weeks of pregnancy has resulted in neonatal CNS depression. Restoril is contraindicated in pregnant women. Consider a possibility of pregnancy when instituting therapy or whether patient intends to become pregnant.

**WARNINGS:** Patients receiving Restoril (temazepam) should be cautioned about possible combined effects with alcohol and other CNS depressants.

**PRECAUTIONS:** In elderly and/or debilitated patients, it is recommended that initial dosage be limited to 15 mg. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary.

If Restoril is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, due consideration should be given to potential additive effects.

*Information for Patients:* Patients receiving Restoril should be cautioned about possible combined effects with alcohol and other CNS depressants. Patients should be cautioned not to operate machinery or drive a motor vehicle. They should be advised of the possibility of disturbed nocturnal sleep for the first or second night after discontinuing the drug.

*Laboratory Tests:* The usual precautions should be observed in patients with impaired renal or hepatic function. Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines.

*Pregnancy:* Pregnancy Category X. See Contraindications.

*Pediatric Use:* Safety and effectiveness in children below the age of 18 years have not been established.

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# Evaluation of Left Ventricular Performance Using Digital Subtraction Angiography

MARVIN W. KRONENBERG, MD, RONALD R. PRICE, PhD, CLYDE W. SMITH, MD, ROSE MARIE ROBERTSON, MD, JAMES M. PERRY, MD, DAVID R. PICKENS, PhD, MICHAEL J. DOMANSKI, MD, C. LEON PARTAIN, PhD, MD, and GOTTLIEB C. FRIESINGER, MD

**Cardiac applications for digital subtraction angiography appear promising, but few correlative studies with contrast ventriculography have been done. Left ventricular volume, ejection fraction, and regional wall motion by digital subtraction angiography were evaluated after intravenous injection of 40 ml of iodinated contrast medium and after left venticular injection of 5 to 10 ml of contrast medium. A film-based system of the authors' own design was used. Results were compared with those after direct left ventricular injection of 40 ml of contrast medium.**

**The ventriculograms after intravenous injection were of diagnostic quality in 9 of 12 studies, and there were close correlations between intravenous and direct-injection studies for left ventricular ejection fraction ($r = 0.89$, $n = 9$, and $p = 0.001$) and for left ventricular volume ($r = 0.91$, $n = 18$, and $p < 0.001$). Regional wall motion scores showed close correspondence in 83% of sectors. After small-volume left ventricular injections, the ventricular image was enhanced considerably by digital subtraction. Correlations between small- and large-volume ventriculograms were close for left ventricular ejection fraction ($r = 0.91$, $n = 8$, and $p = 0.002$) and for left ventricular volume ($r = 0.96$, $n = 16$, and $p < 0.001$). There was close correspondence of wall motion scores in 87% of sectors.**

**Thus, digital subtraction angiography improves the visibility of the left ventricle after either intravenous or small-volume direct left ventricular injection. Digital images produce excellent estimates of left ventricular volume and should have considerable usefulness for the study of cardiac performance and anatomy.**

Digital subtraction angiography offers new prospects for evaluation of cardiovascular anatomy and physiology.[1-16] For cardiac applications, images of the thorax are stored in a computer digital matrix before and during passage of a contrast bolus dose through the central circulation. Subtraction of a control, unopacified (mask) image from a contrast-filled image is designed to produce images of contrast-filled structures without interference from soft tissue or bone. Initial reports have been encouraging; however, there is little quantitative, functional information concerning the heart. Thus, we undertook a study with 3 goals: (1) to compare intravenous digital subtraction angiographic images with those produced by conventional left ventricular injection; (2) to compare left ventricular volume and ejection fraction using intravenous angiography with the results of direct left ventricular injection; and (3) to examine the usefulness of digital subtraction angiography to enhance direct left ventriculography performed with small volumes of contrast medium.

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## Methods

The subjects were stable adult patients who underwent cardiac catheterization for diagnostic purposes. All had coronary atherosclerosis. Informed consent was obtained on forms approved by the Vanderbilt Committee for the Protection of Human Subjects. Two protocols were employed.

**Protocol 1:** The results of intravenous and direct left ventriculography were compared in 12 subjects. Pigtail catheters were inserted in the femoral artery and vein using sterile technique, local anesthesia, and the Seldinger method. They were advanced to the abdominal aorta and the origin of the

inferior vena cava, respectively. The chest was marked with radiopaque markers, and cross-hair markers were placed on the image intensifier in most studies to aid image alignment.

Forty ml of a mixture of sodium and meglumine diatrizoate (Renografin®-76, E. R. Squibb and Son, Princeton, New Jersey) was injected into the inferior vena cava during held inspiration using a power injector at rates of either 12 or 15 ml/s. Thirty-five mm cineangiograms of the thorax in the 30° right anterior oblique projection were obtained before and during the passage of the contrast bolus through the central circulation. The film was exposed at either 30 or 60 frames/s with a 9 inch diameter field of view. The electrocardiographic R wave was denoted by a dot in the margin of the appropriate film frame.

The arterial pigtail catheter was advanced to the left ventricle without changing the patient position or the angle of the image intensifier, and 40 ml of contrast medium was injected during held inspiration with identical cineangiographic technique. A wire grid with 1 cm squares was filmed at the height of the heart to allow calculation of left ventricular volume.

Contrast-filled left ventricular end-diastolic and end-systolic frames were identified using R-wave markers and the points of greatest and least left ventricular chamber size. The end-diastolic mask (before contrast injection) was identified by the R-wave marker, and an end-systolic mask was selected by reference to the number of frames between end-diastole and end-systole on the direct left ventricular injection. Images for subtraction were processed without reference to the conventional contrast ventriculograms.

Data were analyzed using an off-line system of our own design. The selected cineangiographic frames were illuminated, placed under a video camera, digitized and displayed in a 512 by 256 pixel matrix with 256 gray levels (Grinnell Interactive Image Display, GMR-27, Grinnell Systems, San Jose, California), and stored using a PDP 11/55 computer (Digital Equipment Corporation, Marlboro, Massachusetts).

The intravenous mask and contrast frames were aligned for subtraction using system software and the radiopaque markers. Mask frames were subtracted from corresponding contrast-filled frames, and the results were displayed using either a linear or logarithmic display. Multiplying the mask image by a factor of 0.75 before subtraction produced optimal visual results. At this point, the quality of each end-diastolic and end-systolic image was judged. The image was classified as acceptable for analysis if definite borders could be seen along the left ventricular contractile perimeter.

The acceptable sets of images and the grid markings were traced onto clear plastic. The mitral and aortic valve planes were determined with reference to the subtracted images, the unsubtracted images, and to the results of (end-diastole minus end-systole) and (end-systole minus end-diastole) subtractions. Later, the digitized unprocessed frames from direct left ventricular injection were displayed and traced in similar fashion. The intravenous and direct-injection outlines were processed using a Numonics Digitizer (North Wales, Pennsylvania) having 0.01 inch resolution and a DEC-1099 computer that executed user-validated software and calculated left ventricular volumes by the area-length method.[17]

Regional left ventricular performance was determined with visual estimation of the area reduction in 45° polar sectors of the left ventricle. Eight sectors were constructed by placing a reference axis along the along axis of the left ventricle, and defining visually the center of the end-systolic ventricle.[18] Sectors 1 and 8, corresponding to the mitral and aortic valve regions, were excluded from analysis, and wall motion was estimated by judging the area reduction of the remaining 6 sectors corresponding to the contractile perimeter of the ventricle. A scale of 0 to 6 was employed, in which 0 represented akinesia/dyskinesia; 2, hypokinesia; 4, normokinesia; and 6, hyperkinesia. Similar methods for analyzing regional performance by area reduction have been validated using contrast ventriculography[19] and radionuclide ventriculography.[18] Also, we have demonstrated that visual estimates of area reduction correlate closely with measured area reduction on contrast ventriculography.[18]

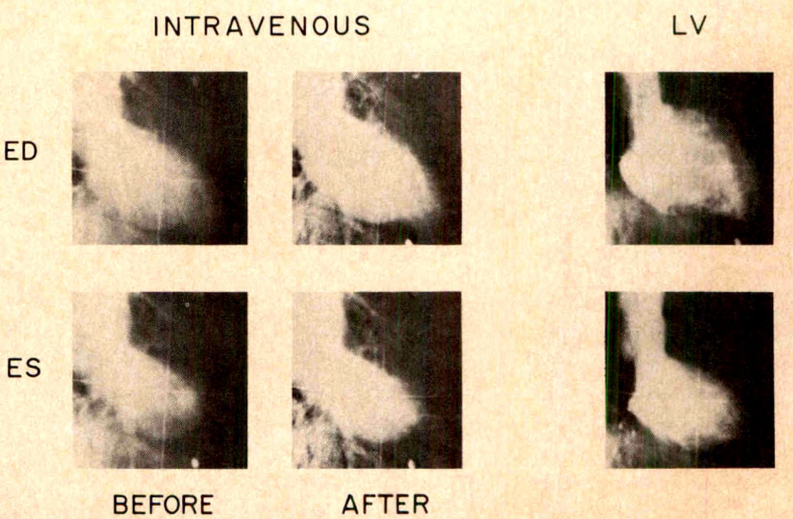



**FIGURE 1.** Images after intravenous and direct left ventriculography. The left ventricle (LV) is visible before subtraction at end-diastole (ED) and end-systole (ES), but the borders are more conspicuous after subtraction of mask images. The intravenous images are highly comparable to the direct left ventricular images.

Data were entered into a medical data base management system (CLINFO, supplied by Division of Research Resources, National Institutes of Health, Bethesda, Maryland). Results were compared by linear regression analysis and the Spearman rank correlation. Statistical significance was defined as $p < 0.05$.

**Protocol 2:** Left ventricular images and left ventricular performance were examined using small-volume direct left ventricular contrast injections that were processed by digital subtraction. In 10 subjects, 5 ml of contrast was injected at end-diastole using a power injector that delivered 12 or 15 ml/s. In 1 subject, 8 ml was injected and in 1, 10 ml was injected. Results were compared with those observed after conventional injections of 40 ml of contrast medium performed within 3 to 5 minutes of the small-volume injection. The details of data processing and analysis were identical to those in Protocol 1.

## Results

All studies were performed without complications. Of 12 intravenous injections, 9 left ventricular images were acceptable for analysis by the criteria described. Of 12 small-volume studies, 8 were acceptable for comparison. Four studies were rejected because of premature ventricular systoles seen with a 40 ml injection in 3 subjects and a very poor image seen with a 5 ml injection in 1 subject who had a very large, poorly contracting ventricle.

**Protocol 1:** Figure 1 demonstrates typical left ventricular images at end-diastole and end-systole before and after digital subtraction, compared with corresponding frames on direct left ventricular injection. The left ventricle was easily visible after intravenous injection, but the details were more conspicuous after subtraction. The images were highly comparable with those seen on direct left ventricular injection. Volume and ejection fraction comparisons for the 9 acceptable studies are shown in Figure 2. The ejection fraction correlation was close ($r = 0.89$, $p < 0.001$), and the correlation for the combined end-diastolic and end-systolic

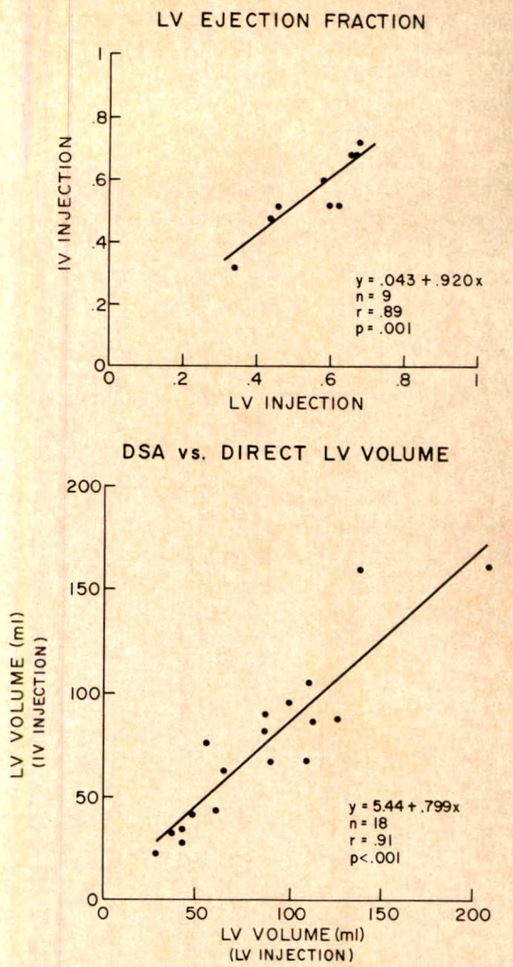



**FIGURE 2.** Comparison of left ventricular (LV) ejection fraction and volume by intravenous (IV) and direct injections. The results for intravenous digital subtraction angiography (DSA) are highly comparable to those for direct injection. However, the left ventricular volume was consistently lower on the intravenous study (see text for details).

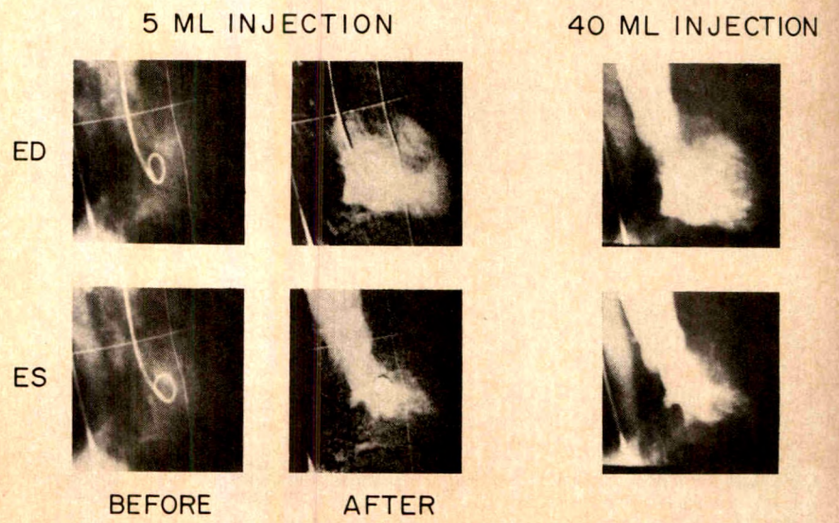



**FIGURE 3.** Images after small-volume (5 ml) and large-volume (40 ml) injections. Digital subtraction produced high quality left ventricular images that demonstrated considerable anatomic detail, including mitral valve prolapse seen on the end-systole (ES) frame in this subject. ED = end-diastole.

volumes was also strong ($r = 0.91$, $n = 18$, and $p < 0.001$), although the intravenous results showed a systematic error of 20% in underestimating the left ventricular volume on direct injection.

The visual estimates of regional ventricular performance were also accurate. Six sectors were graded for each of the 9 subjects. Scores for 45 of 54 sectors (83.3%) were accurate to within 1 grade, and all were accurate within 2 grades. Six of the 9 sectors with inaccuracies of 2 grades were located at the apex and 4 in the inferoapical sector. All grades for the anterior wall sectors were accurate to within 1 grade. There was no systematic error in the wall motion analysis.

**Protocol 2:** The comparison of the small- and large-volume left ventricular contrast injections is shown in Figure 3. In all subjects the left ventricles were barely visible during the 5 ml contrast injections, but their details were easily seen after digital subtraction. The images were highly comparable with those seen on conventional 40 ml contrast injection.

Ejection fraction and volume data for the 8 subjects with acceptable data are shown in Figure 4. For the ejection fraction, there was a close relationship ($r = 0.91$, $n = 8$, and $p = 0.002$). For the volume results, the regression equation demonstrates an x-y intercept near zero, a slope of nearly 1.0, and a strong correlation coefficient ($r = 0.96$, $n = 16$, and $p < 0.001$).

The visual estimates for regional performance showed close correspondence. Scores for 42 of 48 sectors (87.5%) were accurate to within 1 grade, and all scores except 1 were accurate to within 2 grades. Anterior wall sectors were analyzed more accurately than inferior wall sectors. Figure 5 shows the regional performance results.

## Discussion

Intravenous angiography for visualization of cardiac and arterial structures was attempted successfully more than 40 years ago, but the results were suboptimal because of technical limitations.[20–22] Improvements in image intensifiers, television cameras and rapid computer-based digital image processing[1,2] now provide excellent results for carotid, aortic, and renal intravenous angiography.[4–7]

Cardiac studies have been initiated recently. Technical refinements and limited descriptive data have been reported.[3,8,9,11–15] We undertook this study to evaluate left ventricular performance quantitatively. An off-line cineangiographic film-based system of our own design was used to process the ventriculograms.

Three fourths (9 of 12) of the intravenous images of the left ventricle were acceptable for analysis. The left ventricle target-to-background ratio was slightly greater for the acceptable images ($2.52 \pm 0.86$) (mean $\pm$ standard deviation) than for the hazy, unacceptable data ($2.36 \pm 0.29$, $n = 3$), but the differences were not statistically significant in this small number of studies. In the acceptable studies, it was usually possible to define the left ventricular borders before subtraction. However, the edges were more conspicuous after subtraction because of the contrast enhancement that digital angiography produces. The film-based system with a 256 by 512 image matrix produced images of higher resolution than present on-line systems for digital angiography.

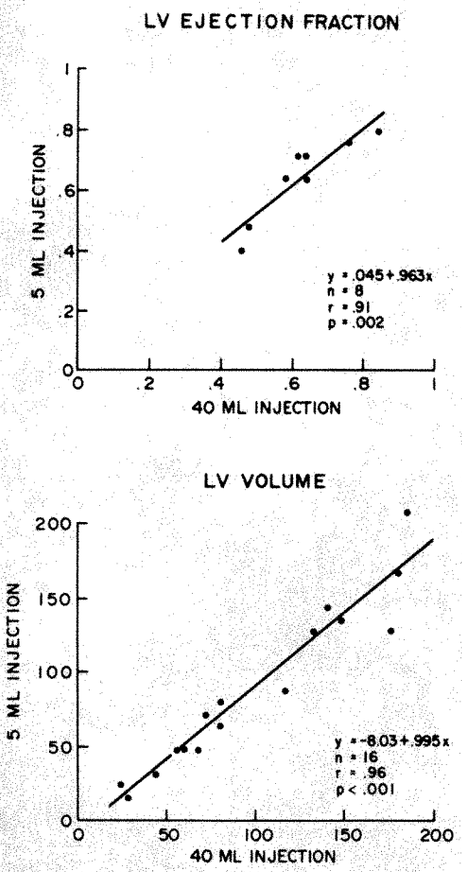



**FIGURE 4.** Comparison of left ventricular (LV) ejection fraction and volume by small-volume and large-volume direct left ventricular injection. Results were highly comparable, with no apparent systematic errors.

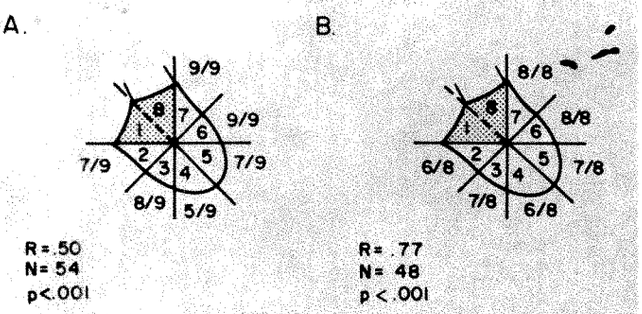



**FIGURE 5.** Comparison of regional performance by digital subtraction and conventional large-volume left ventricular injection. **A,** intravenous injection (9 subjects). **B,** small-volume left ventricular injection (8 subjects). The number of subjects with regional wall motion within 1 grade of that on conventional injection is shown for sectors 2 to 7, which comprise the contractile perimeter. Results of the Spearman rank correlation are listed. There was excellent correspondence in the anterior and anteroapical regions (sectors 5 to 7).

Our volume and ejection fraction data from intravenous injections correlated well with results from direct left ventricular injection, but the results after intravenous injection of contrast medium were systematically lower than those derived from direct injection. This may be due to the osmotic effects of contrast agents. Kloster et al[23] documented an average increase of 223 ml (4%) in blood volume 5 minutes after left ventricular contrast injection in human subjects. Also, Iseri et al[24] found an average increase of 170 ml in plasma volume 5 minutes after contrast left ventriculography (range 100 to 250 ml). In the present study, the direct left ventricular injection was performed 5 to 10 minutes after the intravenous injection. Thus, it is likely that the intravenous injection of contrast medium produced a moderate increase in intravascular volume, based on its osmotic effects. However, this cannot be confirmed because we did not measure blood volume. In addition, the rapid injection of this volume of contrast medium directly into the left ventricle could increase actual ventricular volume. This finding was reported by Sanmarco et al,[25] who documented an immediate, transient 5 to 15% increase in the ventricular volume of dogs after injection of 15 to 20 ml (1 ml/kg body weight) of contrast medium into the left ventricle. Intravenous contrast material is well mixed by passage through the right heart and lungs and does not constitute a bolus injection into the left ventricle. The intravenous injection of contrast medium is likely to have caused transient osmotic effects on the red blood cells[26], but it is unlikely to have greatly increased the total blood volume on its first passage through the central circulation. Thus, the intravenous volume measurements are probably accurate, although there could have been small errors in left ventricular border definition because of fainter borders seen on intravenous injection and errors in estimating valve plane location, or both.

Digital angiography greatly improved the visibility of small-volume direct left ventricular injections. Images that were barely visible before subtraction were easily seen afterward. Eleven of 12 small-volume injections were analyzable but 3 of twelve 40 ml injections were inadequate for comparison because of numerous premature ventricular systoles during these injections. The single subjects who received intraventricular injections of 8 and 10 ml had images that could be analyzed before subtraction; however, the images for those who received injections of 5 ml could not be analyzed without digital subtraction. After subtraction, the small- and large-volume results were highly comparable, without systematic differences. Left ventricular dilatation due to the larger 40 ml bolus of contrast medium was not apparent. There was no change in left ventricular end-diastolic pressure after the injections of 5 ml in the 3 subjects in whom this was measured. However, all 8 subjects had an increase in left ventricular end-diastolic pressure after the 40 ml injections.

The digital subtraction technique can lower the dosage of contrast needed for direct injection ventriculography. The potential physiologic benefits include a lower contrast load and a reduced chance of nephrotoxicity in susceptible patients.[27] It is also possible to study left ventricular performance more carefully by performing several small-volume ventriculograms rather than 1 or 2 conventional studies. Detectable volume and pressure alterations do not occur with small-volume injections. This freedom can allow accurate analysis of alterations in left ventricular loading or of drug therapy. Our data confirm the recent study of Sasayama et al[10] regarding the accuracy of data for small-volume left ventricular injections. Tobis et al[15] recently demonstrated excellent results using direct injections of 10 ml.

Regional wall motion analysis demonstrated accurate results in nearly all sectors, but the inferior and apical regions were more difficult to demarcate on the single static end-diastolic and end-systolic images we employed. Wall motion, volume, and ejection fraction results should improve considerably when moving, endless loop "playback buffers" are employed.

Our preliminary results with digital subtraction angiography are quantitative and encouraging. Problems can occur because of patient movement, slow circulation time, large cardiac volumes, and the intrinsic cardiac motion. Demonstration of left ventricular performance should improve considerably with future refinements in both radiographic hardware and image processing software.

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## References

1. **Kruger RA, Mistretta CA, Houk TL, Riederer SJ, Shaw CG, Goodsitt MM, Crummy AB, Zweibel W, Lancaster JC, Rowe GG, Flemming D.** Computerized fluoroscopy in real time for noninvasive visualization of the cardiovascular system. Preliminary studies. Radiology 1979;130:49–57.
2. **Ovitt TW, Christenson PC, Fisher HD III, Frost MM, Nudelman S, Roehrig H, Seeley G.** Intravenous angiography using digital video subtraction: X-ray imaging system. AJR 1980;135:1141–1144.
3. **Meany TW, Weinstein MA, Buonocore E, Pavlicek W, Borkowski GP, Gallagher J, Sufka B, MacIntyre WJ.** Digital subtraction angiography of the human cardiovascular system. AJR 1980;135:1153–1160.
4. **Chilcote WA, Modic MT, Pavlicek WA, Little JR, Furlan AJ, Duchesneau PM, Weinstein MA.** Digital subtraction angiography of the carotid arteries: a comparative study in 100 patients. Radiology 1981;139;287–295.
5. **Buonocore E, Meany TF, Borkowski GP, Pavlicek W, Gallagher J.** Digital subtraction angiography of the abdominal aorta and renal arteries. Comparison with conventional aortography. Radiology 1981;139:281–286.
6. **Hillman BJ, Ovitt TW, Nudelman S, Fisher HD, Frost MM, Capp MP, Roehrig H, Seeley G.** Digital video subtraction angiography of renal vascular abnormalities. Radiology 1981;139:277–280.
7. **Smith CW, Winfield AC, Price RR, Harding DR, Tucker SW, Witt WS, Hollifield JW.** Evaluation of digital venous angiography for the diagnosis of renovascular hypertension. Radiology 1982;144:51–54.
8. **Vas R, Diamond G, Forrester J, Swan HJC.** "Noninvasive" ventriculography (abstr). Circulation 1980;62:Suppl III:III-141.
9. **Crummy AB, Strother CM, Sackett JF, Ergun DL, Shaw CG, Kruger RA, Mistretta CA, Turnipseed WD, Lieberman RP, Myerowitz PD, Ruzicka FF.** Computerized fluoroscopy: digital subtraction for intravenous angiocardiography and arteriography. AJR 1980;135:1131–1140.
10. **Sasayama S, Nonogi H, Kawai C, Fujita M, Eiho S, Kuwahara M.** Automated method for left ventricular volume measurement by cineventriculography with minimal doses of contrast medium. Am J Cardiol 1981;48:746–753.
11. **Gerber K, Bhargava V, Slutsky R, Mattrey R, Ashburn W, Higgins C.** Quantitation of regional and global left ventricular (LV) function by digital intravenous ventriculography (DIV) with functional image analysis (abstr). Circulation 1981;64:Suppl IV:IV-219.
12. **Vogel R, LeFree M, Foster R, Smith D, Pitt B.** Integral signed ECG-synchronized difference (ISED): a new technique for performing digital ventriculography (abstr). Circulation 1981;64:Suppl IV:IV-220.
13. **Lipton MJ, Gould RG.** Digital subtraction fluoroscopy—a dual video system (abstr). Circulation 1981;64:Suppl IV:IV-220.
14. **Bogren HG, Bursch JH, Brennecke R, Heintzen PH.** Intravenous angiocardiography using digital image processing: experience with axial pro-

jections in normal pigs (abstr). Circulation 1981;64:Suppl IV:IV-220.
15. **Tobis JM, Nalcioglu O, Seibert JA, Roeck WW, Iseri LT, Elkayam U, Johnston WD, Henry WL.** Use of digital angiography in assessment of ventricular ejection fraction and pacing induced wall motion abnormalities (abstr). Circulation 1981;64:Suppl IV:IV-250.
16. **Eisenberg H, Arnold B, Thomas A, Metherell A, Borger D, Greenfield L, Scheibe P, DeCou F.** Intravenous angiography in the evaluation of patients with coronary artery bypass grafts (abstr). Proc Radiol Soc North Am 1981;95.
17. **Kasser IS, Kennedy JW.** Measurement of left ventricular volumes in man by single-plane cineangiography. Invest Radiol 1969;4:83–90.
18. **Steckley RA, Kronenberg MW, Born ML, Rhea TC, Bateman JM, Rollo FD, Friesinger GC.** Radionuclide ventriculography: evaluation of automated and visual methods for wall motion analysis. Radiology 1982;142:179–185.
19. **Gelberg HJ, Brundage BR, Glantz S, Parmley WW.** Quantitative left ventricular wall motion analysis: a comparison of area, chord and radial methods. Circulation 1979;59:991–1000.
20. **des Plantes BGZ.** Subtraktion: Eine rontgenograhische Methode zur separaten Abbildung bestimmer Teile des Objekts. ROFO 1935;52:69–79.
21. **Castellanos A, Pereiras R, Garcia A.** La angiocardiografia radioopaca. Arch Soc Estud Clin (Habana) 1937;31:523.
22. **Robb GP, Steinberg I.** Visualization of the chambers of the heart, the pulmonary circulation and the great blood vessels in man. AJR 1939;41:1–17.
23. **Kloster FE, Bristow JD, Jacobs WR, Porter GA, Griswold HE.** Hemodynamic effects of angiocardiography. Invest Radiol 1966;1:398–406.
24. **Iseri LT, Kaplan MA, Evans MJ, Nickel ED.** Effect of concentrated contrast media during angiography on plasma volume and plasma osmolality. Am Heart J 1965;69:154–158.
25. **Sanmarco ME, Fronek K, Phillips CM, Davila JC.** Continuous measurement of left ventricular volume in the dog. Am J Cardiol 1966;18:584–593.
26. **Friesinger GC, Schaffer J, Criley JM, Gaertner RA, Ross RS.** Hemodynamic consequences of the injection of radiopaque material. Circulation 1965; 31:730–740.
27. **Harkonen S, Kjellstrand C.** Contrast nephropathy. Am J Nephrol 1981;1: 69–77.

As the soul is dyed by the thoughts, let no day pass without contact with the best literature of the world.

The load of to-morrow, added to that of yesterday, carried today makes the strongest falter.

Sir William Osler, "A Way of Life"

# Evaluation of Intracardiac Thrombus With Computed Tomography

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**Left atrial (LA) and left ventricular (LV) thrombus was evaluated by computed tomography in 56 patients. The patients were divided into 2 groups: Group I, 28 patients with mitral valve disease, and Group II, 28 patients with myocardial infarction. Computed tomography and 2-dimensional echocardiography were performed in all the patients studied. Cineangiocardiography was performed in all Group I and in 13 Group II patients. Open heart surgery or autopsy was performed in all Group I and 4 Group II patients. The sensitivity in detecting LA thrombus was 100% with computed tomography, 70% with angiocardiography, and 60% with 2-dimensional echocardiography. The specificity in detecting LA thrombus was 91% with computed tomography, 86% with 2-dimensional echocardiography, and 88% with angiocardiography. Thrombi located at the LA appendage were associated with great difficulties in detection by other methods, but were well delineated with computed tomography. LV thrombus was also visualized by computed tomography with similar or greater accuracy than other diagnostic methods, although the sensitivity and specificity were not ascertained because surgery or autopsy was performed in only a minority of Group II patients. Therefore, as far as the detection of intracardiac thrombus is concerned, computed tomography has the advantage of offering uniform slices of the heart in an attempt to detect thrombi in unknown areas of cardiac chambers, including the LA appendage or LV apex, without being disturbed by the surrounding cardiac and noncardiac structures. Thus, computed tomography has excellent accuracy in the detection of intracardiac thrombus.**

The detection of intracardiac thrombus is significant in the treatment of patients with cardiac diseases. Evaluation of intracardiac thrombus, especially that of left atrial (LA) and left ventricular (LV) thrombus, has been attempted with angiocardiography,[1–5] M-mode echocardiography,[6,7] 2-dimensional echocardiography,[7–13] and radionuclide techniques.[14,15] Although there have been improvements in sensitivity and specificity in the detection of intracardiac thrombus, these methods still have limitations, depending on the size and location of the thrombus.[1–15] On the other hand, there have been sporadic reports on the detection of intracardiac thrombus with computed tomography; these preliminary experiences suggest the usefulness of computed tomography in the detection of intracardiac thrombus.[16–19] Therefore, the present study was undertaken to clarify the validity of computed tomography in evaluating LA and LV thrombi.

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## Methods

**Patients:** Twenty-eight patients with mitral valve disease were classified as Group I patients. As shown in Table I, their ages ranged from 36 to 68 years (average 50.0 ± 8.4); 21 were women. The group consisted of 11 patients with mitral stenosis, 7 with mitral stenosis and regurgitation, and 10 with combined valvular disease; 24 of these patients had atrial fibrillation.

Twenty-seven of the 28 patients in Group I underwent open heart surgery (open mitral commissurotomy 13, valve replacement 14); a postmortem autopsy was performed on 1 patient to confirm left atrial thrombus. Computed tomography, 2-dimensional echocardiography, and cineangiocardiography were undertaken in all the patients in Group I. The interval from computed tomography to cardiac surgery ranged from 3 to 34 days (average 14.5 ± 9.5). The interval from 2-dimensional echocardiography to cardiac surgery ranged from

**TABLE I Patient Data: Group I (Mitral Valve Disease)**

| Patient | Age (yr) & Sex | Diagnosis | AF | Systemic Embolization | Detection of Thrombus by CT (Size in cm) | CTN | Detection of Thrombus by Echocardiography (Size in cm) | Detection of Thrombus by Angiocardiography | Detection of Thrombus by Surgery or Autopsy (Size in cm) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 47F | MSR, ASR | + | + Cerebral | + Appendage, 2.3 × 2.0 | +42 | 0 | + Appendage | + 20 g (total), fresh |
| | | | | | + Posterolateral, 2.9 × 2.0 | | + Posterolateral, UM | 0 | + |
| 2 | 59F | MS | + | + TIA | + Appendage, 1.6 × 1.2 | +43 | 0 | + Appendage | + 1.5 × 1.5 × 1.5, organized |
| 3 | 45F | MSR, TR | + | 0 | + Appendage, 1.6 × 1.3 | +68 | 0 | 0 | + 2.0 × 1.5 × 1.0, organized |
| 4 | 46M | MS | + | 0 | + Appendage, 3.0 × 2.5 | +64 | + Appendage, 2.0 × 1.0 | 0 | + 3.5 × 3.0 × 1.5, partly organized |
| 5 | 45M | MS | + | + Cerebral | + Posterior, 5.8 × 1.8 | NM | + Posterior, 5.5 × 1.5 | + Posterior | + NM, partly organized |
| 6 | 68F | MSR | + | + Cerebral | + Posterior, 7.5 × 1.7 | +37 | + Posterior, 6.8 × 1.9 | + Posterior | + 40 g, partly organized |
| 7 | 57M | MS | + | + Coronary | + Lateral, 2.2 × 1.4 | NM | + Lateral, 3.3 × 1.7 | + Lateral | + NM, organized |
| 8 | 60F | MS, TR, AR | + | 0 | + Posterior, 7.3 × 3.3 | NM | + Posterior, 7.5 × 3.5 | + Posterior | + 100 g (total), organized |
| | | | | | + Lateral, 5.5 × 1.6 | | 0 | + Lateral | + |
| 9 | 56F | MS, AR | + | 0 | + Appendage, 3.2 × 2.3 | | 0 | 0 | 0 |
| 10 | 66F | MS | + | + TIA | 0 | | 0 | + Appendage | 0 |
| 11 | 47F | MS | 0 | 0 | 0 | | 0 | E Appendage | 0 |
| 12 | 41F | MSR | + | + Iliac | 0 | | 0 | E Appendage | 0 |
| 13 | 42F | MSR | + | 0 | 0 | 0 | + Posterior | 0 | 0 |
| 14 | 58F | MSR, TR | + | 0 | 0 | | E Posterior | 0 | 0 |
| 15 | 47M | MSR | + | + Cerebral | 0 | | 0 | 0 | 0 |
| 16 | 47F | MS | + | 0 | 0 | | 0 | 0 | 0 |
| 17 | 46M | MSR | + | 0 | 0 | | 0 | 0 | 0 |
| 18 | 60F | MSR, TR | + | 0 | 0 | | 0 | 0 | 0 |
| 19 | 38F | MS | 0 | 0 | 0 | | 0 | 0 | 0 |
| 20 | 49F | MSR, AR | + | + Femoral | 0 | | 0 | 0 | 0 |
| 21 | 53F | MS | 0 | 0 | 0 | | 0 | 0 | 0 |
| 22 | 38F | MS, ASR | + | 0 | 0 | | 0 | 0 | 0 |
| 23 | 36F | MS | + | 0 | 0 | | 0 | 0 | 0 |
| 24 | 51F | MSR | + | + Renal | 0 | | 0 | 0 | 0 |
| 25 | 57F | MSR | + | 0 | 0 | | 0 | 0 | 0 |
| 26 | 41M | MS | + | 0 | 0 | | 0 | 0 | 0 |
| 27 | 48M | MR, AR | 0 | 0 | 0 | | 0 | 0 | 0 |
| 28 | 51F | MS, AR | + | 0 | 0 | | 0 | 0 | 0 |

AF = atrial fibrillation; AR = aortic regurgitation; ASR = aortic stenosis with regurgitation; CT = computed tomography; CTN = computed tomography number; E = equivocal; MS = mitral stenosis; MSR = mitral stenosis with regurgitation; NM = not measured; TIA = transient ischemic attack; TR = tricuspid regurgitation; UM = unmeasurable; + = present; 0 = absent.

**TABLE II Patient Data: Group II (Myocardial Infarction)**

| Patient | Age (yr) & Sex | Diagnosis | ECG | Systemic Embolization | Detection of Thrombus by Computed Tomography (Size in cm) | Detection of Thrombus by Echocardiography (Size in cm) | Aneurysm | Detection of Thrombus by Angiocardiography | Detection of Thrombus by Surgery and Autopsy |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 42M | AS | $V_1$-$V_4$ | 0 | + Apical, 3.3 × 1.3 | + Apical, 2.5 × 1.0 | + | + Apical | + |
| 2 | 48M | AS | $V_1$-$V_4$ | 0 | + Apical, 1.7 × 1.3 | + Apical, 1.7 × 1.4 | + | + Apical | + |
| 3 | 76M | I | II, III, aVf | 0 | + Apical, 2.3 × 1.4 | + Apical, 1.7 × 1.6 | + | + Apical | + |
| 4 | 36M | AL | $V_2$-$V_5$, I, aVL | 0 | + Apical, 2.1 × 1.8 | + Apical, 2.0 × 1.3 | 0 | + Apical | − |
| 5 | 56M | AS | $V_1$-$V_4$ | 0 | + Apical, 2.0 × 1.1 | + Apical, 2.9 × 1.1 | + | + Apical | − |
| 6 | 60M | AL | $V_1$-$V_5$, aVL | 0 | + Apical, 4.8 × 2.2 | Insufficient record | | + Apical | − |
| 7 | 55M | AS | $V_1$-$V_4$ | 0 | + Apical, 2.6 × 1.4 | E Apical | 0 | + Apical | − |
| 8 | 55F | AS | $V_1$-$V_4$ | 0 | + Apical, 2.6 × 1.4 | + Apical, 2.3 × 1.2 | + | − | − |
| 9 | 56M | AL | $V_2$-$V_5$, I, aVL | 0 | + Apical, 3.4 × 0.7 | + Apical, 2.4 × 1.0 | + | − | − |
| 10 | 70M | AS, I | $V_1$-$V_3$, II, III, aVF | 0 | + Apical, 3.5 × 0.8 | + Apical, 2.4 × 1.0 | + | − | − |
| 11 | 36M | AS, I | $V_1$-$V_4$, II, III, aVF | 0 | E Apical | 0 | + | 0 | − |
| 12 | 66M | AS | $V_1$-$V_3$ | 0 | 0 | + Apical, 2.1 × 1.2 | + | − | − |
| 13 | 44M | AS | $V_1$-$V_3$ | 0 | 0 | E Apical | 0 | − | − |
| 14 | 45M | AL | $V_1$-$V_6$, I, aVL | 0 | 0 | Insufficient record | | 0 | − |
| 15 | 77M | AS, I | $V_1$-$V_3$, III, aVf | 0 | 0 | 0 | 0 | 0 | − |
| 16 | 50M | AS | $V_1$-$V_3$ | 0 | 0 | 0 | 0 | 0 | − |
| 17 | 49M | AL | $V_1$-$V_6$, I, aVL | 0 | 0 | 0 | + | 0 | − |
| 18 | 47M | AS | $V_1$, $V_2$ | 0 | 0 | 0 | 0 | 0 | − |
| 19 | 60F | AL | $V_1$-$V_6$, I, aVL | 0 | 0 | 0 | 0 | − | 0 |
| 20 | 68M | AS | $V_1$-$V_3$ | 0 | 0 | 0 | + | − | − |
| 21 | 64M | AS | $V_1$, $V_2$ | 0 | 0 | 0 | 0 | − | − |
| 22 | 55M | AS | $V_1$-$V_3$ | 0 | 0 | 0 | 0 | − | − |
| 23 | 52M | AS | $V_1$-$V_4$ | 0 | 0 | 0 | 0 | − | − |
| 24 | 63M | AS | $V_1$-$V_3$ | 0 | 0 | 0 | 0 | − | − |
| 25 | 71M | AS | $V_1$-$V_3$ | 0 | 0 | 0 | + | − | − |
| 26 | 66M | AL | $V_1$-$V_6$, I, aVL | 0 | 0 | 0 | + | − | − |
| 27 | 60M | AS | $V_1$-$V_3$ | 0 | 0 | 0 | 0 | − | − |
| 28 | 65F | AS | $V_1$-$V_4$ | 0 | 0 | 0 | 0 | − | − |

AL = anterolateral myocardial infarction; AS = anteroseptal myocardial infarction; E = equivocal; ECG = electrocardiogram; I = inferior myocardial infarction; − = not done; + = present; 0 = absent.

4 to 45 days (average 17.7 ± 10.6). The interval from angiocardiography to cardiac surgery ranged from 6 to 33 days (average 17.6 ± 9.6).

Twenty-eight patients with previous myocardial infarction, documented by prolonged precordial pain, typical electrocardiographic changes, and significant elevations of serum enzymes, were classified as Group II patients. As shown in Table II, the ages of the patients ranged from 36 to 77 years (average 56.9 ± 11.1); 25 were men. This group included 17 patients with anteroseptal myocardial infarction, 7 with anterolateral myocardial infarction, 1 with inferior myocardial infarction, and 3 with anteroseptal-inferior myocardial infarction. The mean interval between infarction and study was 9.4 ± 23.2 months, with a range of 1 month to 9 years.

Computed tomography and 2-dimensional echocardiography were performed in all patients in Group II. Angiocardiography was performed in 13 and cardiac surgery or autopsy was undertaken in 4. The interval from computed tomography to 2-dimensional echocardiography ranged from 2 to 18 days (average 9.2 ± 1.6) and that from computed tomography to angiocardiography from 2 to 19 days (average 8.3 ± 1.6).

**Computed tomography:** A computed tomographic whole body scanner that utilized a continuously rotating gantry and pulsed anode with x-radiation collimated to form a thin fan-shaped beam (Varian computed tomographic 3-second whole body scanner) was used.[20] A complete section scan was performed in 3 seconds. The scale for transparency was −1,000 for air, 0 for water, and +1,000 for bone. In this study, gated computed tomographic scanning to obtain "stop-action" image was not applied. Every computed tomogram (horizontal slice of the heart) was obtained at a thickness of 0.5 to 1 cm in the position of deep inspiration. Sustained enhancement was obtained with a rapid intravenous infusion of 100 ml of 60% meglumine iothalamate or 200 ml of 30% meglumine iothalamate.

**Two-dimensional echocardiography:** Two-dimensional echocardiographic studies were performed by a 90° Toshiba SSH-11A phase array sector scanner with a 2.5 MHz transducer. Recordings were undertaken with the patient in the supine or 30° left lateral decubitus position. The 2-dimensional echocardiographic findings were initially obtained from the left sternal border in the long- and short-axis planes. Apical and subxiphoid views were then taken, and 4-chamber and 2-chamber views were obtained.[21,22] The images were recorded on videotape, and photographs of single-frame findings were taken on Polaroid® or 35 mm black and white film.

Thrombus was defined by echocardiography as a distinct mass of echoes in the intracardiac cavity that was seen clearly throughout the cardiac cycle and that was contiguous with the endocardium.[11] LV aneurysm was defined as a distinct akinetic or dyskinetic bulge interrupting the normal ventricular configuration during systole and diastole.

**Cineangiocardiography:** In patients with mitral valvular disease (Group I), levophase pulmonary angiograms were obtained with the methods described by Parker et al.[1] An 8Fr National Institutes of Health angiographic catheter was inserted into the main pulmonary artery by way of the percutaneous femoral venous route, and 1 ml of 76% sodium meglumine diatrizoate per kilogram of body weight was injected over a 2.5-second period with a power injector. In patients with mitral valve disease (Group I) and those with myocardial infarction (Group II), LV cineangiocardiography was performed with a 7Fr pigtail catheter introduced into the left ventricle by way of the percutaneous femoral arterial route.

Forty milliliters of 76% sodium meglumine diatrizoate was injected into the left ventricle over a 2-second period with a power injector. The LA and LV angiographic studies were performed in the right anterior oblique position with 35 mm film exposed at 50 to 60 frames/s. Cineangiocardiographic criteria for LA thrombus were persistent fixed or mobile filling defects in the body of the left atrium or atrial appendage.[2] LV thrombus was diagnosed if there was evidence of a persistent filling defect in the LV cavity during both systole and diastole.[3]

**Interpretations and measurements:** The computed tomographic findings were interpreted by 3 of the authors (SK, MO, and SM), the 2-dimensional echocardiographic findings by 2 (MH and HF), the angiocardiographic findings by 1 (HT), and the surgical findings by 3 (SKo, SKa, and AS), independently. Measurements of the sizes of the thrombi were attempted as the largest long and short axes on the computed tomographic and 2-dimensional echocardiographic planes.

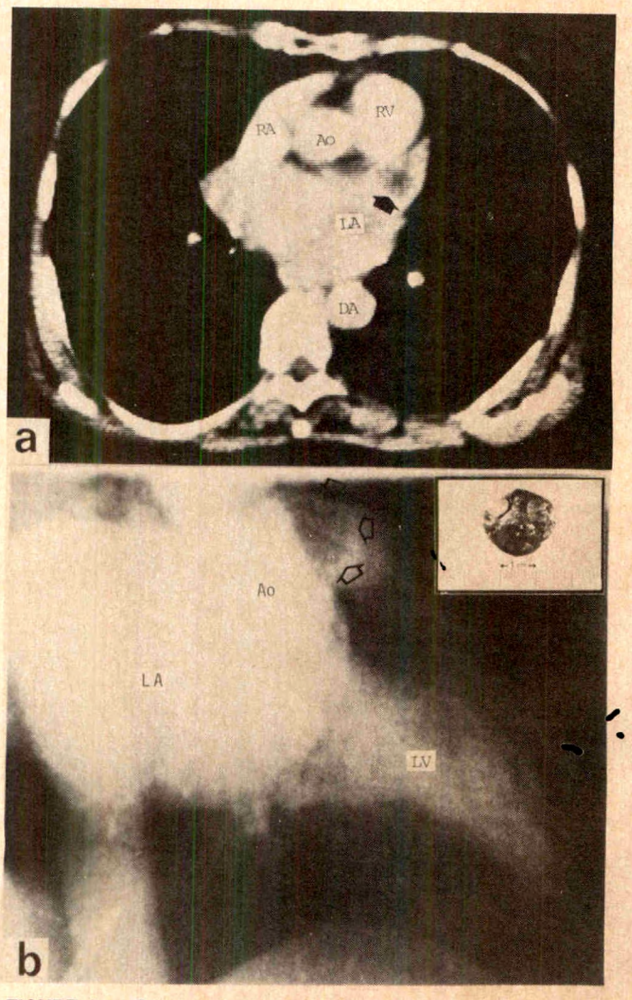



**FIGURE 1. a,** Computed tomogram of a patient with mitral stenosis (Case 2, Group I). There was a small filling defect (1.6 × 1.2 cm) (**arrow**) at the left atrial appendage, which was also identified by cineangiocardiography (**b**) (**arrows**). Open heart surgery later confirmed this to be an organized spherical thrombus 1.5 cm in diameter (**inset**). The thrombus was not revealed by 2-dimensional echocardiography. Ao = aorta; DA = descending aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

## Results

**Left atrial thrombus:** In 28 patients with mitral valve disease (Group I), 9 LA thrombi were confirmed in 7 patients by open heart surgery (Cases 1 to 5, 7, and 8), and a thrombus was identified in another patient by autopsy (Case 6). No LA thrombus was seen in the rest of the patients by open heart surgery (Table I).

All of the 10 LA thrombi confirmed by surgery or autopsy were delineated by computed tomography in each of the 8 patients. Six of the 10 thrombi in the 8 patients with LA thrombus were identified by 2-dimensional echocardiography. Three of the thrombi overlooked echocardiographically were located in the LA appendage (Cases 1 to 3), and 1 was attached to the lateral wall of the left atrium (Case 8) (Fig. 1 and 2). Three of the 10 thrombi in the 8 patients were not identified by cineangiocardiography. Two were located at the appendage (Cases 3 and 4), and 1 was present at the posterior wall of the left atrium (Case 1). Among 20 patients in whom LA thrombus was not detected by surgery, there was a positive diagnosis of LA appendage by computed tomography (Case 9) and a positive and an equivocal diagnosis was made at the posterior wall of the left atria by 2-dimensional echocardiography (Cases 13 and 14). A false-positive and 2 equivocal diagnoses were made at the LA appendage by angiocardiography (Cases 10 to 12).

Although the possibility of dissolution of the thrombi could not be ruled out completely, no patient received anticoagulant therapy, and the interval from the clinical evaluation to surgery was relatively short, ranging from 6 to 21 days; there was no systemic embolization during this period in these patients.

Thus, the sensitivity in detecting LA thrombus was 100% with computed tomography, 60% with 2-dimensional echocardiography, and 70% with cineangiocardiography. When both positive and equivocal study results were considered to indicate the presence of thrombus, the specificity in detecting LA thrombus was 91% with computed tomography, 75% with 2-dimensional echocardiography, and 70% with cineangiocar-

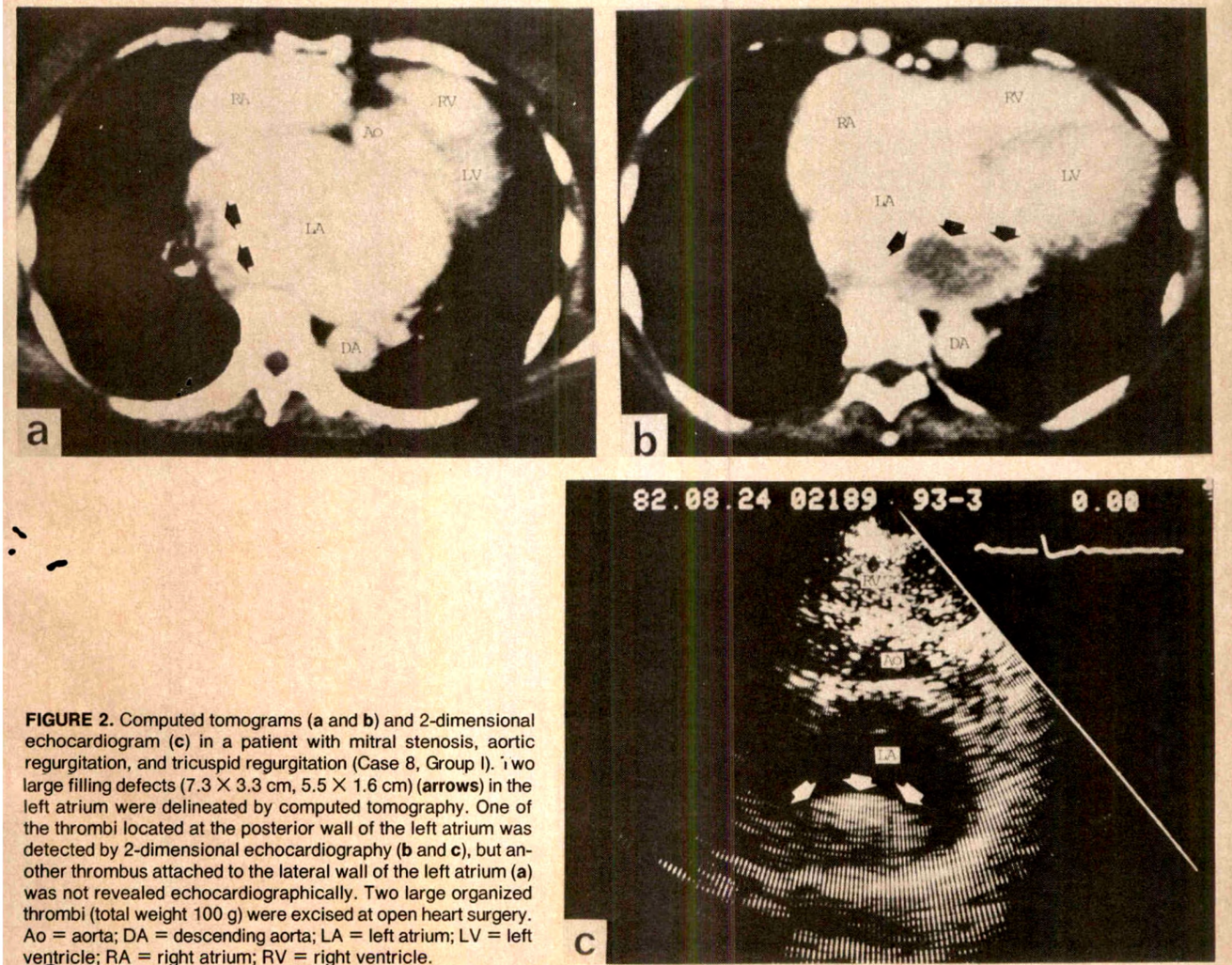



**FIGURE 2.** Computed tomograms (**a** and **b**) and 2-dimensional echocardiogram (**c**) in a patient with mitral stenosis, aortic regurgitation, and tricuspid regurgitation (Case 8, Group I). Two large filling defects (7.3 × 3.3 cm, 5.5 × 1.6 cm) (**arrows**) in the left atrium were delineated by computed tomography. One of the thrombi located at the posterior wall of the left atrium was detected by 2-dimensional echocardiography (**b** and **c**), but another thrombus attached to the lateral wall of the left atrium (**a**) was not revealed echocardiographically. Two large organized thrombi (total weight 100 g) were excised at open heart surgery. Ao = aorta; DA = descending aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

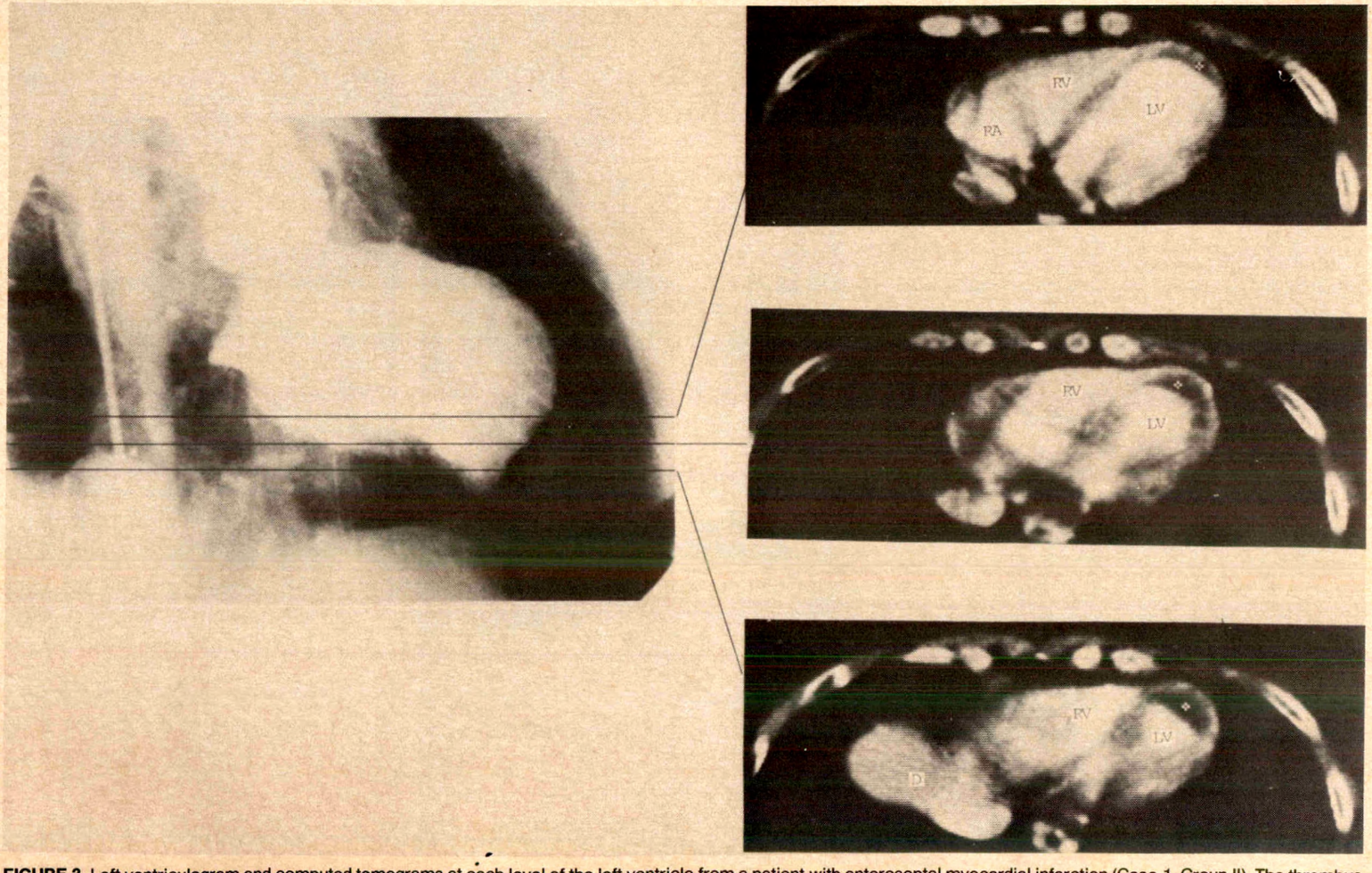



**FIGURE 3.** Left ventriculogram and computed tomograms at each level of the left ventricle from a patient with anteroseptal myocardial infarction (Case 1, Group II). The thrombus is indicated by **asterisks**. D = diaphragm; LV = left ventricle; RA = right atrium; RV = right ventricle.

diography. If equivocal study results were instead considered negative, the specificity in detecting LA thrombus was 91% with computed tomography, 86% with 2-dimensional echocardiography, and 87.5% with angiocardiography.

Five of the 8 patients with LA thrombus (62.5%) and 5 of the 20 patients without LA thrombus (25%) had a history of systemic embolization. The measurements of the thrombi were grossly similar with computed tomographic, echocardiographic, or surgical methods, although strict comparisons were not possible as the planes on which the measurements were attempted were not exactly the same with each method (Table I).

The values of x-ray transparency expressed as computed tomographic numbers ranged from +37 to +68 at the areas of the LA thrombi. The values, however, had no definitive correlation with the pathologic findings of the excised thrombi (Table I).

**Left ventricular thrombus:** There were 10 positive findings, that is, filling defects, compatible with LV thrombi and an equivocal finding by computed tomography (Fig. 3, Table II). There was 1 equivocal and 8 positive echocardiographic findings in the 10 patients with positive findings on computed tomography; satisfactory recordings were not obtained in 1 patient by echocardiography (Fig. 4). The LV filling defects were identified angiocardiographically in all 7 patients with positive computed tomographic findings in whom angiocardiography was performed; the thrombi were confirmed by open heart surgery in 2 patients (Cases 1 and 2) and by autopsy in 1 (Case 3). On the other hand, among the 18 patients in whom thrombus was not delineated by computed tomography, positive findings of LV thrombus were indicated in 1 patient (Case 12) and equivocal findings in another (Case 13) by 2-dimensional echocardiography.

LV aneurysms were noted echocardiographically in 7 of the 10 patients with thrombi proven by computed tomography and in 6 of the 18 patients without thrombus. There was no cineangiocardiographically positive finding in any of the 6 patients with negative computed tomographic findings who underwent LV angiocardiography.

The sizes of the thrombi were similar when measured by computed tomography and 2-dimensional echocardiography, although the comparisons may not be valid due to the differences in the planes at which the mea-

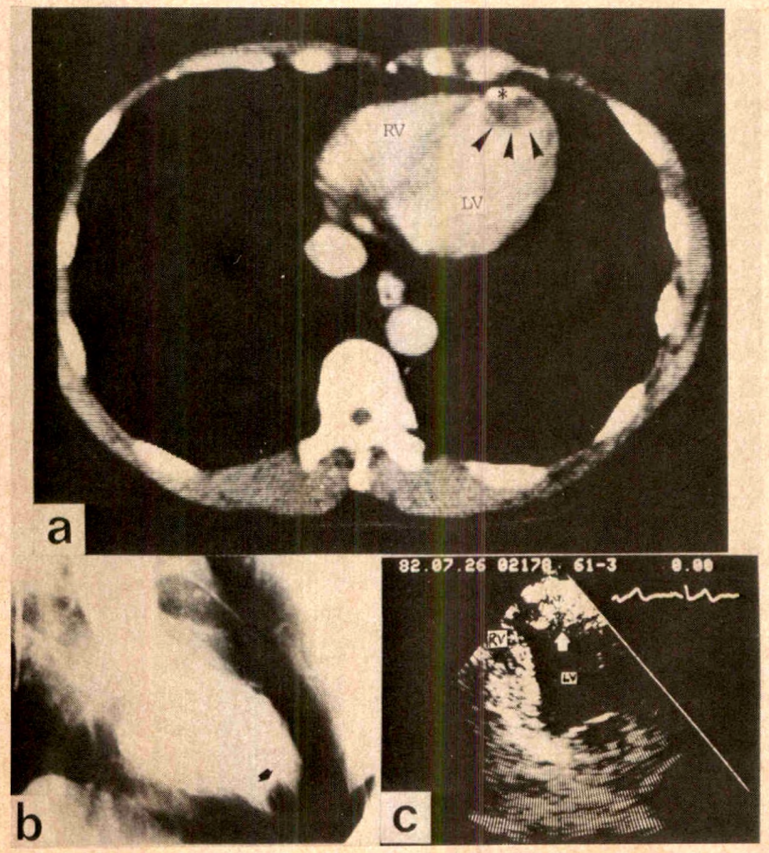



**FIGURE 4.** Computed tomogram (**a**), left ventriculogram (**b**), and 2-dimensional echocardiogram (**c**) of a patient with anteroseptal myocardial infarction (Case 7, Group II). There was a filling defect at the left ventricular apex (**arrows**) in the angiogram and computed tomogram; this was not clearly delineated by echocardiography most probably because of reverberations from the calcified infarct area (**asterisk**) as shown by computed tomography. LV = left ventricle; RV = right ventricle.

surements were attempted (Table II). No history of systemic embolization was detected in any patient in Group II.

## Discussion

The detection of intracardiac thrombus is important regardless of the size of the thrombi because the patients are exposed to the possibility of systemic embolization. Systemic embolization has been reported to originate from rheumatic heart disease in 26 to 40%[23–26] and from myocardial infarction in 22 to 36% of these patients.[23–26]

Thrombus formation was detected in 9 to 17% of patients with mitral valve disease[1,2] and in 14 to 33% of patients with myocardial infarction[11,13,27–29]; in our study, the incidence was higher in patients with mitral valve disease (29%) and similar in those with myocardial infarction (36%). Systemic embolization was encountered in 29 to 60% of patients with LA thrombosis[1,2] and in 5 to 45% of those with LV thrombosis.[11,27,28,30,31] The incidences are not necessarily compatible with those in the present study, which involves a relatively small number of patients: 62.5% of those with LA thrombosis and none of those with LV thrombosis.

**Detection of left atrial thrombus:** Although there has been no report on sensitivity and specificity in the detection of LA thrombus either by echocardiography or cineangiocardiography, the sensitivity and specificity were highest with computed tomography. Mikell et al[8] successfully detected a small LA thrombus 1 cm in diameter, which was located on an artificial valve. In our study, however, only 1 out of 4 LA thrombi lodged in the LA appendage was demonstrated echocardiographically, even though multiple acoustical windows with various sector orientations were used to provide complete imaging of the left atrium. On the other hand, there were also 2 false-positive diagnoses by echocardiography at the posterior wall of the left atrium, if we include an equivocal diagnosis as positive, which was most probably due to reverberations from the aorta or mitral apparatus.

With angiocardiographic methods, there were also 3 false-positive and 2 false-negative findings at the LA appendage. In 1 patient with a false-positive result (Case 10) with a defect at the LA appendage, surgery revealed that the appendage was shrunken without thrombus inside. In 2 other equivocal cases (Patients 11 and 12), thinly stained appendages could not exclude the possibility of atrial thrombus, which was denied at open heart surgery. According to Lewis,[2] the sensitivity in detecting LA thrombi by cineangiocardiography was 71%; this value is similar to that in the present study. However, the puncture of the interatrial septum is possibly associated with dislodgment of atrial thrombi[2]; as a result, we performed levophase pulmonary angiography instead. It is important to visualize the possible thrombi on multiple views to minimize the false-positive or false-negative results. However, angiographic procedures applied to mitral valve disease also include left ventriculography to evaluate coexistent mitral regurgitation or changes in the subvalvular apparatus. Thus, multiprojectional LA angiograms are usually not performed due to the limitation in the permissible volume of angiographic contrast material.

Computed tomography has the advantage of offering uniform slices of the left atrium in an attempt to detect thrombi in unknown areas of this chamber. Computed tomography is not disturbed by the lungs or bones, and slices of the entire atrium can be displayed on a plane including the appendage and lateral wall of the left atrium (Fig. 1 and 2). Although there was a false-positive result in 1 patient with computed tomography (Case 9), the suspected area showed low density (minus computed tomographic value) in a repeated study; this should have been identified as pericardial fat tissue.

In the present study, estimation of the characteristics of the thrombi based on the difference in computed tomographic numbers was unsuccessful. The most probable explanation for this result may be the artifacts in density with adjacent high-density structures such as the cardiac chamber filled with contrast material, as Godwin[16] noted.

**Detection of left ventricular thrombus:** In our study, LV cineangiocardiography, open heart surgery, or autopsy to confirm the existence of LV thrombus was performed in a limited number of patients. Therefore, evaluation of the sensitivity and specificity in detecting LV thrombus with computed tomography or 2-dimensional echocardiography is not possible.

In 7 patients with a positive computed tomographic diagnosis in whom angiocardiography was performed, the LV thrombi were identified angiocardiographically in all; the thrombi were also confirmed by surgery or autopsy in 3. On the other hand, in a patient in whom a small LV thrombus was suspected by computed tomography (Case 11), there was no positive finding by 2-dimensional echocardiography or left ventriculography. Thus, this case might be a false-positive computed tomographic finding, and the confusion was most probably caused by the papillary muscle. The possibility that the thrombus might have dissolved during the intervals between the different diagnostic procedures could not be denied, but this phenomenon is frequently encountered in recent myocardial infarction.[13] In the present study, however, only remote myocardial infarction of more than 1 month's duration was studied. The cardiac apex is the site of most LV thrombi[3,12,29] and, in this study, all of the left ventricular thrombi were located there. Hence, 2-dimensional echocardiographic apical views were valuable in detecting intraventricular thrombus, but an equivocal echocardiographic diagnosis (Case 7) was apparently due to reverberations from the calcified infarct focus (Fig. 4).

The sensitivity in detecting LV thrombus by 2-dimensional echocardiography has been reported as 50 to 95%[11,32,33] and the specificity as 86 to 95%.[10,11,33] The sensitivity in detecting LV thrombus angiocardiographically was reported as 41 to 50%[4,5] and the specificity as 75%.[4] Hence, the sensitivity and specificity of computed tomography in detecting LV thrombus are estimated to be similar to those with other methods, but the demarcation of the thrombus is usually outstanding with computed tomography (Fig. 3 and 4).

The reason for the absence of thromboembolic events

in our patients with LV thrombus is not known. Anticoagulant therapy was used in only 1 of the 10 patients with LV thrombus and in none of the 18 patients without thrombus. There is a possibility that embolic events were clinically silent. Cabin et al[30] reported the incidence of systemic embolization to be as low as 5% in patients with LV thrombus. According to Haugland et al,[34] the incidence of embolization was 24% with recent myocardial infarction and 9% with remote myocardial infarction (more than 3 weeks); all of our patients had remote myocardial infarction of more than 1 month's duration.

**Advantages and limitations of computed tomography:** Computed tomography demands the injection of contrast material by way of a peripheral vein and thus is not completely noninvasive, although we have found no anaphylactic reactions, heart failure, or renal insufficiency induced by this procedure. However, computed tomography avoids the insertion of a catheter into the LV cavity, and the information regarding the presence or absence of thrombus is important in preventing iatrogenic thrombotic events induced by angiographic procedures.

Echocardiography, on the other hand, is a completely noninvasive method. However, there is a definitive limitation in the projection of the echo beam due to surrounding structures such as the sternum, ribs, or lungs. Echocardiography demands high standards of proficiency and, even with a high level of technique, a small thrombus located at the LA appendage is difficult to detect echocardiographically. There is also some uncertainty as to whether newly formed thrombi that have an acoustic impedance similar to that of the blood or cardiac walls can be identified,[7] although it was suggested recently that thrombi can be imaged within days of their formation.[35]

However, in the detection of intracardiac thrombus, computed tomography has the advantage of offering uniform slices of the heart in an attempt to detect thrombi in unknown areas of cardiac chambers including the LA appendage, and the thrombus does not have to be projected in tangent to be detected because of its cross-sectional format.[16]

The stop-action method gated with echocardiography was not applied in the present study. Therefore, it should be noted that the configuration of the various cardiac structures obtained by computed tomography are influenced by the effects of cardiac movements. Fortunately, however, the cardiac movements are relatively limited in enlarged atria with fibrillation or LV aneurysms where intracardiac thrombi are located. In fact, the smallest thrombus detected by computed tomography was a LA thrombus weighing 3.5 g (Case 3, Group I), which was comparable to the smallest ventricular thrombus measuring 2 to 3 $cm^3$ detected with computed tomography by Godwin et al.[16]

**Implications:** The possibility of systemic embolization was 3 times greater in patients with LA thrombus than in those without thrombus (Table I). Therefore, to prevent tragedies connected with systemic embolization, detection of LA thrombus is crucial in determining the timing of open heart surgery or the indications for anticoagulant therapy. Although the effects of anticoagulant therapy for myocardial infarction are a controversial issue, the incidence of thromboembolism has been reported to be significantly reduced with the therapy[36,37]; the detection of intraventricular thrombus is also important in determining the indications for such treatment. As the data presented in this study indicate, computed tomography is useful for the detection of intracardiac thrombus, and we believe this technique is the best one for detecting LA thrombus. Moreover, combined applications of computed tomography with other noninvasive or invasive methods will improve the accuracy of diagnosing intracardiac thrombus.

## References


1. **Parker BM, Friedenberg MJ, Templeton AW, Burford TH.** Preoperative angiocardiographic diagnosis of left atrial thrombi in mitral stenosis. N Engl J Med 1965;273:136–140.
2. **Lewis KB, Criley JM, Ross RS.** Detection of left atrial thrombus by cineangiocardiography. Am Heart J 1965;70:612–619.
3. **Hamby RI, Wisoff BG, Davison ET, Hartstein ML.** Coronary artery disease and left ventricular mural thrombi: clinical, hemodynamic and angiocardiographic aspects. Chest 1974;66:488–494.
4. **Reeder GS, Lengyel M, Tajik AJ, Seward JB, Smith HC, Danielson GK.** Mural thrombus in left ventricular aneurysm: incidence, role of angiography, and relation between anticoagulation and embolization. Mayo Clin Proc 1981;56:77–81.
5. **Swan HJC, Magnuson PT, Buchbinder NA, Matloff JM, Gray RJ.** Aneurysm of the cardiac ventricle. West J Med 1978;129:26–40.
6. **Spangler RD, Okin JT.** Echocardiographic demonstration of a left atrial thrombus. Chest 1975;67:716–718.
7. **Come PC, Markis JE, Vine HS, Sacks B, McArdle C, Ramirez A.** Echocardiographic diagnosis of left ventricular thrombi. Am Heart J 1980; 100:523–530.
8. **Mikell FL, Asinger RW, Rourke T, Hodges M, Sharma B, Francis GS.** Two-dimensional echocardiographic demonstration of left atrial thrombi in patients with prosthetic mitral valves. Circulation 1979;60:1183–1190.
9. **DeMaria AN, Bommer W, Neuman A, Grehl T, Weinart L, DeNardo S, Amsterdam EA, Mason DT.** Left ventricular thrombi identified by cross-sectional echocardiography. Ann Intern Med 1979;90:14–18.
10. **Meltzer RS, Guthaner D, Rakowski H, Popp RL, Martin RP.** Diagnosis of left ventricular thrombi by two-dimensional echocardiography. Br Heart J 1979;42:261–265.
11. **Stratton JR, Lighty GW, Jr, Pearlman AS, Ritchie JL.** Detection of left ventricular thrombus by two-dimensional echocardiography: sensitivity, specificity, and causes of uncertainty. Circulation 1982;66:156–166.
12. **Asinger RW, Mikell FL, Sharma B, Hodges M.** Observations on detecting left ventricular thrombus with two-dimensional echocardiography: emphasis on avoidance of false positive diagnoses. Am J Cardiol 1981;47:145–156.
13. **Asinger RW, Mikell FL, Elsperger J, Hodges M.** Incidence of left-ventricular thrombosis after acute transmural myocardial infarction. N Engl J Med 1981;305:297–302.
14. **Stratton JR, Ritchie JL, Hammermeister KE, Kennedy JW, Hamilton GW.** Detection of left ventricular thrombi with radionuclide angiography. Am J Cardiol 1981;48:565–572.
15. **Stratton JR, Ritchie JL, Hamilton GW, Hammermeister KE, Harker LA.** Left ventricular thrombi: in vivo detection by indium-111 platelet imaging and two-dimensional echocardiography. Am J Cardiol 1981;47:874–881.
16. **Godwin JD, Herfkens RJ, Skiöldebrand CG, Brundage BH, Schiller NB, Lipton MJ.** Detection of intraventricular thrombi by computed tomography. Radiology 1981;138:717–721.
17. **Nair CK, Sketch MH, Mahoney PD, Lynch JD, Mooss AN, Kennedy NP.** Detection of left ventricular thrombi by computerized tomography. A preliminary report. Br Heart J 1981;45:535–541.
18. **Tomoda H, Hoshiai M, Tagawa R, Koide S, Kawada S, Shotsu S, Matsuyama S.** Evaluation of left atrial thrombus with computed tomography. Am Heart J 1980;100:306–310.
19. **Tomoda H, Hoshiai M, Furuya H, Shotsu A, Ootaki M, Matsuyama S.** Evaluation of left ventricular thrombus with computed tomography. Am J Cardiol 1981;48:573–577.
20. **Harell GS, Guthaner DF, Breiman RS, Morehouse CC, Seppi EJ, Marshall WH Jr, Wexler L.** Stop-action cardiac computed tomography. Radiology 1977;123:515–517.
21. **Silverman NH, Schiller NB.** Apex echocardiography. A two-dimensional technique for evaluating congenital heart disease. Circulation 1978;57: 503–511.
22. **Chang S, Feigenbaum H, Dillon J.** Subxiphoid echocardiography. Chest 1975;68:233–235.
23. **Barker CF, Rosato FE, Roberts B.** Peripheral arterial embolism. Surg Gynecol Obstet 1966;123:22–26.
24. **Billig DM, Hallman GL, Cooley DA.** Arterial embolism. Arch Surg 1967; 95:1–6.
25. **Young JR, Humphries AW, DeWolfe VG, LeFevre FA.** Peripheral arterial embolism. JAMA 1963;185:621–627.

# Absolute Left Ventricular Volume From Gated Blood Pool Imaging With Use of Esophageal Transmission Measurement

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**A new method for determining absolute left ventricular (LV) volume from equilibrium gated blood pool images was validated in 36 patients by comparing gated blood pool (GBP) imaging with contrast ventriculography (CV) using both Simpson's rule (SR) and area-length (AL) calculations. The technique is geometry-independent and is the first to correct for tissue attenuation with use of an in vivo point source. An orally administered capsule containing 1 to 2 mCi of technetium-99m (Tc-99m) sulfur colloid is used for this purpose. Left ventricular volumes are determined by dividing attenuation and background-corrected count rates obtained from semiautomated LV regions of interest by the count rate per milliliter from a blood sample. The correlation between GBP and CV (SR) was 0.96 (CV [SR] = 0.99 GBP + 1.32 ml; standard error of the estimate [SEE] = 21.2 ml) for diastole and 0.97 (CV [SR] = 0.93 GBP − 0.03 ml; SEE = 11.9 ml) for systole. The correlation between GBP and CV (AL) was 0.92 (CV [AL] = 0.90 GBP + 16.72 ml; SEE = 27.8 ml) for diastole and 0.95 (CV [AL] = 0.87 GBP + 4.56 ml; SEE = 14.4 ml) for systole. The method is noninvasive and can be performed easily as part of routine gated blood pool imaging and analysis.**

Contrast ventriculography is the most frequently used clinical method for measuring absolute left ventricular (LV) volume. However, contrast ventriculography is invasive and requires geometric assumptions regarding the shape of the ventricle.[1–4] Several studies[5–7] have reported that geometry-independent LV volumes can be measured from radionuclide gated blood pool imaging by comparing a background-corrected count rate from the left ventricle with that obtained from a blood sample. However, none of these early reports attempted to correct for tissue attenuation.

Recently, Links et al[8] used gated blood pool imaging to measure absolute LV volume by calculating an attenuation factor for each patient after measuring the depth of the left ventricle and assuming an average linear attenuation coefficient. We have developed a new technique for measuring absolute LV volume which is geometry-independent and corrects for tissue attenuation with use of an in vivo point source.

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## Methods

Thirty-six consecutive patients referred for cardiac catheterization were studied. All patients underwent precatheterization radionuclide gated blood pool imaging after giving written informed consent to swallow a small capsule containing a calibrated dose of technetium 99-m (Tc-99m) sulfur colloid and to have a venous blood sample drawn at the conclusion of the radionuclide study. Twenty-eight male and 8 female patients, ranging in age from 34 to 81 years (mean 59), were studied.

Before beginning the gated blood pool study, a #4 gelatin capsule is prepared by placing a 2.9 mm diameter circular piece of filter paper in one half of the capsule and saturating it with a precalibrated dose of 1 to 2 mCi of Tc-99m sulfur colloid. The capsule is then closed and wrapped in a piece of paraffin paper (Parafilm "M"). At the end of the sealed capsule, a 50 cm length of sewing thread is tied to the capsule. A mark is made on the thread at 40 cm from the end of the capsule.

A capsule count rate is then acquired behind a 9.85 cm thick phantom of tissue-equivalent material using a scintillation camera fitted with a low-energy parallel hole collimator and interfaced to a commercial nuclear medicine computer. The camera is peaked for technetium at 140 keV with a 20% window. The phantom is employed to avoid saturation of the camera count rate, which could occur if the capsule were counted in air.

The patient is then positioned in front of the same camera for a standard left anterior oblique 40° view and instructed

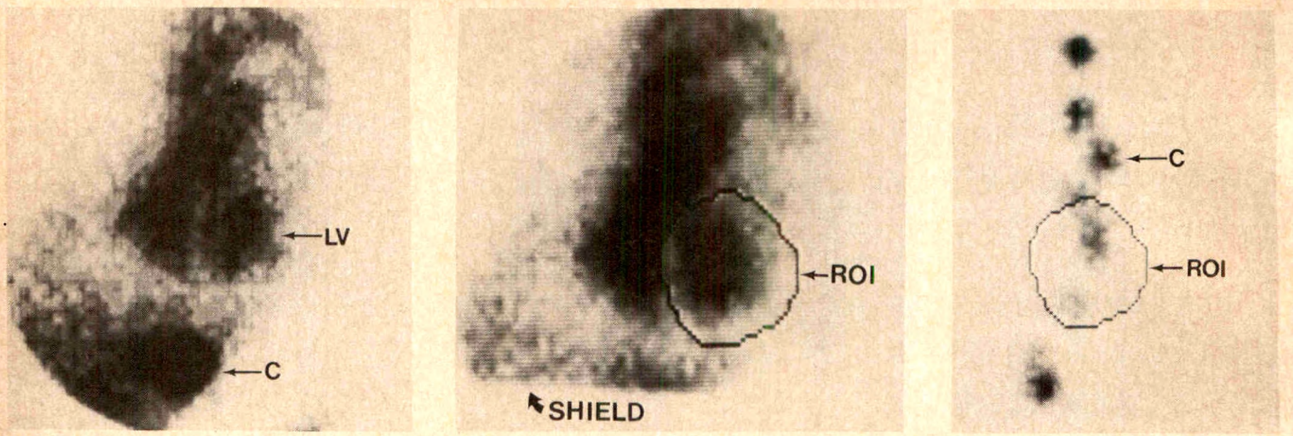



**FIGURE 1. Left,** left anterior oblique image after capsule swallow. The capsule (C) which was swallowed before labeling the patients' red blood cells is shown as it appears in the stomach below the left ventricle (LV). **Center,** left anterior oblique image with shield. A lead shield is placed over the stomach to eliminate counts from the capsule, and gated blood pool imaging is performed without moving the patient. A manual region of interest (ROI) is drawn around the left ventricle. **Right,** esophageal transit study. Several frames from the capsule swallow study are shown to illustrate how the capsule passes through the LV region of interest as it goes behind the left ventricle.

to swallow the capsule. The thread is swallowed with the capsule so that the rate of descent of the capsule can be controlled. As the capsule is swallowed, the esophageal transit is recorded for up to 400 consecutive frames of 0.3 second each. If the esophageal transit takes longer than the allotted time, a remote switch is used to reset the start of computer acquisition. The capsule is observed on the persistence scope until it is positioned behind the left ventricle. This is easily recognized as the intensity of the capsule dims when it reaches the left ventricle. During acquisition the capsule position can also be approximated by the location of the string marker as the distance to the lower esophageal sphincter averages 40 cm. The capsule swallow is considered complete when the capsule enters the stomach.

The patient is kept in the same position and the patient's red blood cells are labeled in vivo with 20 mCi of Tc-99m pertechnetate 20 minutes after previous intravenous administration of stannous pyrophosphate.[9]

After blood pool equilibration, the patient is imaged in the same left anterior oblique 40° position. A lead shield is placed over the stomach (Fig. 1, center). Data are acquired on a magnetic disk in a 64 by 64 matrix until 300,000 counts are collected in at least 1 of 16 frames of the cardiac cycle. After completion of the left anterior oblique image the patient can be moved for acquisition of other views.

When imaging of the patient is completed, a 10 ml venous blood sample is withdrawn into a heparinized syringe from a previously unused venipuncture site. The blood sample is placed in a 100 mm diameter by 15 mm deep petri dish, and the petri dish is counted in air at 10 cm from the collimator face of the camera. Finally, a point source of 200 to 300 $\mu$Ci of Tc-99m pertechnetate is counted in air and behind the 9.85 cm tissue-equivalent phantom in order to derive a build-up factor (see Appendix).

To determine the capsule count rate behind the left ventricle, a LV region of interest at end-diastole is manually drawn from the left anterior oblique 40° gated blood pool study (Fig. 1, center). This region of interest is drawn slightly greater in size than the area of blood pool activity to include the thickness of the left ventricular wall which appears as a halo of decreased activity surrounding the blood pool. If the halo is not easily identified, the thickness of the septum is used to outline the blood pool.

The esophageal transit study is reviewed, and a count profile is generated as the capsule passes through the LV region of interest (Fig. 1, right). A capsule count rate from behind the left ventricle is determined by integrating the count profile curve between points which correspond to the time the capsule is within the LV region of interest (Fig. 2).

End-diastolic and end-systolic count rates from the gated blood pool images of the left ventricle are then obtained from semiautomated regions of interest generated around the left ventricle. We use the same regions generated for routine ejection fraction calculation from a program provided with our nuclear medicine computer system (MUGE, Medical Data Systems). This program uses a combination second derivative and count-threshold algorithm.[10]

The end-diastolic and end-systolic LV counts are corrected for background by using an automatically generated background region which is drawn lateral to the left ventricle in the end-systolic frame. During the processing of the ejection fraction program the computer pauses and allows the operator to accept or reject the automatically generated background. The background region is visually inspected to ensure that it does not include an area of increased activity from adjacent vascular structures (aorta or spleen) or decreased activity from an area such as a fluid- or gas-filled stomach. If the automatically generated region of interest is not considered representative of average background, the operator can manually select a region from the end-systolic image which is adjacent to the left ventricle. In 10 cases the automatically drawn background was rejected because it included increased activity from adjacent vascular structures. In these cases a manual background was selected.

The total time for acquisition of the end-diastolic and systolic images is derived from the average time per frame and the number of cardiac cycles acquired. The mathematical basis for calculation of the transmission factor and ventricular volumes is given in the Appendix.

All patients had contrast ventriculography performed within 24 hours of the gated blood pool study. Cardiac catheterization was performed using either the brachial or per-

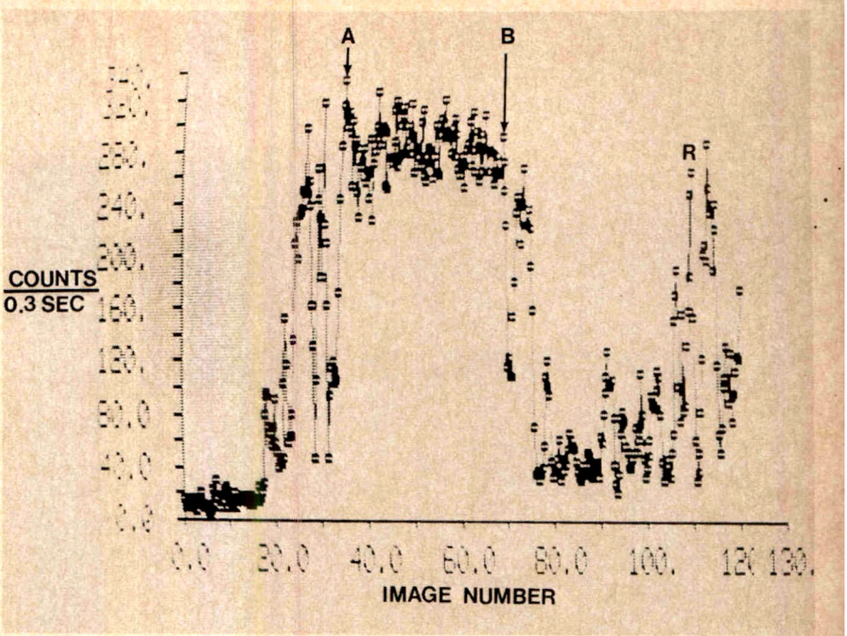



**FIGURE 2.** Capsule count curve from the LV region of interest. The capsule swallow study is used to generate a capsule count curve. Points are chosen (**arrows A and B**) to identify when the capsule is within the LV region of interest. The capsule count rate (total counts from A to B/time from A to B) is derived by integrating the curve between A and B. In the example shown, the study was terminated after 120 images had been collected when reflux (R) of the capsule up the esophagus was noted.

**TABLE I Contrast Angiographic and Radionuclide Volumes**

| | End-Diastolic Volume (ml) | | | End-Systolic Volume (ml) | | | |
|---|---|---|---|---|---|---|---|
| | Contrast Ventriculography | | | Contrast Ventriculography | | | |
| Patient | Simpson's Rule | Area-Length | Radionuclide | Simpson's Rule | Area-Length | Radionuclide | Transmission Factor (T) |
| 1 | 255 | 258 | 278 | 118 | 123 | 120 | 0.12 |
| 2 | 156 | 157 | 190 | 42 | 44 | 75 | 0.14 |
| 3 | 247 | 230 | 253 | 124 | 123 | 146 | 0.19 |
| 4 | 133 | 145 | 155 | 48 | 44 | 75 | 0.20 |
| 5* | 117 | 111 | 109 | 42 | 39 | 30 | 0.14 |
| 6 | 103 | 115 | 95 | 33 | 34 | 49 | 0.21 |
| 7* | 172 | 158 | 175 | 79 | 76 | 88 | 0.15 |
| 8 | 128 | 112 | 149 | 54 | 52 | 64 | 0.24 |
| 9* | 83 | 80 | 88 | 39 | 38 | 40 | 0.35 |
| 10 | 162 | 196 | 158 | 71 | 81 | 89 | 0.23 |
| 11 | 154 | 163 | 173 | 70 | 70 | 77 | 0.21 |
| 12 | 187 | 200 | 177 | 81 | 97 | 91 | 0.16 |
| 13 | 115 | 106 | 130 | 32 | 29 | 21 | 0.18 |
| 14 | 166 | 184 | 162 | 81 | 109 | 68 | 0.26 |
| 15 | 159 | 184 | 178 | 71 | 82 | 84 | 0.19 |
| 16 | 171 | 194 | 177 | 55 | 60 | 70 | 0.14 |
| 17 | 129 | 128 | 149 | 72 | 69 | 76 | 0.20 |
| 18 | 253 | 289 | 194 | 95 | 114 | 99 | 0.23 |
| 19* | 292 | 274 | 255 | 200 | 194 | 207 | 0.23 |
| 20* | 111 | 105 | 92 | 39 | 39 | 42 | 0.35 |
| 21* | 207 | 186 | 187 | 58 | 59 | 63 | 0.26 |
| 22* | 91 | 89 | 96 | 27 | 26 | 27 | 0.33 |
| 23* | 119 | 103 | 101 | 55 | 49 | 28 | 0.34 |
| 24* | 170 | 147 | 192 | 114 | 100 | 110 | 0.19 |
| 25 | 159 | 166 | 165 | 67 | 63 | 82 | 0.20 |
| 26* | 251 | 218 | 270 | 123 | 107 | 117 | 0.20 |
| 27 | 117 | 116 | 121 | 39 | 42 | 54 | 0.25 |
| 28 | 119 | 120 | 129 | 61 | 61 | 69 | 0.26 |
| 29 | 100 | 92 | 91 | 23 | 20 | 30 | 0.15 |
| 30 | 175 | 181 | 176 | 59 | 50 | 59 | 0.17 |
| 31 | 284 | 274 | 243 | 86 | 79 | 81 | 0.20 |
| 32 | 209 | 209 | 165 | 75 | 86 | 59 | 0.15 |
| 33 | 219 | 213 | 208 | 46 | 43 | 53 | 0.11 |
| 34 | 99 | 97 | 102 | 34 | 30 | 49 | 0.21 |
| 35 | 172 | 187 | 185 | 50 | 55 | 62 | 0.13 |
| 36* | 465 | 419 | 470 | 278 | 255 | 297 | 0.28 |

* All contrast ventriculography biplane except where indicated by an asterisk.

cutaneous femoral technique. Left ventricular end-diastolic and end-systolic volumes were obtained from monoplane or biplane cine films using both the Dodge area-length formula and Simpson's rule and a semiautomatic computer processing system which has previously been described.[11]

The volumes from gated blood pool imaging were compared with the contrast angiographic volumes using a paired $t$ test.

## Results

Of the 36 patients studied, 5 with chest pain were found to have no evidence of coronary artery disease and were otherwise considered normal. Twenty-three had significant coronary artery disease involving either 1 vessel (n = 2), 2 vessels (n = 12), or 3 vessels (n = 9). Eight had regional wall motion abnormalities or an aneurysm. Ten patients had either aortic (n = 6) or mitral (n = 4) valve disease. Of those with valvular disease, 2 also had significant coronary artery disease.

The volumes and transmission factors determined from the radionuclide studies are given together with the volumes obtained by contrast ventriculography in Table I. The correlations for the end-diastolic and end-systolic volumes are shown in Figures 3 and 4.

A paired $t$ test at the $\alpha = 0.01$ level revealed no significant difference between scintigraphic and angio-

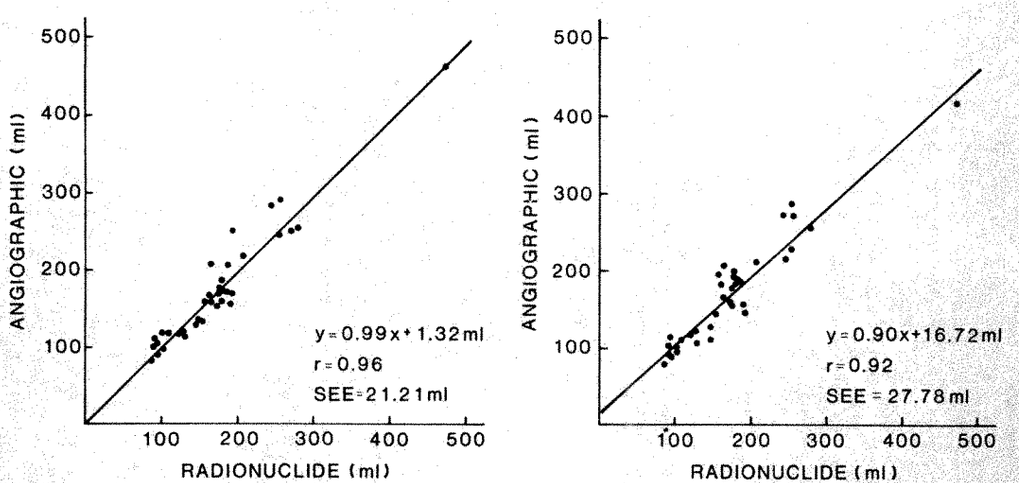



**FIGURE 3.** Correlation of contrast ventriculography with radionuclide end-diastolic volumes. **Left,** Simpson's rule calculation. **Right,** area-length calculation. SEE = standard error of the estimate.

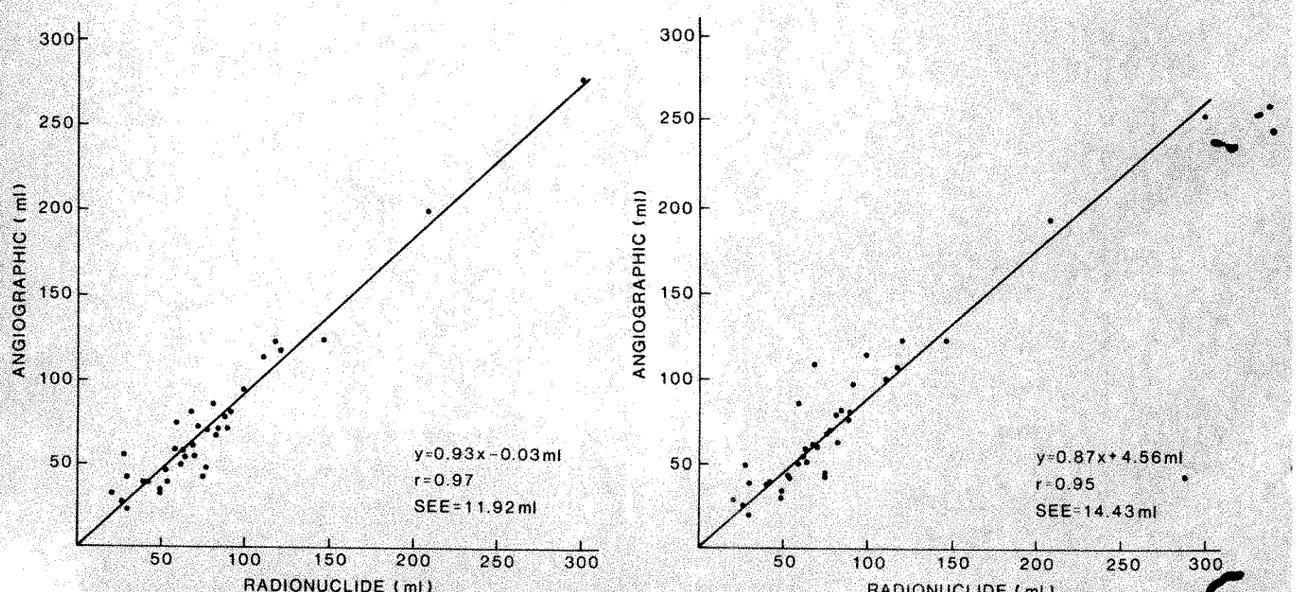



**FIGURE 4.** Correlation of contrast ventriculography with radionuclide end-systolic volumes. **Left,** Simpson's rule calculation. **Right,** area-length calculation. SEE = standard error of the estimate.

graphic end-diastolic volumes using either Simpson's rule (SR) or an area-length (AL) calculation ($p > 0.80$). For the end-systolic volumes the p values were $0.02 < p < 0.05$ for scintigraphy versus contrast ventriculography (CV) using the area-length calculation and $0.001 < p < 0.01$ using Simpson's rule.

There was 1 patient in our series with a very large (465 cc) left ventricle. If this patient were eliminated, there would be little change in the correlation coefficients or standard error of the estimate. Eliminating this patient, the correlation between gated blood pool imaging (GBP) and CV (SR) was 0.93 (CV [SR] = 1.01 GBP − 0.49 ml; standard error of the estimate [SEE] = 21.5 ml) for diastole and 0.94 (CV [SR] = 0.91 GBP + 0.89 ml; SEE = 12.8 ml) for systole. Similarly the correlation between GBP and CV (AL) was 0.88 (CV [AL] = 0.96 GBP + 6.6 ml; SEE = 27.8 ml) for diastole and 0.92 (CV [AL] = 0.91 GBP + 211 ml; SEE = 14.5 ml) for systole.

In 10 randomly selected patients the calculation of the transmission factor was repeated by 2 independent observers. Using a paired $t$ test there was no significant difference at the $\alpha = 0.01$ level between the 2 observers' values ($0.6 < p < 0.8$).

## Discussion

The ability to measure absolute LV volumes using equilibrium gated blood pool imaging has many advantages over contrast ventriculography. The radionuclide method is noninvasive and can be performed at rest and with exercise. Because gated blood pool imaging is geometry independent, it can be used reliably in patients with regional contraction abnormalities.

Previous studies[5–7] have shown that the radionuclide method can give a reliable index of LV volume. However, these early studies required regression equations to convert a volume index to an absolute volume. Links et al[8] were the first to attempt to measure absolute volumes by taking into account attenuation. To do this, however, they assumed a uniform linear attenuation coefficient and had to measure the distance from the chest wall to the center of the left ventricle.

We have developed a new technique which makes no assumptions about attenuation or geometry. We directly measure a transmission factor in each patient. This is done in the same position in which the left anterior oblique gated blood pool image is acquired.

The individual transmission factors measured in our patients ranged from 0.11 to 0.35 with an average of 0.21 ± 0.06. These transmission measurements varied by as much as a factor of 3. If we express the regression curves, as reported by Dehmer et al[6] and Slutsky et al,[5] in the general form $y = mx + b$, where y = contrast ventriculographic volume, x = radionuclide volume index (net ventricular counts/[blood sample counts/ml]), b = y intercept, and m = slope of the line, we see that the slope is the same as 1/T, where T is our measured transmission factor (equation 4, Appendix). Therefore, we can calculate a transmission factor that equals the reciprocal of the slope of the regression line. The regression data from Slutsky,[5] Dehmer,[6] Links,[8] and their co-workers yield transmission factors of 0.13, 0.16, and 0.29, respectively. These values represent average transmission factors which result from grouping their patient data into 1 regression equation. These values are compatible with the range of values we have measured directly. It is evident from the wide range of values we have observed that it is necessary to measure a transmission factor individually for each patient.

Several potential sources of error exist with the radionuclide method. The first is the method of edge detection used to define the systolic and diastolic borders of the left ventricle. The previous studies cited used either manually drawn regions[6,8] or computerized edge detection.[5,7] We have used a semiautomated edge detection program. The reproducibility of this program was previously validated[9] and the use of automated regions of interest makes the technique more reproducible.

A problem common to any radionuclide study is the determination of background. We have used a region of interest drawn adjacent to the left ventricle. Significant differences in volume could be expected if there were large variations in the determination of background.

When the left atrium is enlarged, it may be difficult to separate LV activity from left atrial activity in the standard left anterior oblique image. Counts from the left atrium could affect the accuracy of the LV volume determination. If necessary, a caudal tilt of the collimator can be used to better separate the left atrium and left ventricle. In this series of patients, we did not attempt to systemically evaluate the contribution from left atrial counts.

A large left atrium can also displace the esophagus posteriorly. If the left atrium is enlarged and positioned between the esophagus and left ventricle, it could lead to an underestimation of the transmission factor. We had only 4 patients in this series with large left atria. Atrial enlargement did not appear to be a significant problem in these patients.

In our laboratory the determination of LV volume using this technique adds approximately 45 minutes to the time required for acquisition and processing of a routine resting gated blood pool study. To date, we have found that the capsule swallow is well tolerated by all patients. We have observed much variability in the time needed to complete the swallow. Most younger patients with normal heart size can complete the swallow within 30 to 60 seconds. Older patients with normal heart size may take as much as 5 to 10 minutes for the capsule to reach the stomach. This difference most likely reflects age-related changes in esophageal motility. A large left atrium or left ventricle can also slow esophageal transit. We have found it very helpful to feed the patient a small cracker followed by sips of water when esophageal transit is slow or the heart is enlarged. Little technical skill is required to perform the capsule swallow, but patience is needed when esophageal transit is slow. We have now begun to use the method routinely in our laboratory and are applying the technique to an even larger population of patients.

In summary, we have developed a new technique for determining absolute LV volume from gated blood pool images using an in vivo point source to correct for tissue attenuation. Our early experience with the technique shows a good correlation with contrast ventriculography.

## Appendix

Left ventricular volumes at end-diastole and end-systole were computed for each patient. The basis of these determinations is as follows:

1. *Point source calibration.* A 200 to 300 $\mu$Ci source of Tc-99m is used to determine the build-up factor (B)[12] according to

$$B = \frac{I'}{I'_0} e^{\mu d} \quad (1)$$

where $I'$ = count rate (counts/s) behind phantom from the point source, $I'_0$ = count rate in air from the point source, $\mu$ = linear attenuation coefficient = 0.15 $cm^{-1}$, and d = phantom thickness = 9.85 cm.

2. *Transmission factor for capsule.* Because the capsule is counted behind the phantom, the capsule count rate in air ($I_0$) is given by

$$I_0 = \frac{I_p}{B} e^{\mu d} \quad (2)$$

where $I_p$ = measured capsule count rate behind phantom and B = value obtained from Equation 1. The transmission factor (T) is given as

$$T = e^{-\mu d} = \frac{I_{LV}}{I_0} \quad (3)$$

where $L_{LV}$ = capsule count rate behind the left ventricle and $I_0$ = value obtained from Equation 2.

3. *Left ventricular volumes.* The absolute LV end-diastolic volume (LVEDV) can be calculated as follows:

LVEDV = count rate from left ventricle in the end-diastolic frame (LVED)/ (count rate [counts/s]/ml from blood sample × T) (4)

where LVED = total counts in left ventricle in end-diastolic frame-background counts/ time per frame × number of cardiac cycles. (5)

The count rate for all blood samples was corrected for isotope decay by

$$A_0 = A_t e^{0.693(t-t_0)/T_{1/2}} \quad (6)$$

where $A_0$ = activity of the blood at the midpoint of acquisition of the gated blood pool study (time, $t = t_0$), $A_t$ = activity of the blood sample at midpoint of counting the blood in the petri dish (time, t), and $T_{1/2}$ = half-life of technetium-99m = 6.02 hours.

The left ventricular end-systolic volumes are similarly derived using the end-systolic counts.

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## References

1. **Dodge HT, Sandler H, Baxley WA, Hawley RR.** Usefulness and limitations of radiographic methods for determining left ventricular volume. Am J Cardiol 1966;18:10–24.
2. **Green DG, Carlisle MB, Grant G, Bunnell IL.** Estimation of left ventricular volume by one plane cineangiography. Circulation 1967;35:61–69.
3. **Sandler H, Dodge HT.** Use of single plane angiocardiograms for the calculation of left ventricular volumes in man. Am Heart J 1968;75:325–334.
4. **Kennedy JW, Trenholme SE, Kasser IS.** Left ventricular volume and mass from single plane cineangiocardiogram. A comparison of anteroposterior and right anterior oblique methods. Am Heart J 1970;80:343–352.
5. **Slutsky R, Karliner J, Ricci D, Kaiser R, Pfisterer M, Gordon D, Peterson K, Ashburn W.** Left ventricular volume by gated equilibrium radionuclide angiography: a new method. Circulation 1979;60:556–564.
6. **Dehmer GJ, Lewis SE, Hillis LD, Twieg D, Falkoff M, Parkey RW, Willerson JT.** Nongeometric determination of left ventricular volumes from equilibrium blood pool scans. Am J Cardiol 1980;45:293–300.
7. **Clements IP, Brown ML, Smith HC.** Radionuclide measurement of left ventricular volume. Mayo Clin Proc 1981;56:733–739.
8. **Links JM, Becker LC, Shindledecker JG, Guzman P, Burow RD, Nickoloff EL, Alderson PO, Wagner HN.** Measurement of absolute left ventricular volume from gated blood pool studies. Circulation 1982;65:82–91.
9. **Pavel DG, Zimmer AM, Patterson VN.** In vivo labeling of red blood cells with Tc-99m: a new approach to blood pool visualization. J Nucl Med 1977;18:305–308.
10. **Burow RD, Strauss HW, Singleton R, Pond M, Rehn T, Bailey IK, Griffith LC, Nickoloff E, Pitt B.** Analysis of left ventricular function from multiple gated acquisition cardiac blood pool imaging. Circulation 1977;56:1024–1028.
11. **Bove AA, Kreulen TH, Spann JF.** Computer analysis of left ventricular dynamic geometry in man. Am J Cardiol 1978;41:1239–1248.
12. **Siegel JA, Wu RK.** The elusive build up factor (abstr). Med Phys 1982;9:614.

# Effect of Exercise Protocol on the Left Ventricular Response to Exercise

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**The purpose of this study was to determine whether the left ventricular response during exercise radionuclide angiography would be influenced by exercise protocol. One hundred twenty healthy volunteers (aged 18 to 40 years) performed upright bicycle exercise using 1 of 5 protocols. Ejection fraction was measured using first-pass radionuclide angiography. Exercise protocols were as follows: (1) graded exercise (25 W increase every 2 minutes) to fatigue, heart rate >85% of age-predicted maximum, n = 53; (2) graded exercise to 85% of age-predicted maximal heart rate or to fatigue with heart rate <85% of age-predicted maximum, n = 26; (3) graded exercise to fatigue, with "exercise" imaging performed immediately after exercise, n = 15; (4) abrupt presentation of a supermaximal work load (400 W), n = 10; (5) graded exercise to a work load of 75 W preceding the abrupt presentation of a supermaximal work load (300 to 400 W), n = 16. Protocols 2 and 3, representing less than maximal stress, yield higher ejection fractions than Protocol 1 and may reduce the sensitivity of exercise radionuclide angiography. Protocols 4 and 5, representing supermaximal stress, yield lower ejection fractions than Protocol 1 and may reduce the specificity of exercise radionuclide angiography. Thus, exercise protocol has a significant influence on the left ventricular response during exercise radionuclide angiography.**

| | 1 | | 2 | | 3 | | 4 | | 5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Protocol | HR | EF | HR | EF | HR | EF | HR | EF | HR | EF |
| Rest | 70 | 70 | 67 | 67 | 67 | 68 | 72 | 70 | 78 | 68 |
| Exercise | 177 | 71 | 149* | 73* | 170 | 80* | 148* | 57* | 164* | 65* |

* $p < 0.05$ versus Protocol 1. EF = ejection fraction; HR = heart rate.

Graded exercise testing (GXT) is important in the noninvasive evaluation of patients with known or suspected cardiovascular disease. Hemodynamic and electrocardiographic data obtained during GXT are sensitive and specific markers of coronary artery disease.[1,2] Radionuclide techniques including myocardial perfusion studies with thallium-201 and ventricular function studies with technetium-99m have been shown to improve the diagnostic accuracy of GXT.[3–6]

Interpretation of the exercise radionuclide angiogram depends upon an understanding of the normal and abnormal left ventricular responses to exercise, as well as of the influence of a variety of technical factors. Reports from this and other laboratories have suggested that factors related to exercise protocol may influence the left ventricular response to exercise and, accordingly, the interpretation of diagnostic radionuclide angiography. These include adequacy of exercise,[7] temporal sequence of imaging,[8,9] and degree to which the exercise is graded.[10,11] The present investigation was designed to evaluate the influence of exercise protocol on the left ventricular response during exercise radionuclide angiography. Healthy volunteer subjects were used as subjects for this investigation in order to remove the potentially confounding effect of patients with chest pain and normal coronary arteries who have often been used as control patients in studies of this nature.

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## Methods

**Subjects:** The subjects for this investigation were 120 healthy male volunteers aged 18 to 40 years (Table I). All subjects were normotensive, asymptomatic for cardiovascular disease, and demonstrated normal electrocardiographic, hemodynamic, and symptomatic responses during screening

**TABLE I Characteristics of the Subjects***

| | Protocol | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Number | 53 | 26 | 15 | 10 | 16 |
| Age (yr) | 29 ± 8 | 32 ± 11 | 31 ± 8 | 28 ± 5 | 31 ± 6 |
| Height (cm) | 178 ± 7 | 178 ± 6 | 176 ± 7 | 180 ± 7 | 177 ± 7 |
| Weight (kg) | 75 ± 10 | 76 ± 10 | 73 ± 7 | 78 ± 8 | 78 ± 14 |

* Mean ± standard deviation.

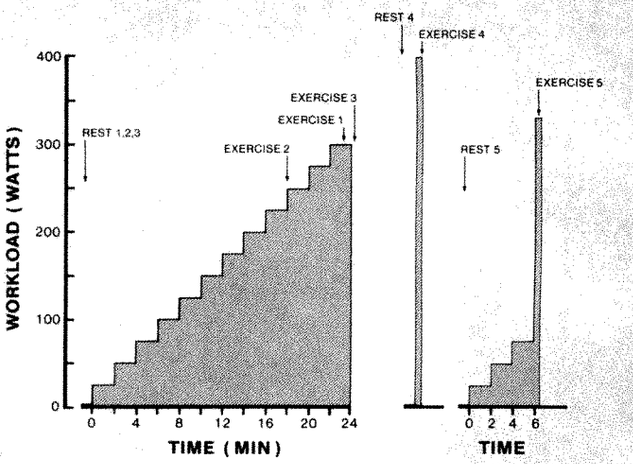



**FIGURE 1.** Schematic presentation of the exercise protocols employed in this investigation. Protocols 1 to 3 were accomplished during or after graded (25 W every 2 minutes) incremental bicycle exercise beginning at a work load of 25 W. Protocols 4 and 5 represent abrupt increases in work load from rest (Protocol 4) or graded submaximal exercise (Protocol 5).

symptom-limited GXT. On the basis of age, lack of symptoms, and normal exercise test results, the likelihood of significant coronary artery disease in this population is very low.[12] Ninety of the subjects (75%) were regular exercisers while the remaining 30 (25%) were sedentary. Twenty-six (22%) had a family history of cardiovascular disease and 18 (15%) were smokers. None were taking medications at the time of study. All subjects provided informed consent before participation.

**Protocol:** Each subject was assigned to 1 of 5 exercise protocols, or was placed in a particular protocol on the basis of responses during the exercise test (Protocol 1 versus Protocol 2). All exercise was performed with the patient in the upright posture on an electrically braked bicycle ergometer (W. E. Collins, Braintree, Massachusetts) at a pedal frequency of 60 to 80 rpm. Resting radionuclide angiograms were obtained before exercise with the subject seated on the ergometer in a position identical to that employed in the subsequent exercise study.

Protocol 1 represented symptom-limited GXT with the subject attaining >85% of the age-predicted maximal heart rate. The exercise radionuclide angiogram was obtained during exercise while the subject continued to pedal the ergometer at the peak work load attained. The work load was 25 W initially and was increased by 25 W increments every 2 minutes. The electrocardiogram ($V_5$) and blood pressure were obtained at the end of each stage of exercise. Fifty-three subjects completed this protocol.

Protocol 2 was identical to Protocol 1 except that the subjects stopped secondary to fatigue before the heart rate reached 85% of the age-predicted maximum (n = 11) or were studied during submaximal exercise when the heart rate reached 85% of the age-predicted maximal heart rate (n = 15). A total of 26 subjects completed this protocol.

Protocol 3 was identical to Protocol 1, except that in addition to the study performed during maximal exercise, an additional study was obtained immediately after exercise. Injection of the radionuclide for the postexercise study coincided with the cessation of exercise. The results of this study have been previously reported.[8] For purposes of comparison with Protocol 1, the postexercise study was taken as the "exercise" study. Fifteen subjects completed this protocol.

Protocol 4 represented the abrupt (<1 second) presentation of a supermaximal work load (400 W) which was continued for 30 seconds. This represents sudden strenuous exercise and has been previously reported from this laboratory.[10] The exercise radionuclide angiogram was during the last 15 seconds of the 30-second work bout. The electrocardiogram was monitored throughout the exercise and blood pressure was measured during the last 15 seconds of exercise. Ten subjects completed this protocol.

Protocol 5 represents the effects of warm-up on the response to sudden strenous exercise and has, in part, been previously reported.[11] Each subject performed 6 minutes of incremental exercise to a work load of 75 W according to Protocol 1. The work load was then rapidly increased to a work load calculated to represent approximately 125% of the subject's previously determined maximal working capacity. This work load was continued for 30 to 60 seconds and the exercise radionuclide angiogram was obtained during the last 15 seconds of exercise. Ten of the 16 subjects in this protocol were also studied at the end of the warm-up period. The electrocardiogram and blood pressure were measured at the end of each stage of warm-up and during the last 15 seconds of exercise.

The structures of Protocols 1 to 5 are depicted schematically in Figure 1. Protocol assignment was not entirely random in that Protocols 3 to 5 were performed as separate studies during a longer period of time in which Protocols 1 and 2 were completed; only physically active subjects were assigned to Protocol 4 (out of concern for subject safety); and subjects completing Protocol 3 were also included in Protocol 1.

**Radionuclide technique:** First-pass radionuclide angiograms were obtained with a computerized multicrystal scintillation camera (Baird System 77, Bedford, Massachusetts). The technique employed has been described previously.[10,11,13,14]

**Statistical methods:** Mean values of heart rate, double product, and left ventricular ejection fraction (LVEF) at rest and during exercise, as well as rest to exercise changes in these variables, were compared using analysis of covariance with exercise protocol as the main effect and age and resting parameters as covariants. When significant differences were noted, individual comparisons were made using either paired or unpaired $t$ tests as appropriate. A p value $\leq 0.05$ was accepted as statistically significant. Comparisons of the serial responses within Protocols 3 and 5 were made using repeated measures analysis of variance and $t$ tests as indicated.

## Results

The mean values and responses of heart rate, double product, and LVEF for each of the protocols are presented in Table II. Analysis of covariance indicated significant main effect (protocol) differences in the comparisons for heart rate ($F = 26.46$, $p < 0.01$), double product ($F = 16.74$, $p < 0.01$), and LVEF ($F = 26.10$, $p < 0.01$), even when the resting values for these param-

**TABLE II Heart Rate, Double Product, and Ejection Fraction at Rest and During Exercise in Each Protocol Group***

| | Protocol | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Heart rate (beats/min) | | | | | |
| Rest | 70 ± 12 | 67 ± 12 | 67 ± 10 | 72 ± 17 | 78 ± 8† |
| Exercise | 177 ± 11‡ | 149 ± 16†‡ | 170 ± 19†‡ | 143 ± 14†‡ | 164 ± 14†‡ |
| Double product (mm Hg × beats/min × $10^2$) | | | | | |
| Rest | 78 ± 18 | 77 ± 14 | 73 ± 11 | 79 ± 25 | 87 ± 13† |
| Exercise | 340 ± 41‡ | 281 ± 52†‡ | 274 ± 38†‡ | 247 ± 31†‡ | 287 ± 63†‡ |
| Ejection fraction (%) | | | | | |
| Rest | 70 ± 7 | 67 ± 8 | 68 ± 4 | 70 ± 10 | 68 ± 5 |
| Exercise | 70 ± 7 | 73 ± 9† | 80 ± 5†‡ | 57 ± 8†‡ | 65 ± 7†‡ |
| Change in ejection fraction (%) from exercise to rest | +1 ± 7 | +6 ± 9† | +12 ± 7† | −13 ± 7† | −3 ± 6† |

* Mean ± standard deviation.
† Significantly ($p < 0.05$) different from Protocol 1.
‡ Significant ($p < 0.05$) rest to exercise change within protocol.

eters and age were entered as covariates. Mean values for these variables were tested using $t$ tests for paired and group comparisons. These are presented in Table II. The response of LVEF from rest to exercise during each of the protocols is depicted in Figure 2. No electrocardiographic abnormality was observed during any protocol except in 1 subject who developed inverted T waves during Protocol 4. Blood pressure responses generally conformed to accepted standards for normality.

During Protocol 1, the heart rate increased to 90.2 ± 7.4% of the age-predicted maximal heart rate. This value was significantly ($p < 0.01$) lower than the heart rate attained during the screening test on the treadmill (187.0 ± 12.1 beats/min) and is representative of the difficulty inherent in pedaling the ergometer while seated in front of the scintillation camera as well as the tendency for bicycle exercise tests to be limited by local muscular fatigue. LVEF did not change significantly from rest to peak exercise during Protocol 1. In 21 cases (40%) ejection fraction decreased from rest to exercise. The greatest rest to exercise decrease in LVEF was 18% (76 to 58%) and was associated with normal symptomatic, blood pressure, and regional wall motion responses. The lowest absolute value for peak exercise LVEF observed during Protocol 1 was 54%. Individuals demonstrating increased or decreased LVEF from rest to exercise were compared (Table III). Only the resting LVEF was different between these groups. The change in ejection fraction from rest to exercise was significantly correlated ($r = -0.51$) with the resting ejection fraction and could be described by the following regression equaton: Protocol 1: $\Delta LVEF = 38.6 - 0.52$ (rest LVEF).

During Protocol 2 the heart rate increased to 79.6 ± 6.7% of the age-predicted maximal heart rate. LVEF increased significantly ($p < 0.05$) from rest to exercise. Although the absolute value of the LVEF during exercise (72.7 ± 8.7%) was not significantly ($p = 0.29$) different than in Protocol 1 (70.6 ± 7.3), the rest to exercise change in LVEF (+5.6 ± 9.4%) was significantly ($p < 0.05$) greater than in Protocol 1 (+0.8 ± 7.4%). LVEF decreased from rest to exercise in 5 of 21 cases (24%) and

**TABLE III Comparison of Protocol 1 Subjects Demonstrating Increased or Decreased LVEF From Rest to Exercise***

| | Decreased LVEF (n = 21) | Increased LVEF (n = 32) | p |
|---|---|---|---|
| Age (yr) | 29 ± 9 | 28 ± 7 | 0.61 |
| Height (cm) | 176 ± 8 | 178 ± 5 | 0.21 |
| Weight (kg) | 74 ± 11 | 76 ± 10 | 0.61 |
| Resting heart rate (beats/min) | 71 ± 13 | 69 ± 11 | 0.52 |
| Resting double product (mm Hg × beats/min × $10^2$) | 81 ± 22 | 75 ± 15 | 0.30 |
| Resting LVEF (%) | 74 ± 6 | 67 ± 7 | 0.01 |
| Maximal heart rate (beats/min) | 177 ± 10 | 178 ± 12 | 0.83 |
| Maximal double product (mm Hg × beats/min × $10^2$) | 339 ± 38 | 340 ± 44 | 0.97 |
| Maximal LVEF (%) | 68 ± 7 | 72 ± 7 | 0.06 |

* Mean ± standard deviation.

the lowest absolute value observed was 50%. As in Protocol 1, the resting LVEF was significantly related to the change in LVEF with exercise ($r = -0.52$) ($\Delta LVEF = 45.1 - 0.59$ [rest LVEF]).

During Protocol 3 the heart rate was 89.6 ± 8.2% of the age-predicted maximal heart rate during the immediate postexercise imaging period used for comparison to Protocol 1. This was not significantly different from that observed during Protocol 1. The LVEF increased significantly from rest to immediately after exercise. Both the absolute value of the postexercise LVEF as well as the rest to postexercise change in LVEF were significantly different from Protocol 1. A comparison of the LVEF responses at rest, peak exercise, and immediately after exercise is presented in Figure 3. Heart rate decreased significantly from peak to immediately after exercise although the absolute magnitude of the decrease (5 beats/min) was small. LVEF did not change significantly from rest (67.9 ± 4.1%) to peak exercise (69.2 ± 3.4%), then increased significantly during the postexercise period (80.4 ± 5.2%).

During Protocol 4 there was a significant decrease in

LVEF after the abrupt presentation of sudden strenuous exercise. This response was significantly different than observed in Protocol 1 and occurred despite a comparatively small increase in heart rate and double product.

During Protocol 5 the ejection fraction was decreased during peak exercise relative to the resting studies. This also occurred despite a lower response of heart rate and double product compared to Protocol 1. The serial responses of the 10 subjects studied at rest, during submaximal exercise control studies, and during peak exercise are presented in Figure 3. LVEF increased from the resting (66.0 ± 5.2%) to control exercise studies (70.5 ± 6.3%), then decreased significantly during supermaximal exercise (64.8 ± 8.2%). The decrease in ejection fraction from the submaximal exercise control study to supermaximal exercise was significantly lower than observed without warm-up during Protocol 4.

## Discussion

The general principles of GXT have evolved greatly since Master and Jaffe[16] first introduced the concept of exercise electrocardiography and a standard exercise protocol. These principles are well summarized by Bruce.[15] Protocol 1 conforms to these principles in several important ways: (1) exertion is initially submaximal, (2) increments of work output are small, (3) each stage is of sufficient duration to allow physiologic adaptation, (4) functional capacity is related to exercise duration, (5) the work is familiar to most adults, and (6) exercise is terminated for patient specific factors. Protocol 1, accordingly, represents the reference standard for this investigation. Other studies have demonstrated that various factors may exert a significant influence on the interpretation of diagnostic GXT. These include the adequacy of exercise,[7,17,18] the temporal sequence of imaging,[8,9] and resting LVEF.[18–21]

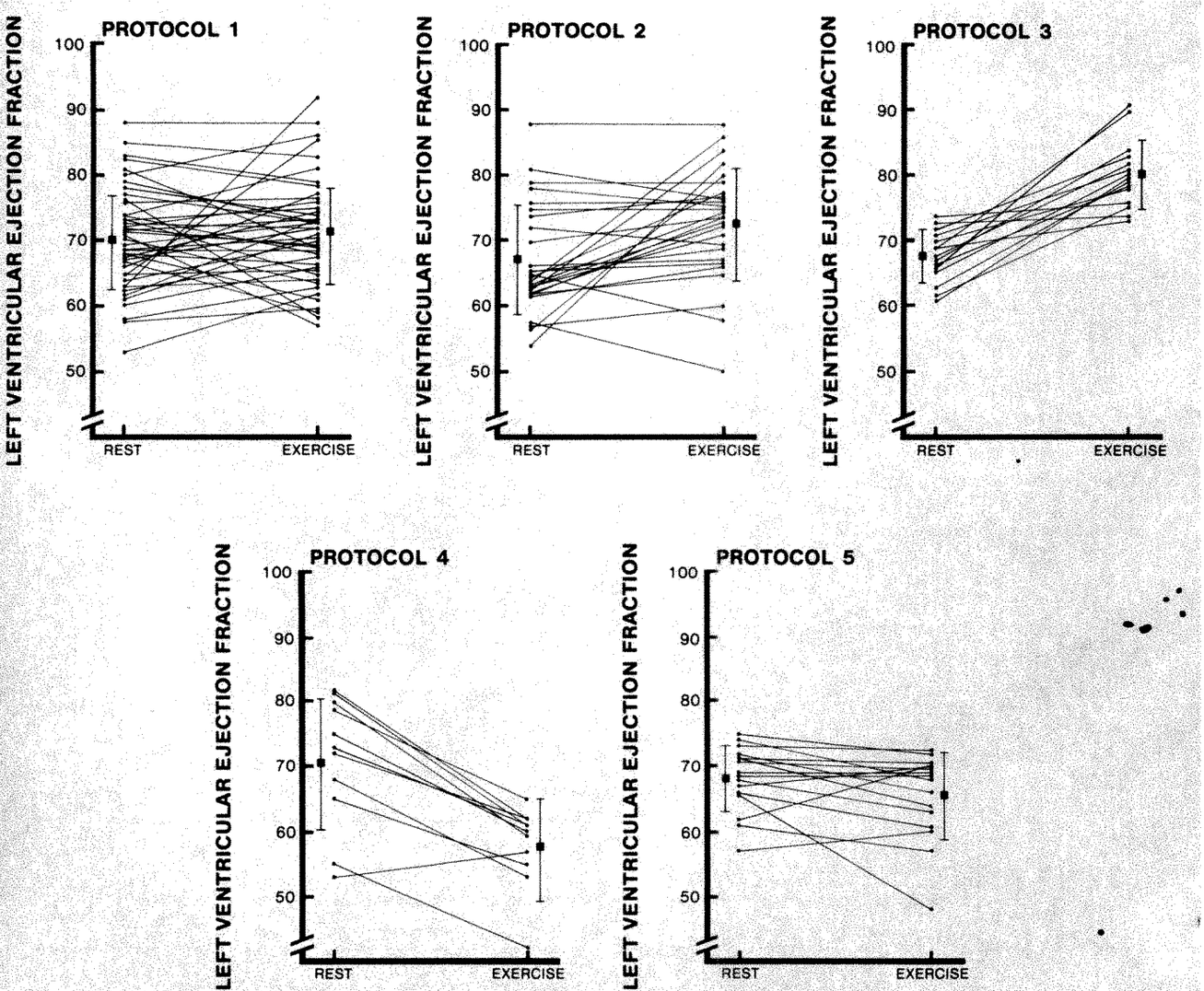



**FIGURE 2.** Rest to exercise changes in LVEF in each protocol. The ejection fraction response was significantly different in Protocols 2 to 5 from that in Protocol 1, which represents the reference standard for this investigation.

During Protocol 2 exercise was stopped either during submaximal exercise when 85% of the age-predicted heart rate had been attained or secondary to fatigue but with a low (<85% age-predicted maximal heart rate) heart rate response. Failure to achieve an adequate heart rate response has been shown to reduce the yield of electrocardiographic abnormalities during treadmill testing,[17] and failure to attain adequate levels of either heart rate[18] or double product[7] has been shown to reduce the diagnostic sensitivity of exercise radionuclide angiography. The same absolute values for heart rate and double product cannot be applied to the present data because of the difference in age between this group of young normal subjects and other series using middle-aged subjects.[7,18] Nevertheless, the results from Protocol 2 suggest that expectations of the LVEF response to exercise based on symptom-limited GXT with a good heart rate response may not be valid with a less satisfactory heart rate response. This observation is of particular importance, since termination of GXT at a fixed percentage of the age-predicted maximal heart rate is a relatively common practice in laboratories employing radionuclide angiography.[18–20] In the context of the less-than-maximal exercise test is the issue of functional capacity. Gibbons et al[20] demonstrated that the LVEF response in patients with chest pain and normal coronary arteries is related to functional capacity. Likewise, reports on exercise testing are replete with observations that good effort tolerance minimizes the prognostic significance of positive electrocardiographic findings,[22] whereas poor effort tolerance is a negative prognostic factor independent of electrocardiographic responses.[23,24]

Protocol 3 represents a common procedural variant in the conduct of exercise radionuclide angiography.[25,26] It allows for adequate levels of exercise but takes advantage of the reduced body motion after exercise to achieve technically better images. The results of the present investigation indicate, however, that the hemodynamic state inferred from radionuclide angiographic studies during the immediate postexercise period may not be representative of that actually occurring during peak exercise. This is true despite only modest differences in peak heart rate and double product. The marked increase in LVEF during the first few seconds after exercise may serve to mask abnormal left ventricular function which occurs during peak exercise.[9] Accordingly, this variant of the technique may reduce the diagnostic sensitivity of first-pass radionuclide angiography. However, as recently demonstrated by Rozanski et al,[27] postexercise imaging may be useful for predicting which patients are likely to demonstrate hemodynamic improvement after myocardial revascularization surgery.

Protocol 4 represents an extreme violation of GXT principles 1 to 3 enumerated earlier. This protocol, which was previously reported,[10] was initially accomplished in order to evaluate a potential model of subendocardial ischemia. It demonstrates that even the normal left ventricle can behave abnormally under certain circumstances. While no clinician would consider initiating an exercise protocol at 400 W, patients

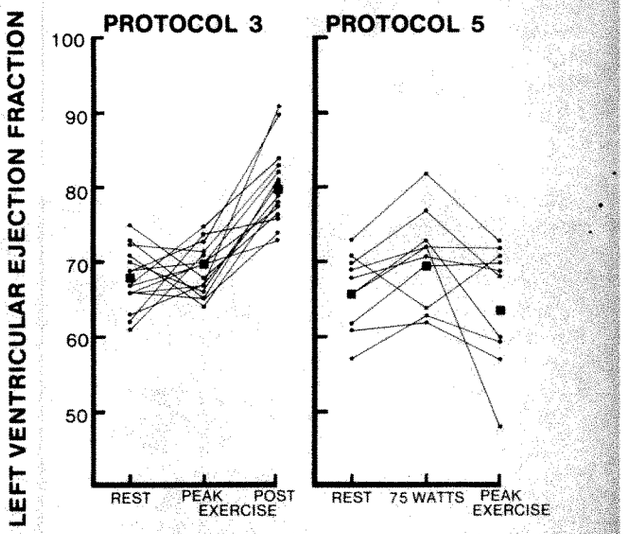



**FIGURE 3.** Serial ejection fraction responses during Protocols 3 (rest, peak exercise, immediately after exercise) and 5 (rest, 75 W exercise, peak exercise).

with very low work capacity may inadvertently start exercise protocols at supermaximal work loads. For example, completion of the first stage of Protocol 1 requires an oxygen uptake of about 600 ml/min. For a 70 kg patient, this represents about 2.5 multiples of the resting metabolic rate. Functional capacity will be lower than this in a small but significant number of patients. Thus, for these patients even the first stage of a well-designed GXT protocol may be functionally equivalent to sudden strenuous exercise in young athletes. Interpretation of the exercise radionuclide angiogram in patients with very low exercise tolerance should, accordingly, be tempered by these findings.

Protocol 5 was accomplished as a follow-up[11] to our published findings in Protocol 4 and, like Protocol 4, represents a somewhat contrived example that, regardless, may be of clinical significance. The results of this protocol suggest that warm-up exercise does not completely normalize the response to abruptly presented supermaximal exercise. The serial studies (Fig. 3) indicate, in concurrence with the findings in Protocol 3, that LVEF can change dramatically during very short time periods and can significantly affect the interpretation of the exercise radionuclide angiogram. As with Protocol 4, the exercise pattern employed in Protocol 5 is unlikely to be intentionally employed clinically. However, if an exercise protocol involves relatively large increments between stages, the work load could go from clearly submaximal to clearly supermaximal and create a situation similar to Protocol 5.

The importance of the resting LVEF on the LVEF response to exercise has been previously discussed.[18–21] The present results confirm these findings. The slope of the regression line between resting LVEF and the change in LVEF (−0.52 in Protocol 1, and −0.59 in Protocol 2) is similar to that described previously and suggests the great importance of resting LVEF to the results of exercise radionuclide angiography. It also

suggests that the LVEF response cannot be viewed outside the context of the total left ventricular response, including changes in left ventricular volume,[18] resting LVEF,[18–21] age,[28] heart rate response,[7,18] and functional capacity.[20] It suggests the utility of a multivariate approach to defining the LVEF response to exercise.[29] It also indicates the importance of accurate measurement of left ventricular volumes during exercise. We have chosen not to report left ventricular volumes in the present series because we, unlike Upton et al,[30] have found left ventricular end-diastolic volume to be poorly reproducible using the angiographic silhouette method and because attempts to develop a geometry-independent method similar to that employed with gated blood pool angiography[31] are not complete.

The results of this investigation obviously suggest that the LVEF response is related to how the exercise load is presented. This suggests that considerable standardization is necessary before literature values can be used to define the "normal" LVEF response and, thereby, provide the reference standard for diagnostic testing. It is pertinent to point out that regardless of the exercise protocol, the LVEF never fell below 48%. This suggests that the absolute value of LVEF may be as important diagnostically as the pattern of LVEF response. This remains an interesting problem for future study since it suggests that a single radionuclide angiogram may be effective, thus minimizing the cost, radiation exposure, and processing time for these studies.

The implications of the present investigation to clinical exercise testing using first-pass radionuclide angiography are clear. The present results indicate that comparatively minor variations in exercise test protocol can yield considerable variations in the LVEF response to exercise. Accordingly, laboratories using this procedure should ensure that the technical aspects of GXT are comparable before relying upon literature-based values for normal and abnormal responses with this procedure. The lack of correlation between the behavior of heart rate-double product and LVEF during the serial studies in Protocols 3 and 5 further suggests that the hemodynamic situation implied by changes in heart rate-double product should not lead to unwarranted assumptions regarding other indexes of left ventricular function. In the context of previous studies relating to the LVEF response[7–11,18–21,28] and of studies demonstrating multiple factors influencing the interpretation of clinical exercise testing,[22–24] the present results indicate that the overall utility of exercise radionuclide angiography in the diagnosis of cardiovascular disease may also depend on compliance with the principles of GXT.

## References


1. **Bruce RA, Hornstein TR.** Exercise stress testing in evaluation of patients with ischemic heart disease. Prog Cardiovasc Dis 1969;11:371–390.
2. **Ellestad MH, Cooke BM, Greenberg PS.** Stress testing: clinical applications and predictive capacity. Prog Cardiovasc Dis 1979;21:431–460.
3. **Bodenheimer MM, Banke VS, Fooshee CM, Helfant RH.** Comparative sensitivity of the exercise electrocardiogram, thallium imaging and stress radionuclide angiography to detect the presence and severity of coronary heart disease. Circulation 1979;60:1270–1278.
4. **Caldwell JH, Hamilton GW, Sorenson SG, Ritchie JL, Williams DL, Kennedy JW.** The detection of coronary artery disease with radionuclide techniques: a comparison of rest-exercise thallium imaging and ejection fraction response. Circulation 1980;61:610–619.
5. **Jengo JA, Freeman R, Brizendine M, Mena I.** Detection of coronary artery disease: comparison of exercise stress radionuclide angiography and thallium stress perfusion scanning. Am J Cardiol 1980;45:535–441.
6. **Pfisterer ME, Williams RJ, Gordon DG, Swanson SM, Battler A, Ceretto WJ, Ashburn WL, Froelicher VF.** Comparison of rest/exercise ECG, thallium-201 scans and radionuclide angiography in patients with suspected coronary artery disease. Cardiology 1980;66:43–55.
7. **Brady TJ, Thrall JH, Lo K, Pitt B.** The importance of adequate exercise in the detection of coronary heart disease by radionuclide ventriculography. J Nucl Med 1980;21:1125–1130.
8. **Foster C, Anholm J, Dymond D, Carpenter J, Pollock M, Schmidt DH.** Left ventricular function at rest, peak exercise and immediately post exercise. Cardiology, 1982;69:224–230.
9. **Dymond DS, Foster C, Saleem T, Patel K, Carpenter J, Schmidt DH.** Influence of the temporal sequence of imaging on the results of exercise radionuclide angiography (abstr). Eur Heart J 1981;2:178.
10. **Foster C, Anholm JD, Hellman C, Carpenter J, Pollock ML, Schmidt DH.** Left ventricular function during sudden strenuous exercise. Circulation 1981;63:592–596.
11. **Foster C, Dymond DS, Carpenter J, Schmidt DH.** Effect of warm-up on the left ventricular response to sudden strenuous exercise. J Appl Physiol 1982;55:380–383.
12. **Diamond GA, Forrester JS.** Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979;300:1350–1358.
13. **Hellman CK, Kamath ML, Schmidt DH, Anholm JD.** Improvement in left ventricular function after myocardial revascularization. J Thorac Cardiovasc Surg 1980;79:645–655.
14. **Dymond DS, Elliott A, Stone D, Hendrix G, Spurrel R.** Factors that affect the reproducibility of measurements of left ventricular function from first-pass radionuclide ventriculograms. Circulation 1982;65:311–322.
15. **Bruce RA.** Exercise testing of patients with coronary heart disease: principles and normal standards for evaluation. Ann Clin Res 1971;3:323–332.
16. **Master AM, Jaffe HL.** The electrocardiographic changes after exercise in angina pectoris. J Mt Sinai Hosp 1941;F629–F632.
17. **Cumming GR.** Yield of ischemic exercise electrocardiograms in relation to exercise intensity in a normal population. Br Heart J 1972;34:919–924.
18. **Jones RH, McEwan P, Newman GE, Port S, Rerych SK, Scholz PM, Upton MT, Peter CA, Austin EA, Leong K, Gibbons RJ, Cobb FR, Coleman RE, Sabiston DC.** Accuracy of diagnosis of coronary artery disease by radionuclide measurement of left ventricular function during exercise. Circulation 1981;64:586–601.
19. **Port S, McEwan P, Cobb FR, Jones RH.** Influence of resting left ventricular function on the left ventricular response to exercise in patients with coronary artery disease. Circulation 1981;63:856–863.
20. **Gibbons RJ, Lee KL, Cobb F, Jones RH.** Ejection fraction response to exercise in patients with chest pain and normal coronary angiograms. Circulation 1981;64:1952–1957.
21. **Osbakken MD, Merrill D, Boucher CA, Okada RD, Strauss HW, Pohost GM.** Low end systolic volume at rest. An explanation for failure of increase in ejection fraction during exercise in normal patients (abstr). J Nucl Med 1980;21:7.
22. **Tubau JF, Chaitman BR, Bourassa MG, Walters DD.** Detection of multivessel coronary artery disease after myocardial infarction using exercise stress testing multiple ECG lead system. Circulation 1980;61:44–52.
23. **McNeer JF, Margoles JR, Lee KL, Kieslo JA, Peter RH, Kong Y, Behar VS, Wallace AG, McCants CB, Rosati RA.** The role of the exercise test in the evaluation of patients with ischemic heart disease. Circulation 1978;57:64–70.
24. **Bruce RA, De Rouen TA, Hossack KF, Blake B, Hofer V.** Value of maximal exercise tests in risk assessment of primary coronary heart disease events in healthy men. Am J Cardiol 1980;46:371–378.
25. **Berger HJ, Johnstone DE, Sands JM, Gottschalk A, Zaret BL.** Response of right ventricular ejection fraction to upright bicycle exercise in coronary artery disease. Circulation 1979;60:1292–1300.
26. **Stone D, Dymond D, Elliot AT, Button KE, Banim SO, Spurrell RAJ.** Exercise first pass radionuclide ventriculography in detection of coronary artery disease. Br Heart J 1980;44:208–214.
27. **Rozanski A, Berman D, Gray R, Diamond G, Raymond M, Prause J, Maddahi J, Swan HJC, Matloff J.** Preoperative prediction of reversible myocardial asynergy by post exercise radionuclide ventriculography. N Engl J Med 1982;307:212–216.
28. **Port S, Cobb FR, Coleman RE, Jones RH.** Effect of age on the response of the left ventricular ejection fraction to exercise. N Engl J Med 1980;303:1133–1137.
29. **Foster C, Carpenter J, Schmidt DH.** Determinants of left ventricular ejection fraction response to exercise in healthy subjects (abstr). Clin Res 1982;30:186.
30. **Upton MT, Rerych SK, Newman GE, Bounous EP, Jones RH.** The reproducibility of radionuclide angiocardiographic measurements of left ventricular ejection function in normal subjects at rest and during exercise. Circulation 1980;62:126–132.
31. **Sorensen SG, Ritchie JL, Caldwell JH, Hamilton GW, Kennedy JW.** Serial exercise radionuclide angiography: validation of count-derived changes in cardiac output and quantitation of maximal exercise ventricular volume change after nitroglycerin and propranolol in normal men. Circulation 1980;61:600–609.

# Influence of Aortic Stenosis on the Hemodynamic Importance of Coronary Artery Narrowing in Dogs Without Left Ventricular Hypertrophy

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**Coronary hemodynamic effects of controlled left ventricular outflow obstruction simulating aortic valve stenosis were studied in 20 open-chest dogs, with and without graded coronary artery diameter narrowing. Aortic stenosis was regulated so that a mean left ventricular-aortic pressure gradient of 46 ± 20 mm Hg (mean ± standard deviation) was created as both heart rate and stroke volume were unchanged. In addition, during aortic stenosis, mean aortic pressure (105 ± 17 to 84 ± 15 mm Hg, p <0.05) and diastolic pressure time index/systolic pressure time index ratio (1.2 ± 0.3 to 0.6 ± 0.2, p <0.05) decreased and end-diastolic left ventricular pressure (7 ± 4 to 14 ± 6 mm Hg, p <0.05) increased. With no coronary narrowing, mean coronary flow increased during aortic stenosis (53 ± 23 to 62 ± 23 ml/min) as the percentage of diastolic flow increased (83 ± 6 to 89 ± 4) and endocardial/epicardial ratio decreased (1.14 ± 0.16 to 0.95 ± 0.24) (all p <0.05). Peak reactive hyperemic flow also decreased (168 ± 85 to 125 ± 73 ml/min, p <0.05). This value with no coronary narrowing was similar to peak hyperemic flow with 60% narrowing without aortic stenosis. With 90% coronary narrowing, mean coronary flow decreased with or without aortic stenosis. Transmural flow distribution also decreased but was lower during aortic stenosis (0.86 ± 0.19 to 0.61 ± 0.25, respectively; p <0.05).**

**These data suggest that although mean coronary flow is increased during aortic stenosis, endocardial flow may be limited, and coronary reserve exposed during reactive hyperemia appears decreased. When a coronary artery is narrowed, aortic stenosis has an even more important hemodynamic influence on the coronary circulation.**

Aortic stenosis is often accompanied by clinical, electrocardiographic, and histologic findings that suggest myocardial ischemia.[1] These findings usually imply valvular obstruction of hemodynamic importance but do not necessarily indicate accompanying severe coronary artery disease.[1,2] Although most patients with important coronary artery disease and aortic stenosis have angina, in some series approximately 75% of middle-aged patients with aortic stenosis and normal coronary angiograms also have angina. Patients with aortic stenosis have both left ventricular hypertrophy and changes in aortic and left ventricular pressures. Either or both of these factors would conceivably alter left ventricular perfusion at rest and during stress.

The problem of aortic stenosis and myocardial ischemia has been evaluated previously, but results have often conflicted. In patients with aortic stenosis, both normal and reduced left ventricular blood flow per unit mass has been reported.[3–6] A seemingly appropriate increase during isometric or exercise stress has been reported.[4,5] In contrast, reduced flow responses after pharmacologic or ischemic induced vasodilation were also reported.[6,7] The diastolic pressure time index/systolic pressure time index (DPTI/SPTI) ratio was reduced in many patients with aortic stenosis.[4] In short-term animal models, studies usually suggested an increase in basal coronary flow.[8–10] Some studies have also indicated changes in transmural myocardial blood flow and metabolism, whereas others have not.[10–13]

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We investigated coronary hemodynamic responses due to acute aortic stenosis in an animal model without left ventricular hypertrophy. This model of aortic stenosis was chosen to allow evaluation of the coronary hemodynamic effects of changes in aortic and left ventricular pressure that occurred during aortic stenosis, separate from changes related to left ventricular hypertrophy. Results were obtained with and without coronary artery narrowing.

## Methods

**Animal preparation:** Twenty large healthy dogs (average weight 29 kg, range 20 to 40) were studied. After premedication (1 mg/kg of morphine), dogs were anesthetized (either 100 mg/kg of alpha-chloralose or 30 mg/kg of pentobarbital) and intubated. Respiration was controlled to maintain arterial blood gases and pH within the physiologic range. A left thoracotomy was performed in the fifth intercostal space, and the heart was supported by a pericardial cradle. Both carotid arteries, the ascending aorta, and either the left circumflex or anterior descending artery were isolated.

**Instrumentation:** Electromagnetic flow probes were positioned on the proximal coronary artery and ascending aorta. Use and calibration of these probes in our laboratory has been described previously.[14–16] Catheter tip micromanometers (Millar) were positioned in the left ventricle from the right carotid artery and left atrial appendage. After confirmation of equally sensitive calibration, the catheter positioned from the right carotid artery was withdrawn to the ascending aorta.

**Creation of coronary narrowings:** Two techniques were used to create controlled reduction of coronary diameter. In 8 dogs, a calibrated snare was used.[14–16] In 12 dogs, narrowings were created with 1 mm long plastic occluders chosen to produce estimated narrowings of 60, 80, and 90%.[14–16]

**Creation of reversible subvalvular obstruction:** Reversible subvalvular obstruction was created using a balloon catheter positioned in the left ventricle (Fig. 1).[10,12] Magnitude of outflow obstruction was controlled by manipulating catheter position or balloon size with fluoroscopic or pressure monitoring or both. The aortic flow signal was monitored to detect the presence or absence of aortic insufficiency.[15,17] In 3 experiments the left ventricular-aortic obstruction was released simultaneously with release of the 10-second coronary occlusion. The purpose of these additional studies was to verify that the coronary bed was at least as responsive during the aortic stenosis period as during control periods.

**Endocardial/epicardial ratio:** The endocardial/epicardial ratio was determined by radioactive microsphere (8 to 10 $\mu$m) technique in 12 experiments.[18] Approximately 3 million spheres were injected into the left atrium. Injections were done when a 90% narrowing was applied to either the proximal anterior descending or the circumflex artery. Thus, either the anterior or posterior region was perfused by an artery with a 90% narrowing, and the other left ventricular region was perfused by an artery without narrowing.

At the conclusion of the experiment, the heart was removed and placed in formalin for 72 hours. The left ventricle was "bread-loafed" into 4 slices. Samples from the anterior and posterior papillary muscle regions of the middle 2 slices were divided into endocardial, midwall, and epicardial pieces and weighed. The number of radioactive counts/gram in the endocardial and epicardial pieces were used to estimate transmural flow distribution. In experiments in which endocardial/epicardial ratios were measured, coronary narrowings were created with plastic occluders. Ratios were combined according to whether perfusion was through an artery with no narrowing or a 90% narrowing.

**Experimental sequence:** Each experiment consisted of 3 periods beginning with a *first control period.* Each period consisted of a "sequence" of duplicate recordings at fast trace (100 mm/s) and slow trace (2.5 mm/s) of flow, and pressure signals before and after a 10-second complete coronary occlusion. This was repeated after a 60 and 80% coronary narrowing had been applied for 5 minutes. The 10-second coronary occlusion was omitted after a 90% coronary narrowing was applied. During the *aortic stenosis period*, the balloon was inflated, positioned, and fixed. Flow and pressure stabilization (±5%) occurred in <5 minutes, and approximately 10 minutes was allowed before measurements were repeated. During the *second control period*, the balloon was deflated. Five minutes after pressure and flow stabilized, recordings were repeated again according to sequences outlined for the first control period.

If differences between repeated responses within a period were >10%, the sequence was not used in this report. When differences ≤10% were found between paired reactive hyperemic responses, the higher value was used. However, if small differences (≤10%) were found comparing systemic or coronary hemodynamic values from the 2 control periods, the value closest to that during aortic stenosis was used for comparison.

**Measurements and calculations:** All measurements were made over at least 10 heart beats and averaged during control and aortic stenosis periods with no coronary diameter reduction and with narrowings estimated at 60, 80, and 90%.

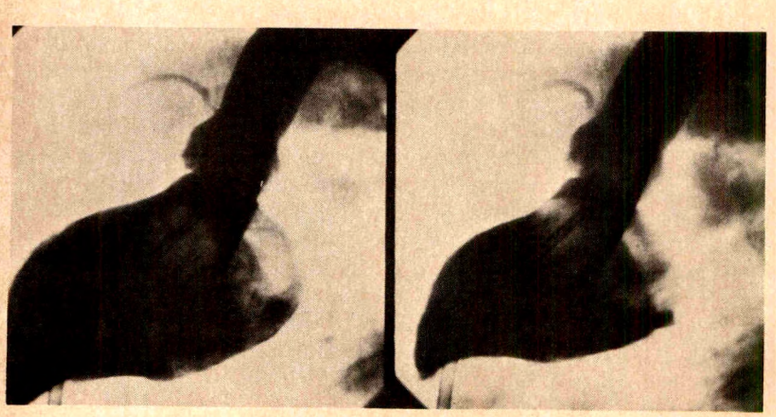


**FIGURE 1.** Left ventriculogram end-diastolic (**left**) and end-systolic (**right**) frames (left lateral projection) showing the balloon catheter positioned in the left ventricle below the aortic valve. No mitral regurgitation was seen.

Total coronary blood flow before 10-second occlusion was used as an index of basal flow. Peak reactive hyperemic flow was used as an index of flow reserve. Indexes of coronary artery resistance were calculated as ratios of mean aortic pressure and mean coronary flow, mean aortic pressure minus left ventricular end-diastolic pressure and mean coronary flow, and late diastolic aortic pressure minus left ventricular end-diastolic pressure and late diastolic coronary flow. Systolic and diastolic phasic coronary and aortic flows were quantified by cutting these areas out and weighing them on an analytic balance. The DPTI/SPTI ratio and the mean systolic pressure gradient were calculated from the left ventricular and aortic pressure signals by weighing the respective portion of the tracing and correcting for calibration. This technique yields a coefficient of variation <1%. Stroke volume was calculated from aortic flow. The systolic ejection period was measured from the initial upstroke of the aortic velocity signal to the point where it crossed the zero baseline. The aortic flow signal position at end-diastole, defined from the left ventricular pressure trace, with the balloon deflated in the left ventricle was taken as zero aortic flow.[15,17]

**Analysis of results and definitions:** Mean values and standard deviations were calculated. An analysis of variance for repeated measures, Duncan's multiple comparison procedure, and a paired $t$ test were used for statistical comparisons. A multiple regression analysis was performed to test the following variables for a relation with the endocardial/epicardial ratio during control and aortic stenosis and the change in each variable from control to aortic stenosis: mean coronary flow, left ventricular systolic and end-diastolic pressure, mean aortic and aortic diastolic pressure, DPTI/SPTI, and mean left ventricular-aortic pressure gradient. A p value ≤0.05 was considered statistically significant.

## Results

Evaluation of recordings with the balloon catheter "fixed" did not suggest variable left ventricular outflow obstruction in any dog. Specifically, no additional changes in either aortic pulse pressure or flow were observed during monitoring. In addition, when the left ventricular micromanometer was moved within the left ventricular cavity, no intraventricular gradients were detected.

In some dogs certain variables were not obtained, and in 2 dogs 2 complete experiments were done. Acceptable aortic velocity signals were not obtained in 5 experiments. In 5 experiments, hemodynamic instability developed during aortic stenosis when the coronary artery was transiently occluded with or without coronary narrowing. Values at these times were excluded from analysis. Because hemodynamic measurements were stable at other times during these experiments, paired data were included.

**Hemodynamic findings (Table I):** During aortic stenosis, the left ventricular-aortic pressure gradient averaged 46 ± 20 mm Hg (range 18 to 122 mm Hg), whereas heart rate and stroke volume were similar to control period values. Left ventricular systolic and end-diastolic pressures increased, and mean aortic pressure decreased during aortic stenosis. The systolic ejection period increased and the DPTI/SPTI ratio (1.2 ± 0.3 to 0.6 ± 0.2) decreased during aortic stenosis. These values were not significantly changed during coronary narrowing.

**TABLE I Summary of Hemodynamic Findings in Acute Aortic Stenosis**

| | Heart Rate (beats/min) | | Stroke Volume (ml/beat) | | Systolic Ejection Period (s/beat) | | Pressure (mm Hg) | | | | | | Mean LV-AO Pressure Gradient (mm Hg): |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | LVSP | | LVEDP | | Mean AoP | | |
| Experiment | C | AS | C | AS | C | AS | C | AS | C | AS | C | AS | AS |
| 1 | 150 | 167 | 16.0 | 14.4 | 0.14 | 0.20 | 119 | 149 | 3 | 13 | 99 | 89 | 32 |
| 2 | 175 | 180 | 16.0 | 16.1 | 0.10 | 0.14 | 155 | 195 | 10 | 10 | 132 | 106 | 39 |
| 3 | 140 | 140 | 17.1 | 12.9 | 0.12 | 0.15 | 135 | 165 | 3 | 10 | 113 | 88 | 42 |
| 4 | 205 | 250 | 10.2 | 6.0 | 0.12 | 0.11 | 116 | 175 | 0 | 7 | 100 | 91 | 44 |
| 5 | 128 | 128 | 16.4 | 18.8 | 0.16 | 0.20 | 101 | 112 | 10 | 10 | 84 | 70 | 50 |
| 6 | 158 | 177 | 15.8 | 9.6 | 0.12 | 0.14 | 125 | 127 | 5 | 13 | 106 | 70 | 24 |
| 7 | 140 | 140 | 9.3 | 11.4 | 0.18 | 0.20 | 108 | 165 | 9 | 14 | 83 | 81 | 54 |
| 8 | 140 | 130 | 9.3 | 13.5 | 0.18 | 0.26 | 122 | 159 | 8 | 27 | 107 | 60 | 64 |
| 9 | 154 | 158 | 9.7 | 13.1 | 0.13 | 0.16 | 95 | 146 | 0 | 6 | 82 | 80 | 46 |
| 10 | 167 | 160 | 18.0 | 23.5 | 0.15 | 0.21 | 119 | 149 | 11 | 19 | 106 | 75 | 43 |
| 11 | 100 | 100 | 27.0 | 36.7 | 0.18 | 0.22 | 112 | 178 | 3 | 10 | 84 | 93 | 40 |
| 12 | 130 | 140 | 18.5 | 12.9 | 0.15 | 0.18 | 150 | 180 | 7 | 14 | 127 | 112 | 45 |
| 13 | 130 | 150 | 18.5 | 18.5 | 0.16 | 0.16 | 129 | 116 | 7 | 13 | 107 | 93 | 33 |
| 14 | 150 | 98 | — | — | — | — | 173 | 264 | 10 | 28 | 100 | 63 | 122 |
| 15 | 180 | 200 | — | — | — | — | 143 | 175 | 7 | 10 | 123 | 83 | 51 |
| 16 | 130 | 130 | 16.2 | 18.9 | 0.16 | 0.19 | 130 | 191 | 5 | 10 | 93 | 91 | 46 |
| 17 | 125 | 135 | — | — | — | — | 107 | 130 | 3 | 10 | 91 | 83 | 25 |
| 18 | 140 | 140 | — | — | — | — | 109 | 126 | 5 | 6 | 91 | 83 | 18 |
| 19 | 140 | 150 | — | — | — | — | 173 | 200 | 5 | 10 | 143 | 112 | 45 |
| 20 | 100 | 115 | 26.0 | 32.5 | 0.16 | 0.20 | 124 | 171 | 11 | 17 | 103 | 99 | 54 |
| 21 | 125 | 130 | 19.2 | 17.5 | 0.17 | 0.19 | 127 | 148 | 10 | 25 | 110 | 72 | 50 |
| 22 | 120 | 136 | 19.1 | 15.3 | 0.15 | 0.21 | 140 | 170 | 12 | 18 | 127 | 63 | 49 |
| Mean | 142.1 | 147.9 | 16.6 | 17.1 | 0.14* | 0.18 | 127.8* | 163.2 | 6.5* | 13.6 | 105.0* | 84.4 | 46.2 |
| SD | 24.7 | 33.4 | 5.1 | 7.7 | 0.02 | 0.03 | 21.07 | 33.65 | 3.6 | 6.3 | 17.0 | 14.9 | 20.1 |

*p = <0.05 comparing control and aortic stenosis values.
AoP = aortic pressure; AS = aortic stenosis; C = control; LV-AO = left ventricular-aortic; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; SD = standard deviation.
— = signal not adequate for interpretation.

**TABLE II Summary of Coronary Hemodynamic Findings in Acute Aortic Stenosis**

| | CBF (ml/min) No Narrowing | | % Diastolic CBF | | CBF (ml/min) 90% Narrowing | | Reactive Hyperemic CBF (ml/min) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No Narrowing | | 60% Narrowing | | 80% Narrowing | |
| Experiment | C | AS | C | AS | C | AS | C | AS | C | AS | C | AS |
| 1 | 79 | 114 | 84 | 89 | 40 | 40 | 316 | 277 | 292 | 237 | 174 | 126 |
| 2 | 60 | 75 | 91 | 94 | 45 | 60 | 300 | 270 | 210 | 195 | 175 | 150 |
| 3 | 130 | 104 | 86 | 90 | 52 | 59 | 260 | 195 | 208 | 143 | 182 | 104 |
| 4 | 57 | 75 | 88 | 86 | 43 | 50 | 163 | 141 | 128 | 106 | 101 | 70 |
| 5 | 53 | 62 | 89 | 92 | 33 | 33 | 156 | 62 | 111 | 90 | 86 | 49 |
| 6 | 70 | 64 | 82 | 82 | 41 | 23 | 186 | 93 | 150 | 110 | 116 | 75 |
| 7 | 57 | 74 | 78 | 89 | 49 | 49 | 119 | 84 | 111 | 70 | 98 | 57 |
| 8 | 53 | 41 | 79 | 87 | 49 | 29 | 111 | 41 | 94 | 41 | 86 | 29 |
| 9 | 50 | 60 | 72 | 88 | 40 | 50 | 200 | 140 | 150 | 110 | 140 | 100 |
| 10 | 64 | 73 | 87 | 87 | 27 | 36 | 319 | 246 | 273 | 155 | 228 | 91 |
| 11 | 50 | 72 | 82 | 95 | 40 | 35 | 135 | 125 | 115 | 100 | 75 | 75 |
| 12 | 40 | 52 | 80 | 89 | 28 | 32 | 150 | 120 | 72 | 52 | — | — |
| 13 | 28 | 36 | 83 | 95 | 20 | 20 | 84 | 76 | 76 | 60 | — | — |
| 14 | 25 | 34 | 78 | 90 | — | — | 85 | 43 | — | — | — | — |
| 15 | 75 | 98 | 98 | 91 | 60 | 68 | 293 | 173 | 240 | 113 | 143 | 90 |
| 16 | 25 | 28 | 80 | 91 | 23 | 23 | 55 | 50 | 51 | 45 | 45 | 38 |
| 17 | 34 | 46 | 80 | 88 | 28 | 34 | 113 | 101 | 105 | 84 | 67 | 63 |
| 18 | 41 | 49 | 86 | 95 | 37 | 37 | 135 | 103 | 123 | 94 | 78 | 70 |
| 19 | 32 | 37 | 84 | 87 | 25 | 28 | 81 | 69 | 69 | 62 | 53 | 53 |
| 20 | 36 | 48 | 81 | 94 | 28 | 28 | 98 | 84 | 84 | 70 | 56 | 50 |
| 21 | 60 | 70 | 85 | 81 | 50 | 27 | — | — | — | — | — | — |
| 22 | 52 | 56 | 73 | 80 | 36 | 24 | — | — | — | — | — | — |
| Mean | 53.2* | 62.3 | 83* | 89 | 37.8 | 37.4 | 168.0* | 124.7 | 140.1* | 102.0 | 111.9* | 75.9 |
| SD | 23.1 | 22.9 | 5.8 | 4.3 | 10.8 | 13.6 | 85.3 | 72.9 | 71.3 | 51.1 | 53.2 | 31.6 |

*$p = <0.05$ comparing control and aortic stenosis values.
AS = aortic stenosis; C = control; CBF = coronary blood flow; SD = standard deviation; — = data not obtained.

**Coronary hemodynamic responses (Tables II and III):** Mean coronary flow with no narrowing was higher during aortic stenosis. As the coronary diameter was reduced by 60 and 80%, there was no significant change in coronary flow with or without aortic stenosis. With a 90% diameter reduction, coronary flow was similar with and without aortic stenosis as both decreased compared with values with a lesser amount of coronary narrowing (both $p < 0.05$). The diastolic fraction of coronary flow increased during aortic stenosis. The endocardial/epicardial ratio was reduced during aortic stenosis with no coronary narrowing. With a 90% narrowing, the endocardial/epicardial ratio decreased during the control period and during aortic stenosis compared with their respective values with no coronary narrowing (both $p < 0.05$). The endocardial/epicardial ratio with the 90% coronary narrowing was lower during aortic stenosis ($p < 0.05$).

Coronary artery resistance was lower during aortic stenosis. Resistance calculated as the ratio of mean aortic pressure to mean coronary flow was 2.41 ± 1.27 during control and 1.61 ± 0.70 mm Hg/ml/min during aortic stenosis; resistance calculated as the ratio of mean aortic pressure minus left ventricular end-diastolic pressure to mean coronary flow was 2.27 ± 1.20 and 1.36 ± 0.65 mm Hg/ml/min; and resistance calculated as the ratio of late diastolic aortic pressure minus left ventricular end-diastolic pressure to late diastolic coronary flow was 1.19 ± 0.82 and 0.68 ± 0.35 mm Hg/ml/min (all $p < 0.05$).

In each experiment peak reactive hyperemic flow with no coronary narrowing was reduced during aortic stenosis (Fig. 2). Even in the 5 experiments (Numbers 7, 9, 11, 16, and 20) in which mean aortic pressure was similar during control and aortic stenosis periods, peak reactive hyperemic flow decreased. In general, this decrease was greater in experiments with a larger left ventricular-aortic pressure gradient. A significant ($p < 0.05$) decrease in both control and aortic stenosis reactive hyperemic responses was observed with a 60% narrowing compared with no narrowing and with the 80% narrowing compared with the 60% and no narrowing values during control or aortic stenosis, respectively. Peak hyperemic flow values with a 60 or 80% coronary narrowing were consistently lower during aortic stenosis.

Coronary artery resistance calculated at peak reactive hyperemia was similar during control and aortic stenosis. Resistance calculated as the ratio of mean aortic pressure to mean coronary flow was 0.81 ± 0.47 mm Hg/ml/min during control and 0.88 ± 0.44 mm Hg/ml/min during aortic stenosis; resistance calculated as the ratio of mean aortic pressure minus left ventricular end-diastolic pressure to mean coronary blood flow was 0.76 ± 0.44 and 0.73 ± 0.35 mm Hg/ml/min; and resistance calculated as the ratio of late diastolic aortic pressure minus left ventricular end-diastolic pressure to late diastolic coronary flow was 0.48 ± 0.22 and 0.49 ± 0.23 mm Hg/ml/min, respectively (all $p$ = NS [not significant]).

When the left ventricular-aortic obstruction was released simultaneously with the release of the 10-second coronary occlusion (Fig. 3), peak flow was usually higher (316, 160, and 92 ml/min) than during aortic stenosis

(277, 120, and 76 ml/min) and during control (316, 150, and 84 ml/min), respectively.

During the control period there was no significant relation between the endocardial/epicardial ratio and the coronary and left ventricular hemodynamic variables tested. During aortic stenosis, a lower endocardial/epicardial ratio was usually associated with a lower aortic pressure and DPTI/SPTI ratio and higher values of the left ventricular-aortic pressure gradient and of coronary flow (all $p < 0.05$). When the change in endocardial/epicardial ratio, control to aortic stenosis, was correlated against changes in coronary and left ventricular hemodynamics comparing the 2 periods, no significant relations were observed. However, a trend toward an important relation was found for decreases in mean and diastolic aortic pressures (both $p = 0.08$) from control values to those during aortic stenosis.

## Discussion

Creation of aortic stenosis altered coronary hemodynamic function and increased the coronary hemodynamic importance of a coronary narrowing. These changes occurred in a model without left ventricular hypertrophy. In this model aortic stenosis increased left ventricular systolic and end-diastolic pressures and decreased aortic pressure. Heart rate and stroke volume were unchanged. During aortic stenosis when no coronary narrowing was present, total coronary flow increased and coronary resistance decreased. The endocardial/epicardial ratio was lower during aortic stenosis.

**TABLE III Summary of Transmural Flow Distribution in Acute Aortic Stenosis**

| | Endocardial/Epicardial Ratio | | | |
|---|---|---|---|---|
| | No Narrowing | | 90% Narrowing | |
| Experiment | C | AS | C | AS |
| 1 | 1.24 | 1.30 | 1.19 | 0.95 |
| 2 | 1.01 | 1.27 | 0.70 | 0.81 |
| 3 | 1.15 | 0.82 | 0.56 | 0.40 |
| 4 | 1.19 | 1.07 | 1.04 | 0.83 |
| 5 | 0.99 | 0.87 | 0.88 | 0.91 |
| 6 | 1.40 | 1.17 | 0.94 | 0.29 |
| 7 | 0.96 | 0.99 | 1.05 | 0.45 |
| 8 | 0.96 | 0.67 | 1.05 | 0.39 |
| 10 | 0.94 | 1.07 | 0.71 | 0.76 |
| 11 | 1.23 | 0.95 | 0.71 | 0.78 |
| 21 | 1.30 | 0.72 | 0.77 | 0.45 |
| 22 | 1.30 | 0.55 | 0.77 | 0.34 |
| Mean | 1.14* | 0.95 | 0.86* | 0.61 |
| SD | 0.16 | 0.24 | 0.19 | 0.25 |

*$p = <0.05$ comparing control and aortic stenosis values.
AS = aortic stenosis; C = control; SD = standard deviation.

With a high-grade coronary narrowing, total coronary flow and the endocardial/epicardial ratio decreased with or without aortic stenosis. However, endocardial/epicardial values remained lower during aortic stenosis.

Coronary flow reserve as measured by reactive hyperemia was reduced during aortic stenosis with no coronary narrowing. This value was similar to that

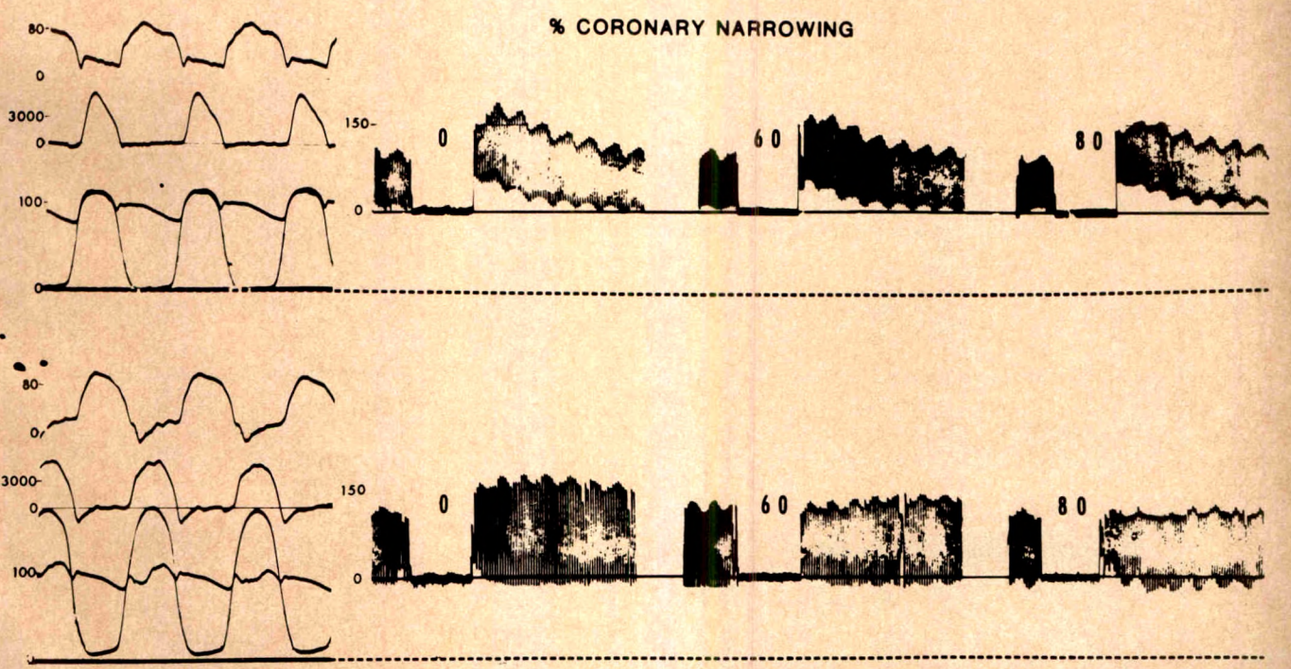



**FIGURE 2. Left,** at fast paper speed, coronary flow, aortic flow, and aortic and left ventricular pressure signals during control (**top**) and aortic stenosis (**bottom**). **Right,** at slow paper speed, phasic coronary flow signals before and during reactive hyperemia after a 10-second coronary occlusion for no coronary narrowing and for 60 and 80% coronary narrowings (control, **top;** aortic stenosis, **bottom**). Reactive hyperemic coronary flow values during aortic stenosis were similar to those during the control period with higher degrees of coronary narrowing. This example was chosen because mean aortic pressure was similar with and without aortic stenosis.

caused by a 60% coronary narrowing without aortic stenosis. Furthermore, aortic stenosis with 60% narrowing caused reductions in coronary reserve similar to those caused by an 80% narrowing without aortic stenosis. Thus, besides potentially inadequate transmural myocardial perfusion during rest and stress, coronary flow reserve could also be limited. The decrease in aortic pressure certainly contributed to the reduction in peak reactive hyperemic flow.[19] However, in the 5 experiments when aortic pressure was similar during the control and aortic stenosis periods, reactive hyperemia was still lower during aortic stenosis (Fig. 2).

Inspection of the phasic coronary flow signal revealed that most dogs had a reversal of flow during early systole during aortic stenosis so that little or no forward systolic flow occurred. This has been observed in dogs with congenital subaortic stenosis[20] and during coronary angiography in patients with aortic stenosis.[21] These changes in phasic coronary flow pattern during aortic stenosis were probably mediated through alterations in aortic and left ventricular pressures.

Results of previous experimental studies of acute aortic stenosis disagreed on the adequacy of endocardial perfusion.[10–12] We found lower endocardial/epicardial ratios during acute aortic stenosis. The reasons disagreements have been reported on the effect of acute aortic stenosis on this value were unclear because experimental models and the magnitude of left ventricular-aortic pressure gradient were similar.[10–12] During aortic stenosis, the increased left ventricular systolic and end-diastolic pressures reflected an increase in demand, whereas the decreased aortic pressure reflected a reduced coronary perfusion pressure. Thus, the DPTI/SPTI ratio decreased, and the value was sufficiently low to predict a reduction in endocardial perfusion even in a model without left ventricular hypertrophy.[22] In a model of chronic subcoronary valvular aortic stenosis accompanied by compensatory left ventricular hypertrophy, Attarian et al[13] found decreases in endocardial perfusion.

In 3 experiments, we released the left ventricular-aortic obstruction simultaneously with the beginning of reactive hyperemia. Peak coronary flow was usually higher than with left ventricular-aortic obstruction maintained or during control (Fig. 3). This seemed to indicate at least 2 things: One was that the reactive hyperemic response would have been higher but was limited during aortic stenosis. The other was that myocardial oxygen demands were probably higher during aortic stenosis, and the reactive hyperemic response after release of the left ventricular-aortic obstruction unmasked increased oxygen demand during aortic stenosis.[23]

These observations were made in an animal model of acute aortic stenosis and conclusions drawn may not apply to animals with chronic aortic stenosis or to patients with aortic stenosis. Although rare, acute aortic stenosis can occur in patients (for example, aortic valve thrombosis or aortic valve replacement with too small a valve in patients with previous aortic insufficiency). Several other factors deserve further comment: (1) These dogs did not have left ventricular hypertrophy. The presence of both left ventricular hypertrophy and changes in aortic and left ventricular pressure that occur during aortic stenosis would probably have additive effects on coronary hemodynamic function. In addition, changes in transmural flow distribution have reportedly been found in some but not all models of left ventricular hypertrophy.[13,24–27] (2) The central-occlusion type of outflow tract obstruction caused by the balloon tech-

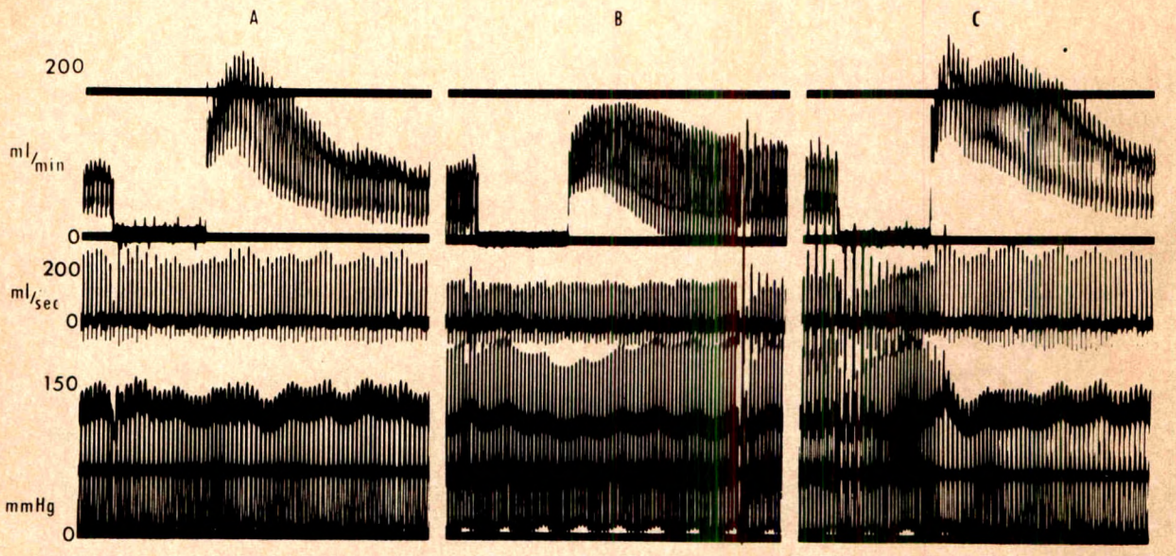



**FIGURE 3.** Example of phasic coronary flow and left ventricular and aortic pressures before and during reactive hyperemia occurring after a 10-second coronary occlusion. Control (**A**), aortic stenosis (**B**), and aortic stenosis with balloon deflation coincident with release of coronary occlusion (**C**) are shown. The reactive hyperemic response was least during aortic stenosis (**B**), intermediate during the control period (**A**), and greatest during aortic stenosis when the balloon was deflated coincident with release of coronary occlusion (**C**).

**TABLE IV Schematic Summary of Effects of Aortic Stenosis and Coronary Narrowing on the Endocardial/Epicardial Flow Ratio and on Total Coronary Flow During Reactive Hyperemia After Coronary Occlusion**

| Animal Model | Coronary Blood Flow | |
|---|---|---|
| | Endocardial/ Epicardial Ratio | Peak Reactive Hyperemic Flow |
| Coronary narrowing | ↓ | ↓ |
| Aortic stenosis | ↓ | ↓↓ |
| Aortic stenosis + coronary narrowing | ↓↓ | ↓↓↓ |

nique differs from the central-open orifice type associated with stenosis of the aortic valve. Although the aortic velocity signal had a normal shape, changes in flow and turbulence near the coronary ostia probably differ in central-occlusion and central-open left ventricular outflow obstruction. (3) Both the left ventricular outflow obstruction and coronary narrowings were maintained for relatively short periods of time. Compensatory left ventricular or coronary circulatory alterations occurring over longer periods could not be assessed. (4) We have shown previously that the length of a coronary stenosis,[14,16] as well as number of stenoses in a vessel,[16] has important coronary hemodynamic effects. (5) Although the calibrated snare technique to create coronary narrowing has been used by several investigators,[14–16,28,29] the precise percentage of narrowing and the ability to precisely reproduce each percentage of narrowing is open to question. Because of possible limitations of the snare technique relative to being able to precisely reproduce a coronary narrowing in the dogs, we used plastic occluders to create coronary narrowings where endocardial/epicardial ratios were measured.

*In summary*, changes in aortic and left ventricular pressures that accompany aortic stenosis can potentially cause decreases in the portion of coronary flow perfusing the endocardium and in total coronary flow during stress (for example, mimicked by reactive hyperemia after coronary occlusion). The coronary hemodynamic effects of coronary narrowing and aortic stenosis seem additive because endocardial perfusion and total flow during reactive hyperemia decreased more in the presence of both, than with either alone (Table IV). These coronary hemodynamic changes occurred even in a model without left ventricular hypertrophy which has an additional effect on coronary flow.

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## References


1. **Wood P.** Aortic stenosis. Am J Cardiol 1958;1:553–571.
2. **Bonchek LI, Anderson RP, Roach J.** Should coronary arteriography be performed routinely before valve replacement? Am J Cardiol 1973;31: 462–466.
3. **Johnson LL, Sciacca RR, Ellis K, Weiss MB, Cannon PJ.** Reduced left ventricular myocardial blood flow per unit mass in aortic stenosis. Circulation 1978;57:582–590.
4. **Bertrand ME, Lablanche JM, Thieuleux FP, Delforge MR, Carre AG.** Coronary sinus blood flow at rest and during isometric exercise in patients with aortic valve disease: mechanisms of angina pectoris in presence of normal coronary arteries. Am J Cardiol 1981;47:199–205.
5. **Rowe GG, Afonso S, Lugo JE, Castillo CA, Boake WC, Crumpton CW.** Coronary blood flow and myocardial oxidative metabolism at rest and during exercise in subjects with severe aortic valve disease. Circulation 1965; 32:252–257.
6. **Pichard AD, Gorlin R, Smith H, Ambrose J, Meller J.** Coronary flow studies in patients with left ventricular hypertrophy of the hypertensive type. Evidence for an impaired coronary vascular reserve. Am J Cardiol 1981;47: 547–554.
7. **Marcus ML, Gascho JA, Mueller TM, Eastham C, Wright CB, Doty DB, Hiratzka LF.** The effects of ventricular hypertrophy on the coronary circulation. Basic Res Cardiol 1981;76:575–581.
8. **Blumenthal MR, Wang H-H, Wang SC.** Effects of acute experimental aortic stenosis on coronary circulation. Circ Res 1962;11:727–735.
9. **Delin NA.** Systolic and diastolic coronary arterial blood flow in experimental valvular and supravalvular aortic stenosis. Scand J Thorac Cardiovasc Surg 1969 (suppl):1–54.
10. **Vinten-Johansen J, Weiss HR.** Oxygen consumption in subepicardial and subendocardial regions of the canine left ventricle: the effect of experimental acute valvular aortic stenosis. Circ Res 1980;46:139–145.
11. **Griggs DM Jr, Chen CC, Tchokoev VV.** Subendocardial anaerobic metabolism in experimental aortic stenosis. Am J Physiol 1973;224:607–612.
12. **Falsetti HL, Verani MS, Cramer JA, Carroll R.** Total, phasic, and regional myocardial blood flow in aortic stenosis. Am Heart J 1979;98:331–338.
13. **Attarian DE, Jones RN, Currie WD, Hill RC, Sink JD, Olsen CO, Chitwood WR Jr, Wechsler AS.** Characteristics of chronic left ventricular hypertrophy induced by subcoronary valvular aortic stenosis. I. Myocardial blood flow and metabolism. J Thorac Cardiovasc Surg 1981;81:382–388.
14. **Feldman RL, Nichols WW, Pepine CJ, Conti CR.** Hemodynamic significance of the length of a coronary arterial narrowing. Am J Cardiol 1978;41: 865–871.
15. **Feldman RL, Nichols WW, Pepine CJ, Conti CR.** Influence of aortic insufficiency on the hemodynamic significance of a coronary artery narrowing. Circulation 1979;60:259–268.
16. **Feldman RL, Nichols WW, Pepine CJ, Conetta DA, Conti CR.** The coronary hemodynamics of left main and branch coronary stenoses: the effects of reduction in stenosis diameter, stenosis length, and number of stenoses. J Thorac Cardiovasc Surg 1979;77:377–388.
17. **Malooly DA, Donald DE, Marshall HW, Wood EH.** Assessment of an indicator dilution technique for quantitating aortic regurgitation by electromagnetic flowmeter. Circ Res 1963;12:487–507.
18. **Heymann MA, Payne BD, Hoffman JIE, Rudolph AM.** Blood flow measurements with radionuclide-labeled particles. Prog Cardiovasc Dis 1977;20:55–79.
19. **Dole WP, Montville WJ, Bishop V.** Dependency of myocardial reactive hyperemia on coronary artery pressure in the dog. Am J Physiol 1981; 240:H709–H715.
20. **Pyle RL, Lowensohn HS, Khouri EM, Gregg DE, Patterson DF.** Left circumflex coronary artery hemodynamics in conscious dogs with congenital subaortic stenosis. Circ Res 1973;33:34–38.
21. **Carroll RJ, Falsetti HL.** Retrograde coronary artery flow in aortic valve disease. Circulation 1976;54:494–499.
22. **Rouleau J, Boerboom LE, Surjadhana A, Hoffman JIE.** The role of autoregulation and tissue diastolic pressures in the transmural distribution of left ventricular blood flow in anesthetized dogs. Circ Res 1979;45:804–815.
23. **Bache JB, Cobb FR, Greenfield JC Jr.** Effects of increased myocardial oxygen consumption on coronary reactive hyperemia in the awake dog. Circ Res 1973;33:588–596.
24. **Rembert JC, Kleinman LH, Fedor JM, Wechsler AS, Greenfeld JC Jr.** Myocardial blood flow distribution in concentric left ventricular hypertrophy. J Clin Invest 1978;62:379–386.
25. **Bache RJ, Vrobel TR, Ring WS, Emery RW, Andersen RW.** Regional myocardial blood flow during exercise in dogs with chronic left ventricular hypertrophy. Circ Res 1981;48:76–87.
26. **Mueller TM, Marcus ML, Kerber RE, Young JA, Barnes RW, Abboud FM.** Effect of renal hypertension and left ventricular hypertrophy on the coronary circulation in dogs. Circ Res 1978;42:543–549.
27. **O'Keefe DD, Hoffman JIE, Cheitlin R, O'Neill MJ, Allard JR, Shapkin E.** Coronary blood flow in experimental canine left ventricular hypertrophy. Circ Res 1978;43:43–51.
28. **Gould KL, Lipscomb K.** Effects of coronary stenoses on coronary flow reserve and resistance. Am J Cardiol 1974;34:48–55.
29. **Gould KL, Lipscomb K, Hamilton GW.** Physiologic basis for assessing critical coronary stenosis. Am J Cardiol 1974;33:87–94.

# Topographic Changes in the Left Ventricle After Experimentally Induced Myocardial Infarction in the Rat

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**The factors that determine the thickness of transmural myocardial infarcts are unknown. Therefore, the relation between the size and thickness of transmural infarcts in 67 rats 21 days after occlusion of the left main coronary artery was studied. On examination of histologic sections, infarct size was determined by planimetry and expressed as a percentage of the left ventricular (LV) area, and thickness was expressed as a percentage of noninfarcted ventricular septal wall thickness. The circumferential length of the infarcted ventricle was measured in millimeters, as well as the circumferential length of the noninfarcted ventricular septum. Septal wall thickness was similar in rats with transmural infarcts and in sham-operated rats. No significant correlation was observed between infarct size and thickness ($r = 0.10$) or between circumferential length of the infarct and infarct thickness ($r = 0.17$). However, large ($\geq 20\%$ of the left ventricle, $n = 37$) and small ($<20\%$ of the left ventricle, $n = 30$) infarcts which were similarly thin ($37 \pm 1\%$ and $34 \pm 2\%$ of septal wall thickness, respectively) affected LV topography differently. Large infarcts resulted in a 23% greater loss of myocardium ($p < 0.001$), greater expansion of the LV cavity ($18 \pm 9$ mm$^2$ compared with $14 \pm 1$ mm$^2$ in small infarcts, $p < 0.005$), and lengthening of the septal wall ($7.2 \pm 1.1$ mm and $6.7 \pm 1.0$ mm in large and small infarcts, respectively [$p < 0.05$], and $6.3 \pm 0.1$ mm in shams). Increase in cavity area and septal length in infarcted ventricles suggested a volume overload hypertrophy, which at 3 weeks was nonetheless inadequate to provide as much normal muscle as was present in sham-operated rats. In an additional 9 rats with subendocardial infarctions (involving $<75\%$ of the LV wall from endocardium to epicardium), the LV walls were thicker ($94 \pm 5\%$ of septal wall thickness, compared with $35 \pm 1\%$ for transmural infarcts, $p < 0.001$) and an inverse correlation was observed between infarct size and thickness. In conclusion, neither the size of a transmural infarct in rat nor the circumferential length of infarction determines the thickness of the infarct; however, infarct size does affect LV topography by increasing LV cavity area and the length of the noninfarcted septal wall. Subendocardial infarcts result in less myocardial thinning than do transmural infarcts.**

It is now appreciated that the left ventricular (LV) topography after myocardial infarction is not static but that this chamber may undergo varying degrees of thinning of the infarcted area, hypertrophy of the noninfarcted walls, and dilatation of the cavity. It has been suggested that thinning and expansion of the infarct may be associated with poor cardiac function, increased mortality rates, and ventricular wall rupture.[1,2] Little information is available concerning the determinants of these topographic changes. This study assesses whether the size (percentage of LV area) or circumferential length of a transmural infarct are important factors in determining the ultimate transmural thickness of the myocardial scar and in the development of hypertrophy of the remaining normal myocardium. Hearts in 76 rats were examined 21 days after coronary occlusion, a time when scar formation is complete.[3] In this animal model, the free anterior wall of the left ventricle is infarcted and the ventricular septum is spared.[3,4]

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## Methods

A retrospective analysis was performed on the hearts of 76 rats that had been subjected to coronary occlusion and 35 rats that had been subjected to a sham operation. Some rats had been used as nontreated controls in a previous study.[3] The operative techniques are described elsewhere,[3,4] but, briefly, thoracotomies were performed in male albino Sprague-Dawley rats, weighing 250 to 300 g, under ether anesthesia, and the left main coronary artery was occluded 1 to 2 mm from its origin. Other than anesthesia, these rats received no pharmacologic agents. The chests were closed and the rats allowed

to recover. Twenty-one days after occlusion, the rats were reanesthetized and the hearts were excised. Sham-operated rats, without coronary occlusion, also were killed at 21 days after thoracotomy and served as controls. After fixation in 10% phosphate-buffered formalin for ≥48 hours, the ventricles were cut into 4 transverse slices 2 to 2.5 mm thick in a plane parallel to the atrioventricular groove. The slices were dehydrated, cleared, embedded, and cut into sections 5 μm thick, which were mounted on 5 × 5 cm glass slides and stained with hematoxylin-eosin and Mallory's stain for connective tissue.

**Measurement of extent of infarction:** The 2 largest sections from each heart which traversed the infarct were projected onto a screen and the following 3 areas were traced separately on paper: (1) the area of the infarct, which was clearly visible as darkly staining blue tissue, (2) the area enclosed by the LV endocardial circumference, and (3) the area enclosed by the LV epicardial circumference (Fig. 1). The areas were measured by videoplanimetry as described elsewhere.[5] The LV area in each section was calculated by subtracting the area enclosed by the endocardial circumference (LV cavity area) from that enclosed by the epicardial circumference. The viable LV myocardial area was determined by subtracting the infarct area from the LV tissue area. The extent of the infarct within the endocardial and epicardial ventricular rings (infarct size) was calculated as the ratio of infarct area to LV area and expressed as a percentage. Values were first determined for each section; the 2 sections of each heart were then averaged. Therefore, in this report the term *infarct size* is used to represent the percentage by area of the LV rings which developed necrosis.

The extent of infarction was also analyzed in another fashion. The circumferential lengths of the infarcts and of the noninfarcted septal wall were measured approximately midway between endocardium and epicardium from enlarged projections and expressed in millimeters (Fig. 2). The values for the 2 sections of each heart were averaged.

**Measurement of anterior free wall thickness containing infarct:** The same 2 histologic sections utilized for the measurement of infarct size were projected onto a screen and magnified 12.5 times. The transmural thickness, from endocardium to epicardium, of the anterior free wall containing infarct and of the septal wall was measured every 1.6 mm along these circumferences (Fig. 2). The thickness was measured along an axis perpendicular to the endocardial and epicardial outlines. These multiple measurements of thickness were averaged to arrive at a single anterior free wall thickness and septal wall thickness for each section. LV free wall thickness containing infarct was expressed as a percentage of noninfarcted ventricular septal thickness. Values were first determined for each section, then averaged to obtain a single value for each heart.

The sham-operated rats were analyzed in a similar fashion. Since none had infarcts, an infarct size ratio could not be determined and only LV muscle area was calculated. In addition, rather than infarct thickness, the anterior LV free wall thickness was measured to allow calculation of the ratio of free wall to septal wall thickness.

**Statistical methods:** The data are presented as mean ± standard error of the mean and compared using Student's *t* test. To determine whether there was a correlation between infarct size and thickness (ratios), the family regression test was used to provide a coefficient of correlation.

## Results

In 67 rats that developed transmural myocardial infarcts (Table I), septal wall (noninfarcted tissue) thickness (2.6 ± 0.1 mm) was similar to that in 35 sham-operated rats (2.7 ± 0.1 mm, difference not significant [NS]). Transmural infarcts resulted in the following significant alterations in LV topography when compared with the sham-operated controls: (1) LV free wall thickness was markedly reduced in the infarcted region (ratio of infarcted to noninfarcted septal wall was 35 ± 1% compared with 112 ± 2% in sham-operated controls ($p < 0.001$); (2) total LV tissue area was reduced by approximately 30% (38 ± 1 $mm^2$ compared with 53 ± 1 $mm^2$, $p < 0.001$); viable LV myocardium was reduced by 42% (31 ± 1 $mm^2$ compared with 53 ± 1 $mm^2$ in shams, $p < 0.001$), (3) the area enclosed by the endocardial circumference was approximately 250% greater (16 ± 1 $mm^2$ in infarcted rats compared with 6 ± 0 $mm^2$

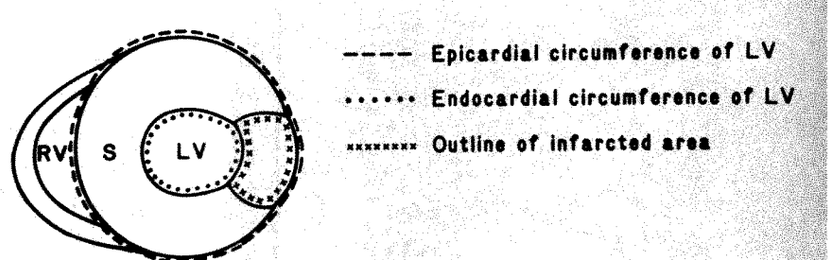



**FIGURE 1.** Schematic drawing of transverse section through the rat left ventricle showing epicardial and endocardial circumferences of the left ventricle and the outline of the area of infarction. LV = left ventricular cavity; RV = right ventricular cavity; S = ventricular septum.

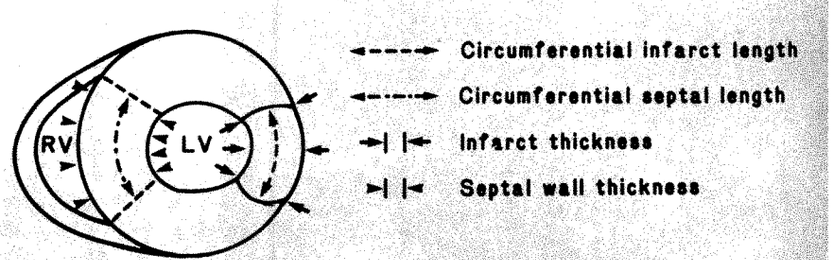



**FIGURE 2.** Schematic drawing of transverse section through rat left ventricle. Circumferential infarct and septal lengths are shown, as well as how thickness measurements of the infarct and noninfarcted septal wall were obtained. Abbreviations as in Figure 1.

**TABLE I Measurements in Myocardial Infarctions and Shams**

| | Rats (n) | Infarct Size (% LV Area) | Anterior Free Wall (Infarct) Thickness (% Septal Wall) | Infarct Circum Length (mm) | Septal Circum Length (mm) | Septal Wall Thickness (mm) | Area Enclosed by Endocardial Circum ($mm^2$) | Area Enclosed by Epicardial Circum ($mm^2$) | LV Tissue Area ($mm^2$) | Viable LV Myocardial Area ($mm^2$) |
|---|---|---|---|---|---|---|---|---|---|---|
| A. All transmural infarcts | 67 | 20 ± 1 | 35 ± 1 | 8.1 ± 2.3 | 7.0 ± 0.1 | 2.6 ± 0.1 | 16 ± 1 | 54 ± 1 | 38 ± 1 | 31 ± 1 |
| B. Sham-controls | 35 | NA | 112 ± 2 | NA | 6.3 ± 0.1 | 2.7 ± 0.1 | 6 ± 0 | 59 ± 1 | 53 ± 1 | 53 ± 1 |
| p Value (A versus B) | ... | ... | <0.001 | ... | <0.001 | NS | <0.001 | <0.005 | <0.001 | <0.001 |
| C. Large transmural infarcts (≥20% of left ventricle) | 37 | 25 ± 1 | 37 ± 1 | 9.6 ± 1.2 | 7.2 ± 1.1 | 2.6 ± 0.1 | 18 ± 1 | 53 ± 2 | 36 ± 1 | 27 ± 1 |
| D. Small transmural infarcts (<20% of left ventricle) | 30 | 14 ± 1 | 34 ± 2 | 6.4 ± 2.1 | 6.7 ± 1.0 | 2.7 ± 0.1 | 14 ± 1 | 54 ± 2 | 40 ± 1 | 35 ± 1 |
| p Value (C versus D) | | <0.001 | NS | <0.001 | <0.05 | NS | <0.005 | NS | <0.005 | <0.001 |
| E. Subendocardial infarctions | 9 | 16 ± 2 | 94 ± 5 | 9.9 ± 0.9 | 7.4 ± 0.3 | 2.5 ± 0.1 | 12 ± 2 | 57 ± 4 | 45 ± 3 | 38 ± 3 |
| p Value (E versus A) | | NS | <0.001 | NS | NS | NS | NS | NS | <.01 | <.01 |
| p Value (E versus B) | | ... | <0.001 | ... | <0.001 | NS | <0.001 | NS | <.001 | <.001 |

Circum = circumferential; NA = not applicable.

in sham-operated controls, $p < 0.001$); and (4) the circumferential length of the noninfarcted septal wall was greater (7.0 ± 0.1 mm in infarcted compared with 6.3 ± 0.1 mm in sham-operated rats, $p < 0.001$). No significant correlation was observed between infarct size and thickness ($r = 0.10$). No correlation was observed between the circumferential length of the infarct and infarct thickness ($r = 0.17$).

When the 67 rats with transmural infarcts were divided into 37 with large infarcts (≥20% of LV muscle area) and 30 with small infarcts (<20% of LV muscle area), the ratio of infarct to septal wall thickness was similar (37 ± 1% and 34 ± 2%, p = NS) (Fig. 3, top and center), and neither group showed a significant correlation between infarct size and infarct thickness ($r = 0.14$ for both groups). Large and small infarcts, however, differed in their effect on LV topography. Larger infarcts resulted in larger LV cavity areas (18 ± 1 $mm^2$ in large compared with 14 ± 1 $mm^2$ in small infarcts, $p < 0.005$), and greater circumferential length of the septal wall (7.2 ± 1.1 mm compared with 6.7 ± 1.0 mm in small infarcts, $p < 0.05$). The septal wall thickness was similar in both groups (2.6 ± 0.1 mm and 2.7 ± 0.1, $p > 0.2$). Viable LV myocardial area was less in larger compared with smaller transmural infarcts (27 ± 1 $mm^2$ and 35 ± 1 $mm^2$).

Nine rats had subendocardial myocardial infarcts involving <75% of the LV wall from endocardium to epicardium. In these rats, the thickness of the anterior LV free wall in the subendocardium was significantly greater (2.3 ± 0.1 mm) than in those with transmural infarcts (0.9 ± 0.0 mm, $p < 0.001$). Consequently, the ratio of the thickness of the infarcted LV free wall to that of the noninfarcted subendocardial wall in the 9 rats with subendocardial infarcts (94 ± 5%) (Fig. 3 bottom), was significantly greater than in the 67 rats with transmural infarcts (35 ± 1%, $p < 0.001$) (Table I). Unlike transmural infarcts, a moderate negative correlation was observed between subendocardial infarct size (percentage of LV area) and wall thickness (percentage of septal wall thickness) (wall thickness = −1.45 infarct size + 117.8, $r = -0.70$, $p < 0.05$). There was a weak negative correlation between circumferential length of infarction and anterior wall thickness in these 9 rats ($r = -0.41$). Subendocardial infarcts were associated with significant lengthening of the septal wall compared with the sham-controls. A significant increase was observed in LV cavity area compared with shams and a trend toward a smaller cavity area compared with transmural infarcts. Viable LV myocardial area was significantly greater in subendocardial (38 ± 3 $mm^2$) compared with transmural myocardial infarctions (31 ± 1 $mm^2$, $p < 0.01$). The thickness of the septal wall was similar between transmural and subendocardial infarcts (2.6 ± 0.1 mm and 2.5 ± 0.1 mm, p = NS), and the circumferential length of the infarcted LV wall was similar between transmural and subendocardial infarcts (8.1 ± 2.3 mm and 9.9 ± 0.9 mm, p = NS).

## Discussion

This study suggests that in transmural myocardial infarcts in the rat, LV free wall thickness containing infarct is not a function of the amount of myocardium

infarcted, measured as a percentage of LV area or measured circumferentially. A transmural infarct involving only a small portion of the LV free wall may be as thin as one which involves the entire LV free wall (Fig. 3, top and center). Twenty-one days after coronary occlusion in our rats, transmural infarcts were approximately one-third the thickness of the LV free wall in sham-operated rats.

Transmural infarcts did not cause an increase in thickness of the ventricular septal wall but did cause a circumferential lengthening of the septum, which was not infarcted in any animals. The lengthening of the septum without an increase in septal thickness suggests a volume overload-type of hypertrophy in the nonischemic myocardium, that is, an increase in cell length without an increase in cell diameter. Since the viable LV myocardium was smaller in area in infarcted ventricles compared with sham-operated animals, the degree of hypertrophy was inadequate at this time. Whether the muscle eventually hypertrophies to equal that in sham-operated animals remains to be determined. This increase in septal length coupled with an increase in LV cavity area initially may serve to compensate for depressed LV function through operation of the Frank-Starling mechanism. Long-term volume overload may result in deleterious changes within the myocardium. It remains to be determined whether agents which reduce preload (diuretics), LV cavity area (digitalis), or afterload (vasodilators) administered shortly after infarction would prevent cavity dilatation and the lengthening of the septum, and perhaps improve long-term LV function.

Although there was no difference in anterior free wall thickness or septal wall thickness between large and small transmural infarcts, the 2 did differ in some respects. Larger infarcts were associated with greater lengthening of the noninfarcted septum, a larger LV cavity area, and greater loss of viable myocardium compared with smaller infarcts. The profound increase in the size of the LV cavity in rats with large infarcts may be due to several factors including loss of tissue, volume overload hypertrophy of the viable septum, and the process of myocardial infarct "expansion." A recent study suggests that this latter process occurs within the first week of infarction in rats.[6]

Subendocardial infarcts resulted in anterior free LV walls which were only slightly thinned compared with the noninfarcted septal wall or the thickness of the LV free wall in sham-operated rats. In subendocardial, but not transmural infarcts, a correlation between infarct size and infarct wall thickness was observed. Subendocardial infarcts did not cause an increase in thickness of the noninfarcted ventricular septal wall, but, similar to transmural infarcts, did cause lengthening of the noninfarcted septum. Subendocardial infarcts resulted in an increase in LV cavity area compared with shams; the degree of dilatation was less than that observed with large transmural infarcts.

Our observations may be relevant to new clinical approaches in treating patients with evolving myocardial infarction. Recently, coronary reperfusion has been shown to be both safe and feasible in the early phases of acute myocardial infarction.[7,8] Previous animal studies have shown that early reperfusion may interrupt the normal evolution of an infarct and result in a subendocardial rather than a transmural infarct.[9] Thus, it is possible that early coronary reperfusion will result in less wall thinning and possibly less LV cavity dilatation.



**FIGURE 3.** Photomicrographs of transverse sections of rat left ventricles subjected to coronary occlusion for 21 days. **Top,** large transmural infarction of the entire free wall showing considerable thinning of the infarct compared with the septal wall. **Middle,** small transmural infarction of the anterior free wall showing an equivalent amount of infarct thinning compared with the top panel. **Bottom,** subendocardial infarction showing very little free wall thinning compared with the top and middle panels. (Approximate magnification ×5.6, reduced 50%.)

Recent studies in man[1,2] suggest that after infarction the necrotic tissue may thin and stretch. This process termed *infarct expansion* has clinical significance as it may predispose to increased congestive heart failure, ventricular rupture, and aneurysm formation. Therefore, measures which would limit such topographic alterations in the left ventricle might reduce the incidence of these complications of infarction.

The present study suggests that the primary process of infarction may cause long-term secondary changes within the noninfarcted tissue. Noninfarcted septal lengthening and cavity dilatation may have been a manifestation of volume overload hypertrophy. It is conceivable that some patients with so-called ischemic cardiomyopathy, who have had remote infarcts and then present with the clinical picture of congestive heart failure in the absence of active ischemia or new infarction, may have an element of LV dysfunction due to chronic volume overload.

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## References

1. **Hutchins GM, Bulkley BH.** Infarct expansion versus entention: two different complications of acute myocardial infarction. Am J Cardiol 1978;41: 1127–1132.
2. **Schuster EH, Bulkley BH.** Expansion of transmural myocardial infarction: a pathophysiologic factor in cardiac rupture. Circulation 1979;60:1532–1538.
3. **Maclean D, Fishbein MC, Braunwald E, Maroko PR.** Long-term preservation of ischemic myocardium after experimental coronary artery occlusion. J Clin Invest 1978;61:541–551.
4. **Kloner RA, Fishbein MC, Lew H, Maroko PR, Braunwald E.** Mummification of the infarcted myocardium by high dose corticosteroids. Circulation 1978;57:56–63.
5. **Roberts CS, Roberts WC.** Cross-sectional area of the proximal portions of the three major epicardial coronary arteries in 98 necropsy patients with different coronary events. Circulation 1980;62:953–959.
6. **Hochman JC, Bulkley BH.** Pathogenesis of left ventricular aneurysms: an experimental study in the rat model. Am J Cardiol 1982;50:83–88.
7. **Markis JE, Malagold M, Parker JA, Silverman KJ, Barry WH, Als AV, Paulin S, Grossman W, Braunwald E.** Myocardial salvage after intracoronary thrombolysis with streptokinase in acute myocardial infarction. N Engl J Med 1981;305:777–782.
8. **Phillips SJ, Kongtahworn C, Zeff RH, Benson PC, Iannone L, Brown T, Gordon DF.** Emergency coronary artery revascularization: a possible therapy for acute myocardial infarction. Circulation 1979;60:241–245.
9. **Reimer KA, Jennings RB.** The "wavefront phenomenon" of myocardial ischemic cell death. Lab Invest 1979;40:633–644.

# Scar Thinning Due to Ibuprofen Administration After Experimental Myocardial Infarction

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**Although much attention has been directed toward interventions which reduce myocardial infarct size, the effect of such agents on the healing phase of myocardial infarction is not well understood. The present study examines the effect of the nonsteroidal anti-inflammatory agent ibuprofen, previously demonstrated to be able to reduce infarct size, and of aspirin on the healing of experimentally produced myocardial infarcts. Thirty-nine anesthetized, open-chest dogs were subjected to proximal left anterior descending coronary artery occlusions for 6 weeks. Four groups of dogs were studied: (1) a control (untreated) group: (2) ibuprofen, 12.5 mg/kg intravenously 15 minutes and 6, 12, 18, and 24 hours after occlusion (high dose); (3) ibuprofen, 12.5 mg/kg intravenously 15 minutes and 3 hours after occlusion (low dose); (4) aspirin, 30 mg/kg intravenously 15 minutes and 3 hours after occlusion. The average thickness of the transmural scar and of the noninfarcted left ventricular wall was determined from multiple measurements of formalin-fixed left ventricular slices. The ratio of transmural scar to noninfarcted wall thickness was determined.**

**In control animals the ratio was 0.87 with only 1 of 15 animals having a ratio <0.60. High-dose ibuprofen-treated animals had an average ratio of 0.59 (difference not significant [NS] compared with control values), with 6 of 9 animals having a ratio <0.60 ($p < 0.02$ compared with control values). Low-dose ibuprofen-treated animals had an average ratio of 0.66 ($p < 0.05$ compared with control values), with 4 of 8 animals having a ratio <0.60 (p = NS compared with control values). In the aspirin-treated animals, the ratio was 0.88 (p = NS compared with control values), with 0 of 7 animals having a ratio <0.60 (p = NS compared with control values). Although 1 of 22 animals had ratios <0.60 in the control and aspirin groups, 10 of 17 had ratios <0.60 in the ibuprofen-treated groups ($p < 0.001$). Scars in treated animals did not differ from those in control animals histologically or by analysis of hydroxyproline content per unit weight. Thus, ibuprofen, a nonsteroidal anti-inflammatory agent which reduces infarct size, is shown to increase the incidence of scar thinning after myocardial infarction.**

Although many investigations have been directed toward the study of interventions which reduce myocardial infarct size,[1,2] there is little information concerning the effect of such interventions on the healing phase of myocardial infarctions. The healing phase has been viewed as a process which follows a predictable morphologic course.[3,4] That this may not be true was demonstrated when multiple doses of glucocorticoids were shown to retard the rate of wound healing,[5–8] cause myocardial scar thinning in animals subjected to coronary occlusion,[9] and possibly lead to formation of left ventricular aneurysms in patients with myocardial infarction.[10] We investigated the effect of 2 nonsteroidal anti-inflammatory agents on myocardial scar formation: ibuprofen, a cyclooxygenase inhibitor, which has been shown to reduce experimental myocardial infarct size[11,12] and aspirin, also a cyclooxygenase inhibitor but one which has no effect on infarct size,[13] and which is widely used for the treatment of postmyocardial infarction pericarditis.

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## Methods

**Experimental preparation:** Mongrel dogs of either sex weighing 10 to 26 kg were sedated with acepromazine maleate (1.0 mg/kg subcutaneously), anesthetized with pentobarbital (30 mg/kg intravenously), intubated, and placed on a Harvard respirator (Harvard Apparatus, Millis, Massachusetts). A thoracotomy was performed in the left fifth intercostal space under sterile conditions. The proximal left anterior descending coronary artery was dissected free from surrounding tissue and a silk ligature was placed around the artery in a location which resulted in epicardial cyanosis during temporary 15-second occlusions. Generally, the tie was immediately distal to the first diagonal branch, approximately 2 cm from the origin of the left anterior descending coronary artery.

**Experimental protocol:** After the administration of lidocaine (1.5 mg/kg intravenously), the left anterior descending coronary artery was permanently occluded with a silk ligature. A second similar dose of lidocaine was administered 5 minutes after coronary artery occlusion. The dogs were assigned at random, although not in equal numbers, into a control group or 1 of 3 treated groups. In the initial phase of the study, dogs were randomly assigned to control versus high-dose ibuprofen. Later in the study, low-dose ibuprofen and aspirin groups were added and dogs were randomized to control or one of these groups. Group 1 was the control group; these animals received 50 ml of saline solution infused over 5 minutes. Group 2, high-dose ibuprofen, received sodium ibuprofen (UpJohn, Kalamazoo, Michigan) (12.5 mg/kg intravenously) in 50 ml of normal saline solution infused over 5 minutes, at 15 minutes and 6, 12, 18, and 24 hours after occlusion (total dose 62.5 mg/kg). Group 3, low-dose ibuprofen, received sodium ibuprofen (12.5 mg/kg intravenously) in 50 ml of normal saline solution infused over 5 minutes, at 15 minutes and again 3 hours after occlusion (total dose 25 mg/kg). Group 4 received aspirin (30 mg/kg intravenously) in 50 ml of normal saline solution infused over 5 minutes, 15 minutes and 3 hours after occlusion. The thoracotomy wounds were closed, the air was evacuated from the thoracic cavity, and the animals were returned to the kennel. At the end of a 6-week period the animals were reanesthetized with thiamylal sodium (30 mg/kg intravenously) and killed with an overdose of potassium chloride, and the hearts were excised. Potassium chloride injection allowed all hearts to be arrested in diastole.

**Assessment of wall thickness:** After removal of the hearts, the left ventricle was isolated by dissecting away the right ventricle and structures above the atrioventricular ring, packed with gauze to prevent collapse of the left ventricular cavity, and allowed to fix in 10% neutral buffered formalin for 3 days. After fixation, the heart was sectioned into 3 to 5 mm transverse sections from base to apex. Measurements of the wall and scar thickness were made on each section as shown in Figure 1; all measurements were made along a line which passed through the center of the ventricular cavity. Normal wall thickness was measured in 3 to 5 widely separated locations and an average scar thickness was determined for each slice. In order to take into account variability in heart size, the thickness of the scar was compared with that of the noninfarcted left ventricular wall, and a ratio of scar thickness to noninfarcted wall thickness was determined. An average ratio in each dog was determined by averaging the ratios in each slice containing infarcted tissue.

**Analysis of infarct (scar) size:** After fixation, the heart was sectioned into 3 to 5 mm transverse sections from base to apex. The normal and infarcted myocardium was traced onto a clear acetate sheet placed over the slices. The extent of infarct (scar) at 6 weeks was determined by 2 methods. In the first method, area of the normal and infarcted (scar) myocardium was measured by planimetry and the area of infarcted tissue was expressed as a percentage of the area of the entire left ventricle. In the second method, endocardial circumference occupied by infarcted tissue and entire endocardial circumference of each of the slices was measured. The endocardial circumference occupied by the infarcted tissue was expressed as a percentage of the total endocardial length for all slices of the left ventricle.

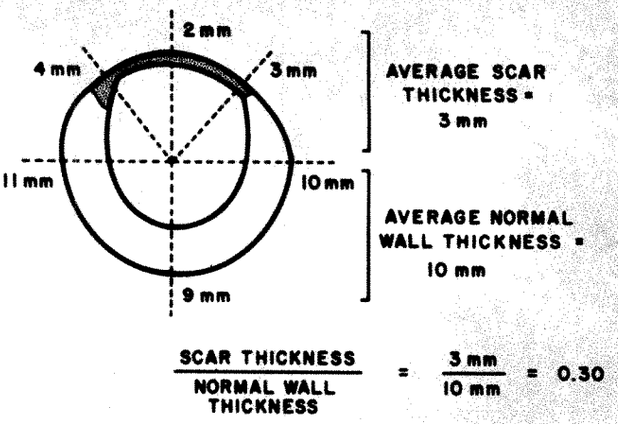



**FIGURE 1.** Schematic diagram demonstrating the technique used to determine the ratio of scar to normal wall thickness.

**Analysis of hydroxyproline content:** Tissue samples weighing between 100 and 200 mg were obtained from the endocardial and epicardial halves of normal and scarred myocardium and oven dried to a constant weight. Samples were then hydrolyzed in 6 N hydrochloric acid at 110°C for 12 hours. After neutralization and decolorization of the hydrolyzate, hydroxyproline was measured by the method of Newman and Logan.[14] Hydroxyproline concentration was expressed as $mg \cdot g^{-1}$ dry weight of the original sample.

**Histologic analysis:** Formalin-fixed transmural, transverse sections of noninfarcted and infarcted myocardium measuring 25 × 10 × 2 mm were conventionally processed and embedded in paraffin. Two to 3 sections, each stained with hematoxylin and eosin and Masson's trichrome, were examined from each heart by an investigator who had no knowledge of treatment. The following histologic features of necrosis and healing were assessed and graded from 0 (not present) to 4 (most prominent), as previously described,[3,4] with respect to (1) necrosis,

**TABLE 1 Fate of Experimental Animals**

| | | Ibuprofen | | | |
|---|---|---|---|---|---|
| | Control | High Dose | Low Dose | Aspirin | Total |
| Operated | 28 | 19 | 16 | 13 | 76 |
| Total excluded | 13 | 10 | 8 | 6 | 37 |
| Reasons for exclusion | | | | | |
| Early ventricular fibrillation (<30 min) | 5 | 1 | 3 | 3 | 12 |
| Sudden death (>30 minutes after coronary occlusion) | 7 | 8 | 4 | 0 | 19 |
| No transmural myocardial infarction | 1 | 1 | 1 | 3 | 6 |
| Animals (n) available for analysis | 15 | 9 | 8 | 7 | 39 |

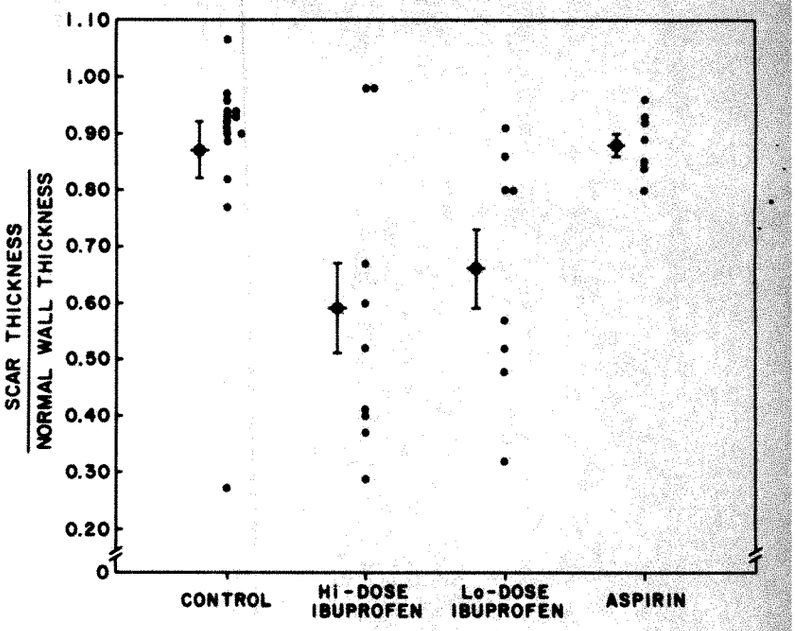



**FIGURE 2.** Ratio of scar thickness to normal wall thickness in control high-dose (Hi-Dose) ibuprofen, low-dose (Lo-Dose) ibuprofen, and aspirin treated dogs. **Closed circles** represent ratios for individual animals in all 4 groups. **Circles and bars** represent mean ± standard error of the mean for each group of animals.

(2) vascular proliferation, (3) neutrophil infiltration, (4) fibroblast deposition, and (5) collagen deposition. The histologic score for each animal was averaged over several slices.

**Statistical analysis:** Because the distribution of the ratios of scar to normal wall thickness was nonnormal (Fig. 2), we compared the 4 treatment groups by the Kruskal-Wallis test based on the ranks of the ratios in the combined sample for each group. Pairwise comparison of treatment groups were based on the Wilcoxon test, with p values interpreted using Bonferroni's method.[15]

We determined the number of dogs showing severe thinning, defined by the ratio of scar thickness to normal wall thickness of <0.6. The number 0.6 was chosen since a recent study showed that canine hearts with myocardial infarct expansion and thinning of the ventricular wall had a mean ratio of scar thickness to normal wall thickness of 0.66.[16] We compared exact p values by using Fisher's exact test and multiplied these p values by 4 to correct for multiple comparisons using Bonferroni's method.[15] Differences in hydroxyproline content between the 4 groups were determined by the analysis of variance.

Differences in infarct size among the 4 groups were determined by analysis of variance and Sheffe's method for multiple comparison. Differences in infarct size calculated as percent area and percent endocardial circumference within each group were determined by Student's $t$ test for paired data.

## Results

Seventy-six dogs were entered into the protocol. Ventricular fibrillation developed in 12 dogs within 30 minutes; these dogs were excluded. Nineteen dogs died suddenly after 30 minutes (range 12 hours to 12 days; mean 3.7) after occlusion. These 19 dogs consisted of 7 in the control group, 12 dogs in the ibuprofen-treated groups, and none in the aspirin-treated group (Table I). Six dogs did not have a transmural myocardial infarction at the time of examination and were excluded. This trend toward a lower incidence of sudden death in the aspirin-treated group was not statistically significant. None of these 19 dogs had evidence of myocardial rupture on postmortem examination. The remaining 39 dogs (51.3%) lived for 6 weeks and had transmural myocardial infarction; the observations in these animals form the basis for the reported results.

**Measurements of wall and scar thickness:** Figure 2 shows the distribution of the ratio of scar thickness to normal wall thickness in the 4 treated groups. The distributions were significantly different in the 4 treatment groups based on the Kruskal-Wallis test ($p < 0.02$). The median ratios of scar thickness to normal wall thickness were 0.92 (control), 0.68 (low-dose ibuprofen), 0.52 (high-dose ibuprofen), and 0.84 (aspirin). The control and low-dose ibuprofen groups were significantly different by the Wilcoxon test after correcting for multiplicity ($p < 0.05$). The control group did not significantly differ from high-dose ibuprofen group because 2 animals in the high-dose group had a thinning index higher than the median value in the control group. In the control group, only 1 of 15 dogs had a ratio of scar thickness to noninfarcted wall thickness of <0.60. In the high-dose ibuprofen–treated animals, 6 of 9 dogs exhibited severe wall thinning with ratios <0.60 ($p < 0.02$ compared with control values) (Fig. 3). However, only 4 of 8 animals in the low-dose ibuprofen group had severe thinning with ratios <0.60 ($p = 0.13$, NS compared with control values); the other 4 animals had little or no thinning and appeared similar to control animals (Fig. 3). The ratio in the aspirin-treated animals did not differ significantly from that in controls, and none of these dogs had ratios <0.60. The number of dogs in the aspirin-treated group with ratios <0.60 differed significantly from that in high-dose ($p < 0.05$) but not the low-dose ($p$ = NS) ibuprofen-treated animals. While 1 of 15 control animals had ratios <0.60, in pooled ibuprofen-treated animals 10 of 17 had thinning ratios <0.60 ($p$

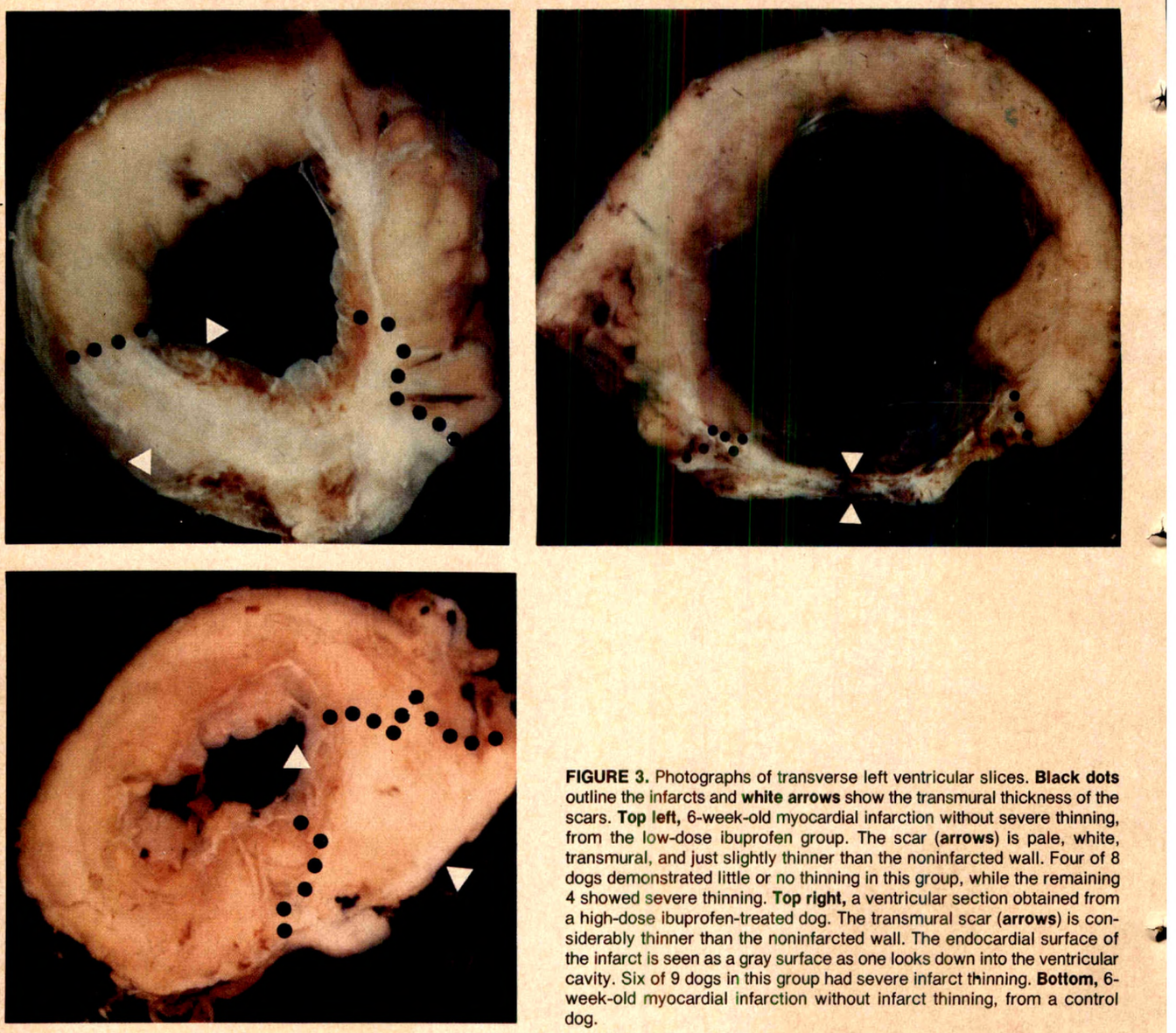


**FIGURE 3.** Photographs of transverse left ventricular slices. **Black dots** outline the infarcts and **white arrows** show the transmural thickness of the scars. **Top left,** 6-week-old myocardial infarction without severe thinning, from the low-dose ibuprofen group. The scar (**arrows**) is pale, white, transmural, and just slightly thinner than the noninfarcted wall. Four of 8 dogs demonstrated little or no thinning in this group, while the remaining 4 showed severe thinning. **Top right,** a ventricular section obtained from a high-dose ibuprofen-treated dog. The transmural scar (**arrows**) is considerably thinner than the noninfarcted wall. The endocardial surface of the infarct is seen as a gray surface as one looks down into the ventricular cavity. Six of 9 dogs in this group had severe infarct thinning. **Bottom,** 6-week-old myocardial infarction without infarct thinning, from a control dog.

<0.01). In combined aspirin and control dogs only 1 of 22 animals showed severe thinning, while in pooled ibuprofen-treated animals 10 of 17 showed severe thinning ($p < 0.001$). Absolute noninfarcted wall thickness was similar in all groups: (8.8 ± 0.4 mm in the low-dose ibuprofen group, 9.7 ± 0.2 mm in the high-dose ibuprofen group, 9.3 ± 0.2 mm in the control group, and 8.9 ± 0.2 mm in the aspirin-treated group; p = NS among groups).

**Myocardial infarct size:** Myocardial infarct size expressed as percent area of the left ventricle and as percent endocardial circumference of the left ventricle is shown in Table II. There were no significant differences among the 4 groups when infarct size was expressed as a percentage of either endocardial circumference or of left ventricular area. There was a trend toward larger circumferences of the scars in the high-dose ibuprofen-treated animals; this most likely represents infarct expansion.

In the control group, infarct size determined as percentage of endocardial circumference (14 ± 2) was not significantly different when compared with infarct size determined as percentage of area (12 ± 1). Similarly, in the aspirin group, infarct size as percentage of endocardial circumference (11 ± 2) was not significantly different when compared with infarct size as percentage of area (10 ± 1). Neither control nor aspirin-treated animals had myocardial scar thinning. However, in both high-dose and low-dose ibuprofen-treated animals, infarct size measured as a percentage of endocardial circumference was significantly larger than infarct size measured as a percentage of area. In the high-dose ibuprofen group, infarct size as a percentage of endocardial circumference was 21 ± 3 while infarct size as a percentage of area was 15 ± 1 ($p < 0.05$). In the low-dose ibuprofen group, infarct size as a percentage of endocardial circumference was 15 ± 2 while infarct size as a percentage of area was 12 ± 1 ($p < 0.05$). It is likely that

**TABLE II Myocardial Infarct (Scar) Size (Mean ± Standard Error of the Mean)**

| | Control | Ibuprofen | | |
|---|---|---|---|---|
| | | High Dose | Low Dose | Aspirin |
| Infarct (scar) size (% endocardial circumference) | 14 ± 2 | 21 ± 3* | 15 ± 2* | 11 ± 2 |
| Infarct (scar) size (% area) | 12 ± 1 | 15 ± 1 | 12 ± 1 | 10 ± 1 |

* Larger than infarct size determined as % area, $p < 0.05$. There were no significant differences among any of the 4 treatment groups by Sheffe's method for multiple comparison.

**TABLE III Hydroxyproline Concentration in Normal Myocardium and in Scar (μg/mg Dry Weight, Mean ± Standard Error of the Mean)**

| | Normal | | Scar | |
|---|---|---|---|---|
| | Epicardium | Endocardium | Epicardium | Endocardium |
| Control | 4.3 ± 0.2 | 3.9 ± 0.2 | 25.3 ± 1.2 | 35.6 ± 2.4 |
| High-dose ibuprofen | 4.5 ± 0.3 | 4.7 ± 0.7 | 30.9 ± 3.6 | 31.7 ± 3.3 |
| Low-dose ibuprofen | 4.9 ± 0.4 | 4.5 ± 0.5 | 33.0 ± 3.7 | 37.1 ± 2.7 |
| Aspirin | 4.6 ± 0.5 | 4.5 ± 0.2 | 29.0 ± 2.8 | 37.8 ± 4.3 |

the circumferential determination of infarct or scar size in the ibuprofen groups was greater than that determined by area because of circumferential expansion and transmural thinning of the infarcts.

**Hydroxyproline assay:** Normal subepicardial and subendocardial tissue, made up primarily of myocardial cells, contained very little collagen, as reflected in hydroxyproline concentration <5.0 μg/mg dry weight. Large quantities of collagen were contained within the subepicardium and subendocardium of the scar, with hydroxyproline concentrations five- to sixfold greater than in noninfarcted tissue (Table III). Treatment with ibuprofen or aspirin did not affect the hydroxyproline concentrations, either in scar or normal tissue.

**Histologic analysis:** As might be expected in 6-week-old scars, there was minimal necrosis and few if any neutrophils; however, extensive vascular proliferation, collagen, and fibroblasts were noted. The findings were similar in all 4 groups (Table IV).

## Discussion

Traditionally, myocardial healing has been viewed as an unalterable process that follows a predictable course. Observations on the effect of glucocorticoids on myocardial healing suggest that this may not always be the case. Glucocorticoids have been shown to reduce infarct size in animals with experimental infarcts,[17–23] to be useful in the treatment of complete heart block,[24,25] to decrease mortality after infarction,[26–28] and to control the pain of Dressler's syndrome in patients not responding to aspirin.[29,30] However, despite

**TABLE IV Histologic Summary (6 Weeks)**

| | Control (n = 15) | Ibuprofen | | |
|---|---|---|---|---|
| | | High Dose (n = 9) | Low Dose (n = 8) | Aspirin (n = 7) |
| Necrosis score (mean) | 0.2 | 0.1 | 0.4 | 0 |
| Neutrophil score (mean) | 0.1 | 0.6 | 0.5 | 0.1 |
| Vascularity score (mean) | 2.8 | 2.9 | 3.2 | 2.1 |
| Macrophage score (mean) | 1.8 | 1.7 | 1.9 | 1.9 |
| Fibroblast score (mean) | 2.8 | 3.0 | 3.4 | 2.4 |
| Collagen score (mean) | 3.5 | 3.4 | 3.5 | 3.3 |
| Dogs (n) with necrosis | 1 | 1 | 2 | 0 |
| Dogs (n) with neutrophils | 1 | 2 | 3 | 2 |

these suggested salutary effects, there is evidence that multiple doses of glucocorticoids adversely affect the healing of myocardial infarctions.[7–10] Administration of multiple doses of methylprednisolone delays removal of necrotic myocardium with reduced phagocytosis, resulting in large sheets of dead but architecturally preserved cells (mummification) and in scar thinning.[9,31] One or 2 doses of methylprednisolone administered early in the course of infarction does not appear to have this effect.[9] There is also suggestive evidence that glucocorticoids interfere with scar formation in patients with myocardial infarcts. In a patient treated with multiple doses of steroids for Dressler's syndrome,[10] the histology of the infarcted myocardium 63 days after myocardial infarction revealed persistent necrosis, inflammatory cells, and small foci of loose fibrous tissue, findings which one would expect 10 to 14 days after myocardial infarction.[3,4] An association between the development of postmyocardial infarction left ventricular aneurysms and treatment with glucocorticoids has also been noted.[10]

Ibuprofen, an agent which has been shown to reduce myocardial infarct size in some animal models,[11,12] initially appeared to be an attractive agent because of its low incidence of adverse effects. Because, like glucocorticoids, ibuprofen is an anti-inflammatory agent, we designed the present investigation to look for any adverse effects on healing. We chose dose schedules of ibuprofen which were similar to the doses which have previously been shown to reduce infarct size.[11] In the present study we chose to examine the healing process at its completed stage. Complete myocardial healing occurs in 3 weeks in the rat,[31] 6 to 8 weeks in humans,[3,4] and approximately 6 weeks in dogs,[32] the time selected for this study.

Marked scar thinning, defined as a ratio of the thickness of the scar to the uninvolved myocardium as <0.60, occurred in 10 of 17 (59%) animals treated with ibuprofen; however, the response was not uniform. In the control and aspirin-treated animals significant thinning was observed in only 1 of 22 dogs. However, both the collagen content, as reflected in the hydroxyproline concentration, and histologic examination results were similar in control and treated animals, suggesting that while the scars were thinner in ibuprofen-treated dogs, the scar tissue was qualitatively similar in all 4 groups. A recent study by Cannon et al[33] actually showed improved collagen deposition in rats

with experimental myocardial infarction treated with ibuprofen.

The mechanism of ibuprofen's action on myocardial healing is unknown. Because aspirin did not alter the healing process, the explanation for ibuprofen's action may lie in differences between aspirin and ibuprofen. Both drugs are nonsteroidal anti-inflammatory agents exhibiting analgesic, antipyretic, and anti-inflammatory properties. Both drugs inhibit prostaglandin biosynthesis in vitro and in vivo, presumably by inhibiting cyclooxygenase, the enzyme which generates the cyclic-endoperoxides from arachidonic acid. Aspirin and ibuprofen are approximately equipotent as to their effect on the inhibition of cyclooxygenase.[34] In addition to their effect on prostaglandin synthesis, these drugs exert inhibitory effects on a variety of enzymes and cellular systems such as oxidative phosphorylation, stabilization of protein, and enzyme release from lysosomes.[34] However, several differences exist in the mechanism of action of these 2 agents. Ibuprofen suppresses prostaglandin synthesis by competitive inhibition of cyclooxygenase activity, compared with the noncompetitive inhibition by aspirin. Aspirin has the unique property of acetylating the active site of cyclooxygenase. In platelets, which cannot synthesize protein, this action is irreversible for the life of the cell.[12] In a study on the effect of anti-inflammatory drugs on leukocyte migration in carrageenan-induced inflammation, it was shown that aspirin significantly increases leukocyte migration, while ibuprofen does not.[35] Ibuprofen is capable of affecting stimulated granulocytes by inhibiting their ability to aggregate, to generate radical oxygen, or to damage the endothelial wall. These effects were not demonstrated by aspirin.[36] It is not clear which if any of these mechanisms was responsible for the difference in scar thickness between ibuprofen and aspirin-treated animals in the present study.

Measurement of infarct or scar size after 6 weeks of healing would not necessarily correlate well with infarct size measured within a few hours to days of the myocardial infarction. Over a period of weeks it is possible and even likely that topographic changes in the infarct occur. In this study there were no significant differences in infarct size among groups when measured as a percentage of the area or circumference of the left ventricle. When comparing the size of infarct by the 2 different methods, percent area and percent endocardial circumference, we detected differences in both ibuprofen groups, while no difference in infarct size measured by these 2 methods was noted in either the control or aspirin groups. We believe a possible explanation for the above difference in infarct size when using the 2 methods is infarct expansion and thinning.

Infarct expansion was first recorded by Tennant and Wiggers[37] and the concept was developed by Bulkley, Hutchins, and co-workers.[16,38–40] They described infarct expansion as a thinning and dilatation of infarcted myocardium. Postmortem studies revealed that this process occurred not only in animals with experimentally induced infarcts[16] but also in approximately one third of patients with transmural myocardial infarctions.[39] If expansion occurred early in the ibuprofen groups, before the deposition of collagen, scar tissue would then be deposited onto a thinned and elongated area of necrotic myocardium. It is possible that the mechanical explanation for scar thinning is early infarct expansion. The similar hydroxyproline content in thinned and nonthinned scars is evidence that thinning or expansion does occur early, before collagen is deposited.

The clinical significance of our observations is not clear. Although reduction in the amount of infarcted tissue after coronary occlusion continues to be a major clinical concern, it is possible that the final prognosis of a patient with myocardial infarction depends also on the outcome of the healing phase.

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## References

1. **Kloner RA, Braunwald E.** Review: observations on experimental myocardial ischemia. Cardiovasc Res 1980;14:371–395.
2. **Rude RE, Muller JE, Braunwald E.** Efforts to limit the size of myocardial infarcts. Ann Intern Med 1981;95:736–761.
3. **Mallory GK, White PD, Salcedo-Salgar J.** The speed of healing of myocardial infarction: a study of the pathologic anatomy in 72 cases. Am Heart J 1939;18:647–671.
4. **Fishbein MC, MacLean D, Maroko PR.** The histopathologic evolution of myocardial infarction. Chest 1978;73:843–849.
5. **Howes EI, Plotz CM, Blunt JW, Ragan C.** Retardation of wound healing by cortisone. Surgery 1950;28:177–181.
6. **Sandberg N.** Time relationship between administration of cortisone and wound healing in rats. Acta Chir Scand 1964;127:446–455.
7. **Hepper NGG, Pruitt R, Donald DE, Edwards J.** The effect of cortisone on experimentally produced myocardial infarcts. Circulation 1955;11:742–748.
8. **Hepper NGG.** The effect of cortisone on healing of experimentally produced myocardial infarction in dogs [thesis]. Rochester, Minnesota: Mayo Graduate School of Medicine, University of Minnesota, 1954.
9. **MacLean D, Fishbein MC, Braunwald E, Maroko PR.** Long-term preservation of ischemic myocardium after experimental coronary artery occlusion. J Clin Invest 1978;61:541–551.
10. **Bulkley BH, Roberts WC.** Steroid therapy during acute myocardial infarction. A cause of delayed healing and of ventricular aneurysm. Am J Med 1974; 56:244–250.
11. **Jugdutt BI, Hutchins GM, Bulkley BH, Becker LC.** Salvage of ischemic myocardium by ibuprofen during infarction in the conscious dog. Am J Cardiol 1980;46:74–82.
12. **Romson JL, Bush LR, Haack DW, Lucchesi BR.** The beneficial effects of oral ibuprofen on coronary artery thrombosis and myocardial ischemia in the conscious dogs. J Pharmacol Exp Ther 1980;215:271–278.
13. **Ogletree ML, Lefer AM.** Influence of nonsteroidal antiinflammatory agents on myocardial ischemia in the cat. J Pharmacol Exp 1976;197:582–593.
14. **Newman RE, Logan MA.** Determination of hydroxyproline. J Biol Chem 1950;184:299–306.
15. **Miller RG.** Simultaneous Statistical Inference. New York: McGraw Hill, 1966.
16. **Eaton LW, Bulkley BH.** Expansion of acute myocardial infarction: its relationship to infarct morphology in a canine model. Circ Res 1981;49:80–88.
17. **Braunwald E, Maroko PR.** Effects of hyaluronidase and hydrocortisone on myocardial necrosis after coronary occlusion. Am J Cardiol 1976;37: 550–556.
18. **Libby P, Maroko PR, Bloor CM.** Reduction of experimental myocardial infarct size by corticosteroid administration. J Clin Invest 1973;52:599–607.
19. **Spath JA Jr, Lane DL, Lefer AM.** Protective action of methylprednisolone on the myocardium during experimental myocardial ischemia in the cat. Circ Res 1974;35:44–51.
20. **Morrison J, Reduto L, Pizzarello R, Geller K, Maley T, Gulotta S.** Modification of myocardial injury in man by corticosteroid administration. Circulation 1976;53:Suppl I:I-200–I-203.
21. **Shatney CH, MacCarter DJ, Lillehei RC.** Temporal factors in the reduction of myocardial infarct volume by methylprednisolone. Surgery 1976;80: 61–69.
22. **Masters TN, Harbold NB Jr, Hall DG, Jackson RD, Mullen DC, Daugherty HK, Robiesek F.** Beneficial metabolic effects of methylprednisolone sodium succinate in acute myocardial ischemia. Am J Cardiol 1976;37:557–563.
23. **Johnson AS, Scheinberg SR, Gerisch RA, Saltzstein HC.** Effect of cortisone on the size of experimentally produced myocardial infarcts. Circulation

1953;7:224–228.
24. **Prinzmetal M, Kennamer R.** Emergency treatment of cardiac arrhythmias. JAMA 1954;154:1049–1054.
25. **Dall JLC, Buchanan J.** Steroid therapy in heart block following myocardial infarction. Lancet 1962;2:8–12.
26. **Dall JLC, Peel AAF.** A trial of hydrocortisone in acute myocardial infarction. Lancet 1963;2:1097–1098.
27. **Gerisch RA, Compeau L.** Treatment of acute myocardial infarction in man with cortisone. Am J Cardiol 1958;1:535–536.
28. **Baroody NB, Baroody WG.** Adrenocorticosteroids in acute myocardial infarction. Am J Med Sci 1965;250:402–405.
29. **Dressler W.** A post-myocardial-infarction syndrome. Preliminary report of a complication resembling idiopathic, recurrent, benign pericarditis. JAMA 1956;160:1379–1383.
30. **Dressler W.** Management of pericarditis secondary to myocardial infarction. Prog Cardiovasc Dis 1960;3:134–140.
31. **Kloner RA, Fishbein MC, Lew H, Maroko PR, Braunwald E.** Mummification of the infarcted myocardium by high dose corticosteroids. Circulation 1978;57:56–63.
32. **Karsner HT, Dwyer JE Jr.** Studies in infarction IV. Experimental bland infarction of the myocardium, myocardial regeneration and cicatrization. J Med Res 1916;29:21–40.
33. **Cannon RO, Speir E, Bolli R.** Beneficial effects of ibuprofen on collagen after acute myocardial infarction. Circulation 1981;64:Suppl IV:IV-138.
34. **Flower JR.** Drugs which inhibit prostaglandin biosynthesis. Pharmacol Rev 1974;26:33–67.
35. **Higgs GA, Eakins KE, Mugridge KE, Moncada S, Vane JR.** The effects of non-steroid anti-inflammatory drugs on leukocyte migration in carrageenan-induced inflammation. Eur J Pharmacol 1980;66:81–86.
36. **Hammerschmidt DE, Flynn PJ, Vercellotti GM, Coppo PA, Jacob HS.** Synergy among agents inhibiting granulocyte responses to activated complement: a rationale for new therapeutic strategies in shock and myocardial infarction. Clin Res 1981;29:334A.
37. **Tennant R, Wiggers CJ.** The effect of coronary occlusion on myocardial contraction. Am J Physiol 1935;112:351–361.
38. **Hutchins GM, Bulkley BH.** Infarct expansion versus extension: two different complications of acute myocardial infarction. Am J Cardiol 1978;41:1127–1132.
39. **Eaton LW, Weiss JL, Bulkley BH, Garrison JB, Weisfeldt ML.** Regional cardiac dilatation after acute myocardial infarction: recognition by two-dimensional echocardiography. N Engl J Med 1979;300:57–62.
40. **Schuster EH, Bulkley BH.** Expansion of transmural myocardial infarction: a pathophysiologic factor in cardiac rupture. Circulation 1979;60:1532–1538.

# Effects of Flurbiprofen in Altering the Size of Myocardial Infarcts in Dogs: Reduction or Delay?

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**Anti-inflammatory agents such as flurbiprofen have been claimed to reduce infarct size in a number of models of coronary artery occlusion. However, several of the studies are controversial and also do not allow the critical distinction between reducing and delaying injury. In the present study, a closed chest method of coronary occlusion was used to generate small areas of regional myocardial ischemia in dogs. The method involved cannulation of the coronary ostium by way of the carotid artery and coronary embolization with 2.5 mm diameter beads. Flurbiprofen (1 mg/kg) was given immediately after occlusion and thereafter every 6 hours. Groups of dogs were subjected to either 6 or 24 hours of elapsed ischemia, after which time the hearts were removed and sectioned. Frozen-tissue slices were stained with triphenyl tetrazolium in order to delineate infarct size. After staining the tissue slices were subjected to autoradiography in which microspheres given immediately after occlusion were visualized to delineate the perfusion bed served by the occluded coronary artery (zone at risk). Risk zone to infarct size ratios for drug treated and control animals revealed that flurbiprofen treatment had no effect upon infarct size as determined 24 hours after occlusion. Despite significant residual coronary flow in the ischemic area, virtually all of the risk zone deteriorated to necrotic tissue. By contrast, after 6 hours of elapsed ischemia, infarct size was considerably reduced in the flurbiprofen-treated group. With the proviso that the drug might have affected only the sensitivity to tetrazolium staining, these results indicate that in severe ischemia, flurbiprofen can greatly delay but not prevent tissue necrosis.**

Numerous studies have aimed to identify interventions which protect the myocardium during ischemia.[1] Unfortunately, no single intervention has gained widespread acceptance and controversy persists, not only over the efficacy of certain drugs, but over the entire concept of infarct size reduction itself.[2,3,4] Most studies have failed to distinguish between a sustained *reduction* versus a *delay* of injury.[2] This problem is particularly relevant when infarct size is assessed soon (for example, 6 hours) after occlusion. Another major problem has been the variability of injury arising from a standard occlusion.[5] This variability makes it difficult to perform statistical comparisons in small groups of animals, even when the amount of salvage is great. The variability has recently been reduced by expressing the eventual zone of necrotic myocardium as a percentage of the zone at risk, that is, the perfusion field of the affected coronary artery.[6–13] Any discordance between the necrotic and the risk zones would reflect either tissue salvage or infarct extension.

The anti-inflammatory agents ibuprofen and flurbiprofen have been reported to be extremely potent in promoting salvage.[10,12,13] However, several methodologic aspects of these studies prevent a definitive claim of infarct size reduction.

In the present study, we endeavored to overcome these problems by developing a method of risk-zone analysis in which radiolabelled microspheres are used to mark the region at risk at the *time of occlusion* rather than after the infarct has evolved.[9] This is important since it is known that there are time-dependent changes in blood flow in and around infarcting tissue.[14,15] We visualized the flow distribution patterns and infarct zones by autoradiography of microspheres and tetrazolium staining of tissue sections either 6 or 24 hours after the onset of ischemia in both control and flurbiprofen-treated dogs.

## Methods

**Occlusion model:** Thirty-nine greyhounds of either sex, weighing 20 to 32 kg, were anesthetized with sodium pentobarbital 30 mg/kg intravenously. Each dog also received penicillin $1 \times 10^6$ $\mu$m intramuscularly at the time of an-

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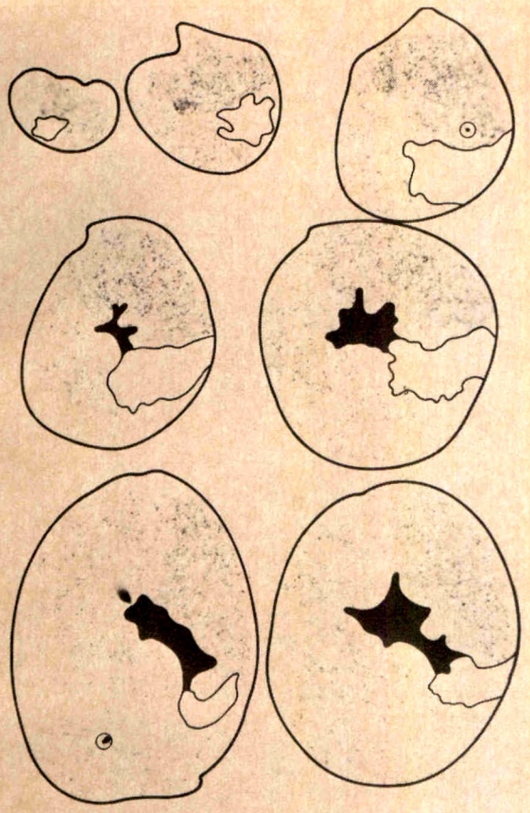


**FIGURE 1.** Typical autoradiogram matched to dye tracing. Autoradiogram of transverse myocardial sections; each small spot corresponds to a single cerium-141–labelled microsphere. Well-perfused, nonischemic areas exhibit a high density of spots, whereas the area served by the occluded coronary contains very few, thus producing a "window." The infarct is indicated by the **solid outline,** and the ventricular lumen is indicated by the **solid black area.**

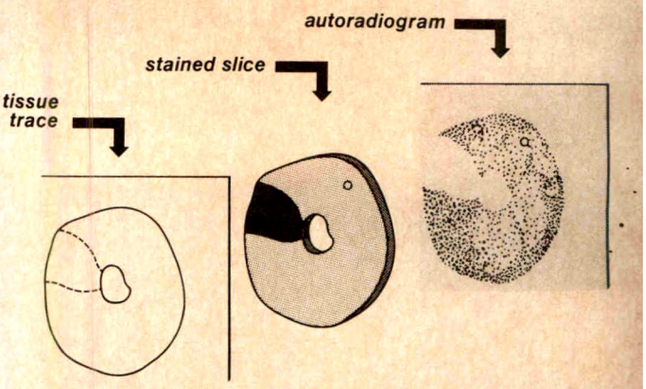



**FIGURE 2.** Delineation of risk zones and infarct zones. Each stained tissue section (**center**) reveals the zone of necrosis (**black shaded area**); the viable tetrazolium positive tissue adjacent to this and surrounding the lumen is the **lightly shaded area.** From this tissue section a tracing on acetate sheet (**left**) can be prepared to record the outline of the necrotic tissue. An autoradiogram (**right**) is also prepared from the tissue section and this indicates the risk zone (no silver grains). Superimposition of the acetate trace and autoradiogram allows the detection of tissue salvage or infarct extension relative to the original zone at risk.

esthetization. A femoral cutdown was performed and a catheter was placed in the femoral artery for withdrawal of a calibration blood sample during microsphere infusion. The left carotid artery was exposed by way of a midline cervical incision and a special cannula[16] with a pressure transducer attached to a side arm was inserted into the carotid artery. The cannula was then advanced into the coronary ostium. Insertion of the cannula was confirmed by a decrease in pressure from aortic to a distal coronary value of about 20 mm Hg. Two plastic beads, 2.5 mm in diameter, followed by 10 ml of saline solution each, were sequentially administered through the cannula so as to embolize the coronary vasculature. Our experience with this technique in open-chest dogs indicates that the beads lodge firmly in place and cause a permanent occlusion. The cannula was then withdrawn from the coronary ostium and advanced past the aortic valve into the left ventricle. Twenty million microspheres labelled with cerium-141 and having a 15 $\mu$m diameter were then injected into the left ventricle. Just before microsphere administration, a 90-second withdrawal of arterial blood from the femoral artery was initiated. This blood sample served as a reference for calculation of regional blood flow.[17] The cannula was then removed. Dogs were randomly divided into 4 groups: Group I was subjected to 24 hours of untreated ischemia. Group II experienced 24 hours of ischemia with flurbiprofen (1 mg/kg) after microspheres and thereafter every 6 hours. Group III was subjected to 6 hours of ischemia with no drug, and Group IV experienced 6 hours of ischemia with a single dose of flurbiprofen (1 mg/kg) immediately after microspheres. The cutdowns were then reconstructed and the animals returned to the recovery room. All surgery was carried out under sterile conditions. To prevent thrombus formation behind the emboli, heparin (5,000 units intravenously) was given every 6 hours. Blood samples for serum drug level determinations were also removed every 6 hours in 3 dogs. Heart rate, electrocardiograms, and blood pressure were recorded throughout each experiment.

**Tissue processing procedures:** At the end of each experimental period, dogs were reanesthetized and the chests opened. The hearts were removed, weighed, and frozen. Once frozen, the hearts were sliced transversely into 5 mm thick sections.

**Infarct visualization:** The slices were placed in 1% weight/volume triphenyl tetrazolium in phosphate buffer at 37°C and were incubated for 20 minutes.[18] The contour of the interface between stained and unstained tissue in each section was marked with a fine line of disulphine blue dye using an artist's brush. The necrotic tissue within the blue boundary line was painted with fluorescein dye. This step was necessary because the triphenyl tetrazolium stain, although plainly visible in warm tissue, was not readily seen once the tissue was frozen as was required in the subsequent step.

**Autoradiographic risk zone visualization:** After staining, tissue slices were placed on an acrylic sheet (20 × 25 × 4 mm). A layer of plastic film was then placed over the tissue slices and on top of this was placed a sheet of x-ray film (Kodak no screen NS-ZT). A second acrylic sheet was then placed on top of the x-ray film and the 2 sheets were held tightly together in a specially made wooden press. The press was placed in a light-proof box and stored at −20°C for a suitable exposure period. Fresh microspheres require a 24-hour exposure period. The exposure period must then be doubled for each half-life which elapses. The film was then removed and developed. Figure 1 shows a typical autoradiogram. Care was taken not to let the tissue, which was firmly frozen to the lower acrylic sheet, thaw. Just before developing, the exact position of the

**TABLE I Hemodynamic and Infarct Size Data for the 4 Groups**

| Experimental Group | Infarct Size ($cm^3$) | Infarct Size (% of Total Ventricle) | Risk-Zone Size ($cm^3$) | Risk-Zone Size (% of Total Ventricle) | Heart Rate (beats/min) | Blood Pressure (mm Hg) |
|---|---|---|---|---|---|---|
| Drug 24 hours | | | | | | |
| Mean | 7.98 | 3.35 | 9.38 | 3.89 | 194 | 180/149 |
| SEM | 1.76 | 0.83 | 1.94 | 0.92 | 9 | 10/8 |
| Control 24 hours | | | | | | |
| Mean | 12.22 | 4.86 | 13.51 | 5.26 | 207 | 169/131 |
| SEM | 2.10 | 0.81 | 2.60 | 0.88 | 15 | 10/7 |
| p | 0.110 | 0.139 | 0.157 | 0.19 | 0.184 | . . . |
| Drug 6 hours | | | | | | |
| Mean | 1.98 | 0.64 | 11.63 | 3.9 | 194 | 201/166 |
| SEM | 0.77 | 0.35 | 1.85 | 0.77 | 12 | 8/7 |
| Control 6 hours | | | | | | |
| Mean | 12.01 | 3.47 | 16.24 | 4.83 | 204 | 213/177 |
| SEM | 4.79 | 1.00 | 4.78 | 0.92 | 19 | 18/16 |
| p | 0.044 | 0.018 | 0.178 | 0.18 | 0.36 | . . . |

p = value of significance between drug and control experimental groups experiencing the same length of coronary occlusion; SEM = standard error of the mean.

tissue section in relation to the film was recorded by driving a sharpened probe through 2 predrilled holes in the acrylic sheets, thus piercing both the film and the tissue (Fig. 2).

**Data analysis:** A clear acetate sheet was placed over the slices and the outline of the sections, the ventricular lumens, the 2 register holes, and the infarcts were traced. This tracing could then be superimposed on the autoradiogram using the 2 register holes for precise alignment. The x-ray film revealed the blood flow pattern around the area served by the occluded artery and thus defined the risk zone. A tracing and its autoradiogram are shown in Figure 1. The cerium-141–labelled microspheres produce sharp spots in the autoradiogram. Studies with specially prepared phantoms indicate that the spots identify individual microspheres in the tissue and that there is little exposure of the film between the spots. This is unlike technetium-99m–labelled microspheres, which produce a blurred autoradiographic image.[7] In Figure 1, the field of the occluded artery is easily identifiable as the region of the autoradiogram which is devoid of spots. This is designated the region at risk. The volume of the region of risk was calculated by planimetering the area of the risk zone for each slice and multiplying this by the thickness (5.0 mm) of the section. The values for sequential slices were summed to provide the total volume for each heart. Using a similar procedure, the total volume of the necrotic tissue was calculated.

**Blood flow measurements:** In order to quantitate regional myocardial blood flow, 4 samples (approximately 250 mg each) were taken from each heart. Using the triphenyl tetrazolium stain as a guide, 2 samples were taken from the center of the infarcted region (1 from the epicardium and 1 from the endocardium) and 2 samples were taken from the epicardial and endocardial regions of normal myocardium well-remote from the infarct. The tissue samples were then weighed and counted using a gamma counter. Blood flow was then calculated.[17]

**Animal numbers and subdivision:** A total of 39 dogs were taken for study. Six of these died from aortic rupture or aneurysm (a hazard of the "blind" coronary cannulation procedure) before or just after embolization. An additional 2 dogs died from ventricular fibrillation soon after coronary embolization. Of the remaining animals, 17 were randomly assigned to the 24 hour series (8 drug treated and 9 controls); however, 1 of the latter group died 4 hours after embolization, probably as a result of injury sustained during cannulation or a lethal arrhythmia. Fourteen were assigned to the 6-hour series (7 drug-treated and 7 controls).

**TABLE II Bead Locations for the 4 Groups of Animals Studied**

| Group | First Branch LAD | Terminal LAD | First Branch Circumflex | Second Branch Circumflex | Terminal Circumflex |
|---|---|---|---|---|---|
| 24 hour control | 2 | 2 | 0 | 0 | 4 |
| 24 hour drug | 0 | 3 | 0 | 1 | 4 |
| 6 hour control | 0 | 5 | 0 | 0 | 2 |
| 6 hour drug | . . . | 3 | . . . | 2 | 2 |

The numbers refer to the incidence of an embolus in that location for each group. LAD = left anterior descending.

## Results

Two series of studies were carried out. In 1 series, infarct sizing and risk-zone analyses were carried out 24 hours after embolization. In the second series, measurements were taken after only 6 hours of ischemia. The second series was carried out: (1) to ascertain whether our procedures and results agreed with those reported by Darsee et al,[10,12] and (2) to attempt to dissociate delaying injury from reducing injury.

**Twenty-four hours of elapsed ischemia (absolute measurements):** Table I shows the infarct size and risk-zone size for the drug-treated and control animals in this group. In both groups relatively small infarcts were produced (about 5% of the ventricular mass) and, as is common with the dog heart, considerable variability between individuals was observed. In the drug-treated group, the mean infarct size was $7.98 \pm 1.76$ $cm^3$. In the control group, the value was $12.22 \pm 2.10$ $cm^3$. There was no statistically significant difference between these values ($p = 0.110$). Table I also reveals a wide individual variability in risk zone with a lower mean value in the drug group; however, as with infarct size, this difference was not statistically significant. Since the selection of animals for drug treatment or control was a random process undertaken before the size of the infarct was

known, then this difference between groups must reflect the large individual variation between animals and not the consequence of drug treatment. This point is reinforced by the range of the sizes of zones at risk (5.5 to 30.3 $cm^3$), which are, of course, determined before the administration of the drug. Table I also shows the heart rate and blood pressure measurements for the 2 groups. These figures serve to further confirm that only 1 population existed. Table II shows the locations of the emboli in these dogs.

The lefthand panel of Figure 3A shows the infarct sizes expressed as a fraction of region at risk. Note that the variability in the 2 groups is small and that no significant differences exist between the drug treatment and the control. One interesting observation was that, unlike in other reports,[11] we found no correlation between the percentage of salvage and the size of the risk zone. These variables are plotted for both groups in Figure 4. In Figure 5 the size of the infarct as a percentage of ventricular mass is plotted against the size of the region at risk as a percentage of the ventricular mass, as was done by Jugdutt et al.[13] Note that a linear relation results and that the lines project to the origin. Also, both drug and control points share the same line. The findings that both groups superimpose reinforce our view that there is no significant difference in infarct size between the 24-hour treatment and the 24-hour control group.

**Six hours of elapsed ischemia:** Although it appears that flurbiprofen cannot afford a sustained protection against ischemic injury, it may well delay injury, as indicated by the 6-hour study of Darsee et al.[10] The pre-

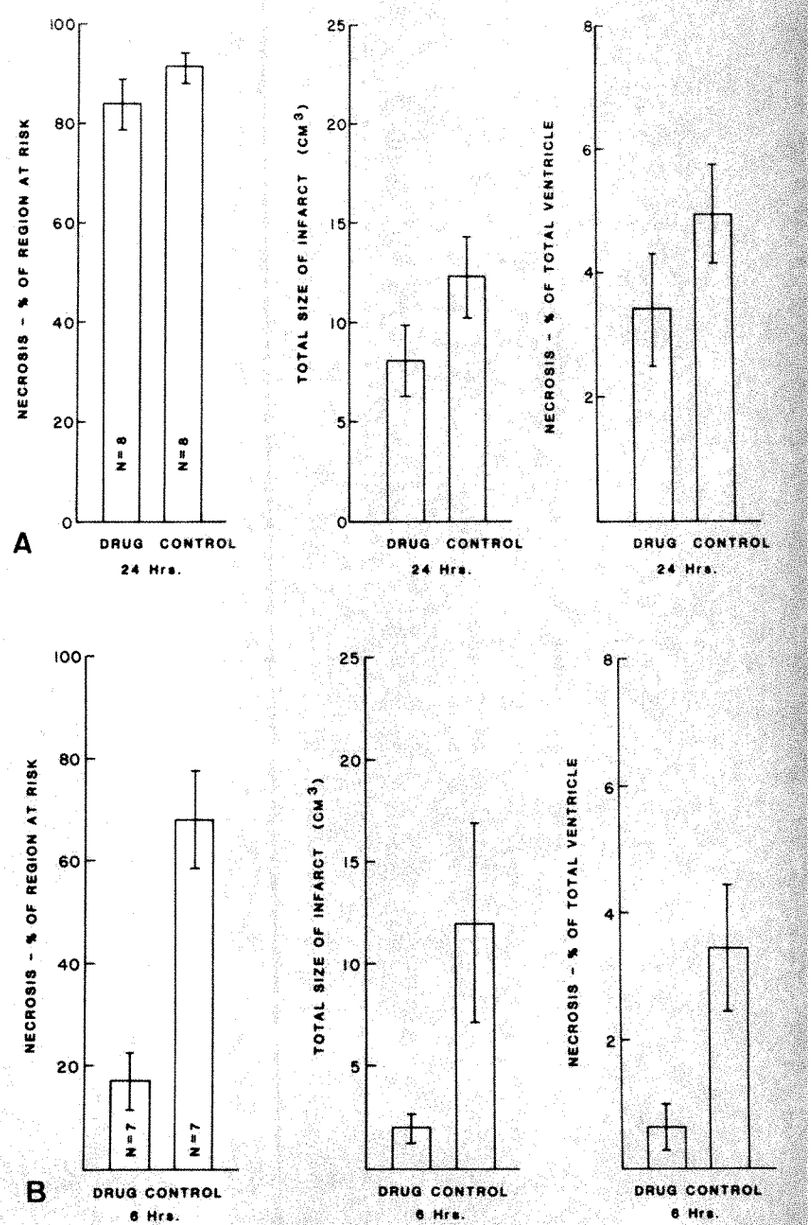



**FIGURE 3.** Three assessments of the effect of flurbiprofen on infarct size. **A: Left,** histogram showing the percentage of the region at risk, which deteriorates to necrosis after 24 hours of occlusion in control and drug-treated dogs. **Center,** histogram showing a comparison of absolute infarct size in these 2 groups. **Right,** histogram showing infarct size expressed as a percentage of the total ventricular weight for the 2 groups. **B:** Similar assessments carried out 6 hours after coronary artery occlusion. The number of dogs in each group is shown in the left-hand histograms and the standard error of the mean is indicated by the bars.

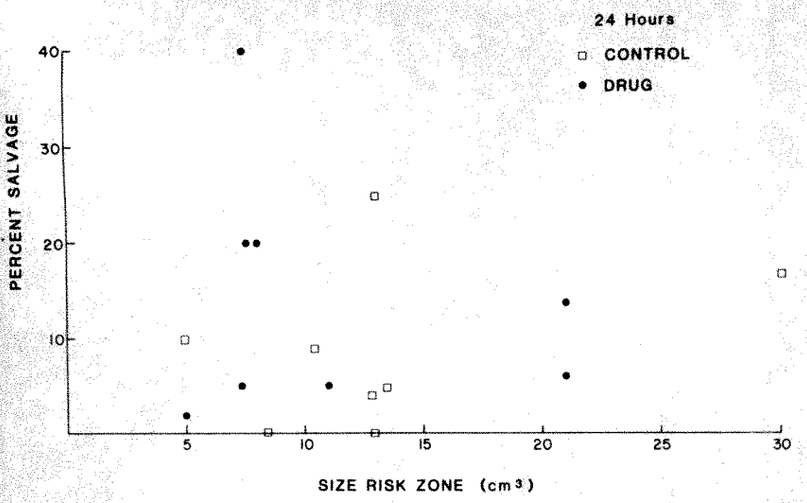



**FIGURE 4.** Tissue salvage and risk zone. The percentage of the risk zone which survived (percent salvage) after 24 hours of ischemia is plotted against the absolute size of the risk zone. No correlation was found, and the flurbiprofen-treated hearts (**closed circles**) do not segregate from the control hearts (**open squares**), suggesting that only 1 population exists.

ceding protocol was therefore repeated except that the duration of elapsed ischemia was reduced to 6 hours. The results (Table I and Fig. 3B) reveal that in the drug-treated groups the amount of necrotic tissue at 6 hours, as revealed by tetrazolium staining, was a much smaller fraction of the zone of risk than that seen at 24 hours (17.3 ± 5.7% versus 84.0 ± 5.0%). In the 6-hour control group this fraction (68.5 ± 9.2) was not significantly different from that in the 24-hour control group (91.8 ± 3.2%). The difference between the 6-hour drug-treated group and 6-hour control group, however, was highly significant when expressed as infarct mass ($p < 0.04$), percentage of ventricular mass ($p < 0.02$), or as a percentage of the risk region ($p < 0.002$). These results, which agree with those of Darsee et al,[10] indicate that flurbiprofen delays tissue injury as assessed by tetrazolium staining at 6 hours. By 24 hours, however, the drug-treated hearts had clearly sustained the same degree of injury as the control hearts.

When infarct size is expressed as a percentage of ventricular mass and plotted against risk-zone size, also expressed as a percentage of ventricular mass (Fig. 6), the drug treatment points and control points tend to segregate into 2 different populations. This contrasts with the 24-hour group (Fig. 5) and again supports the observation that at 6 hours infarct size was smaller in the drug-treated group.

**Blood flow studies:** In order to ascertain whether all of the 4 groups had experienced equivalent levels of ischemia, tissue samples were removed from the center of the ischemic zones and the microsphere content was determined. This allowed an accurate determination of

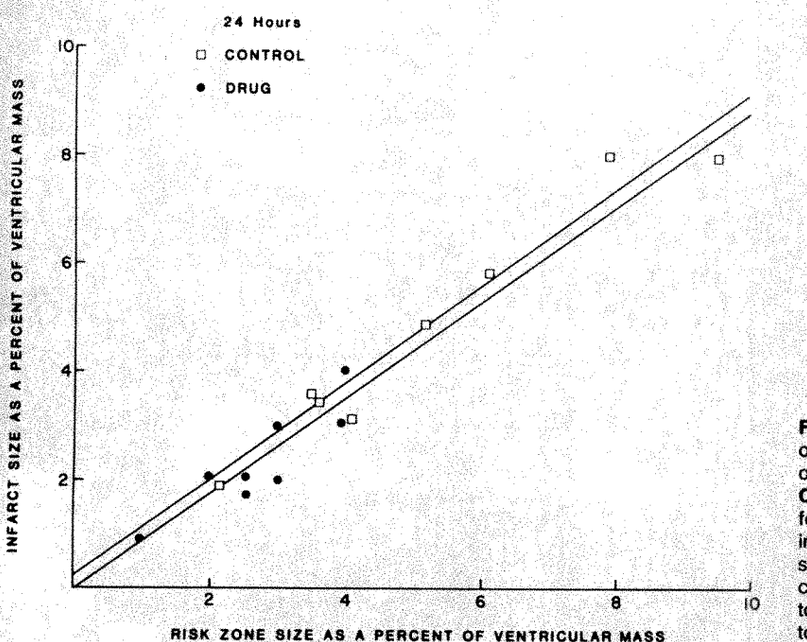



**FIGURE 5.** Relation between infarct size as a percentage of ventricular mass and risk-zone size as a percentage of ventricular mass after 24 hours of elapsed ischemia. **Open squares,** control hearts; **closed circles,** flurbiprofen-treated hearts. Note that the 2 groups superimpose, indicating that there was no significant change in infarct size between the 24-hour drug-treated and 24-hour control groups. The **lines** represent the least-squares fit to the data points in each group. The **upper line** belongs to the control group.

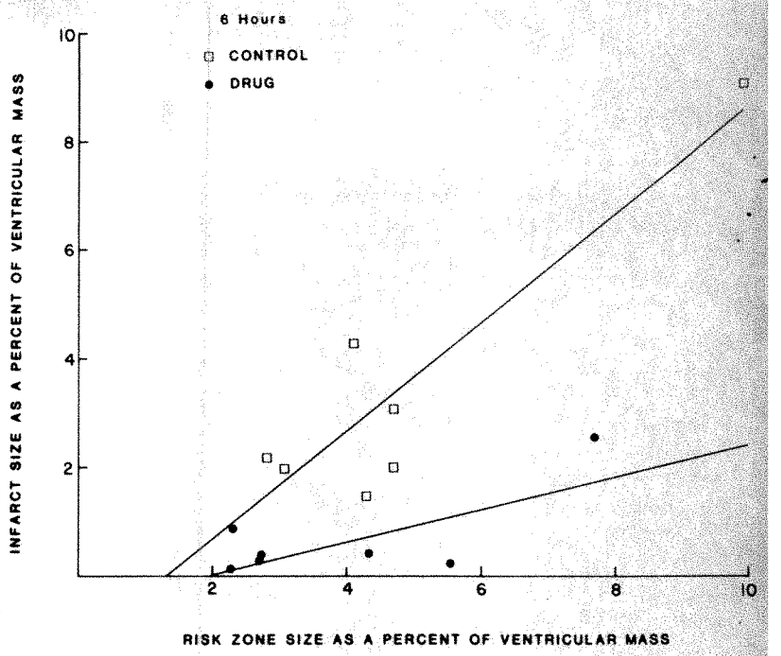



**FIGURE 6.** Relation between infarct size as a percentage of the ventricular mass and risk-zone size as a percentage of ventricular mass after 6 hours of elapsed ischemia. **Open squares,** control hearts; **closed circles,** flurbiprofen-treated hearts. Note that in comparison with Figure 5, the experimental groups segregate into 2 different populations, indicating that at 6 hours the infarct size was smaller as a result of drug treatment. Lines are fit by the least-squares method.

blood flow to these regions. The results showed a surprising degree of variability. All of the ischemic tissue experienced a reduction of flow by at least 75% and the residual flow tended to be higher in the subepicardium than the subendocardium, although these differences did not achieve statistical significance, probably due to the scatter in the data. No differences were seen between the 4 groups, indicating that they were indeed equivalent.

## Discussion

The results indicate that while flurbiprofen was able to limit the size of an infarct 6 hours after coronary artery occlusion in the dog, it was unable to sustain this protection. These results do not necessarily deny the ability of drugs to protect ischemic tissue. Our results suggest that the anti-inflammatory drug was capable of a remarkable delay in apparent tissue injury. If this delay can be equated with a delay in the onset of irreversible injury, then such a delay may be useful in providing additional time to permit secondary interventions such as thrombolysis or coronary artery surgery to be implemented. We must, however, distinguish whether the drug extends the duration of reversible injury or whether it simply alters the responsiveness of tissue to tetrazolium staining. This caution is particularly relevant to anti-inflammatory drugs such as flurbiprofen[19] which might influence permeability to intracellular proteins.[20]

Although our findings (not our conclusions) are in accord with those of Darsee et al,[10,12] our results appear to be at variance with those of Jugdutt et al,[13] who reported positive effects with ibuprofen as long as 48 hours after the onset of ischemia. To resolve this apparent conflict, a number of points of protocol should be considered. Jugdutt et al visualized the zone at risk at the *end* of the 48-hour occlusion period. Unfortunately, the distribution of flow in and around an infarct changes during the first 24 hours.[14,15,21] Thus, if the drug had any effect upon blood flow patterns around the ischemic zone, it might be incorrectly interpreted as a change in infarct size. In our study, the risk zone was marked with radioactive microspheres *immediately after* coronary occlusion and *before* the drug was administered. The only possible effect the drug could have had on the delineation of the risk zone would be to have induced some loss of microspheres from the myocardium over the 24-hour ischemic period. Although small (9 $\mu$m) microspheres can be lost during extended periods of ischemia and although this loss may be augmented by the process of necrosis,[22] we used 15 $\mu$m spheres for the present study and their loss, even from necrotic myocardium, appears limited.[23]

Other differences between our study and that of Jugdutt et al are related to the surgical procedures used. Jugdutt used an occluder which was placed on the circumflex artery several days before occlusion and in the process of implanting the occluder, sympathetic nerves to the region supplied by that vessel were likely to be disrupted. Jones et al[24] have reported that sympathectomy stimulates collateral growth; thus, it is conceivable that the hearts in the Jugdutt et al study may have developed a better collateral circulation than those used in our study. One difference in protocol from our model is that our study required the use of anesthesia, whereas Jugdutt et al were able to induce occlusion in the conscious animal. The possibility that the hypertension and the tachycardia associated with the anesthesia might have augmented the extent of necrosis cannot be ruled out.

One additional difference is related to the size of the ischemic bed under study. We induced ischemia by introducing a plastic bead into a coronary artery, thereby generating a relatively small area of ischemia compared

with those of others.[10,12,13] In our study only about 5% of the ventricular mass was rendered ischemic. Since Schaper et al[25] have suggested that collateral flow to the center of an ischemic region is inversely related to the mass of that region, it can be argued that our smaller risk zones should actually improve the chances of a beneficial drug action. Furthermore, if there is a salvageable zone of tissue of finite thickness at the periphery of an ischemic region, then the ratio of salvageable tissue at the periphery to condemned tissue at the core should be increased as the absolute mass of the ischemic zone gets smaller.[2]

The autoradiograms obtained in these studies revealed a sharp interface between well-perfused tissue and ischemic tissue. Some investigators believe[26,27] that progressive gradients of flow characterize the transition between normal and ischemic tissue. Other groups, including ourselves,[28–31] believe that the interface is sharp. The findings in the present study further reinforce this view.

In studies by others,[7,10–13] tissue salvage has been demonstrated at the lateral borders of the infarct. In the present study, we also observed a lateral region of tissue salvage at 6 hours. Although this zone had disappeared by 24 hours, it does support the view that certain areas within the infarct may be more amenable to protection. We observed that if any viable tissue remains within the risk zone after 24 hours, the tissue inevitably is subepicardial in location. This can probably be attributed to greater collateral flow to the subepicardium than to the subendocardium. In the present study, microsphere counting suggested a transmural gradient of collateral flow, which would agree with the previous reports.[15,32]

Since about 10% of the subepicardium survived in these hearts, any long-term beneficial drug effect would have been expected to have increased the size of that zone. In a previous study[33] from this laboratory, using a similar procedure for estimating changes in infarct size, propranolol increased the amount of epicardial salvage from 15 to nearly 40% of the risk zone after 24 hours of ischemia. Thus, some interventions do promote salvage in this model.

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## References

1. **Hillis DL, Braunwald E.** Myocardial ischemia. Engl J Med 1977;296: 971–978.
2. **Hearse DJ, Yellon DM.** The "border zone" in evolving myocardial infarction: controversy or confusion? Am J Cardiol 1981;47:1321–1334.
3. **Helfant RH, Banka VS, Bodenheim MM.** Perplexities and controversies concerning the myocardial infarction border zone and its salvage. Am J Cardiol 1978;41:345–347.
4. **Factor SM, Sonnenblick EH, Kirk ES.** The histologic border zone of acute myocardial infarction—islands or peninsulas? Am J Pathol 1978;92: 111–124.
5. **Bishop SP, White FC, Bloor CM.** Regional myocardial blood flow during acute myocardial infarction in the conscious dog. Circ Res 1976;38: 429–438.
6. **Lowe JE, Reimer KA, Jennings RB.** Experimental infarct size as a function of the amount of myocardium at risk. Am J Pathol 1978;90:363–376.
7. **DeBoer LWV, Strauss HW, Kloner RA, Rude RE, David RF, Braunwald E, Maroko PR.** Autoradiography with $^{99}$Tc labelled albumin microspheres, a new method for delineation of the ischemic tissue at risk of infarction: demonstration of the protective effect of verapamil (abstr). Am J Cardiol 1980;45:485.
8. **Schaper W, Hofmann M, Muller KD, Genth K, Carl M.** Experimental occlusion of two small coronary arteries in the same heart. A new validation method for infarct size manipulation. Basic Res Cardiol 1979;74:224–229.
9. **Downey JM, Wilkerson RD, Munch DF.** An autoradiographic method for prediction of infarct size in dogs (abstr). Circulation 1979; 60:Suppl II:II-95.
10. **Darsee JR, Kloner RA, Braunwald E.** Demonstration of lateral and epicardial border zone salvage by flurbiprofen and *in vivo* method for assessing myocardium at risk. Circulation 1981;63:29–35.
11. **Jugdutt BI, Hutchins GM, Bulkley BH, Becker LC.** Myocardial infarction in the conscious dog: three dimensional mapping of infarct, collateral and region at risk. Circulation 1979;60:1141–1150.
12. **Darsee JR, Kloner RA.** Dependency of location of salvageable myocardium on type of intervention. Am J Cardiol 1981;48:702–709.
13. **Jugdutt BI, Hutchins BM, Bulkley BH, Becker LC.** Salvage of ischemic myocardium by ibuprofen during infarction in the conscious dog. Am J Cardiol 1980;46:74–82.
14. **Cobb FR, Bache RJ, Rivas F, Greenfield JC.** Local effects of acute cellular injury on regional myocardial blood flow. J Clin Invest 1976;57:1359–1368.
15. **Marcus ML, Kerber RE, Ehrhardt J, Abboud FM.** Effects of time on volume and distribution of collateral flow. Am J Physiol 1976;230:297–285.
16. **Chagrasulis RW, Downey JM.** Selective coronary embolization in closed chest dogs. Am J Physiol 1977;233:H335–H337.
17. **Rudolph AM, Heyman AM.** The circulation of the fetus in utero. Circ Res 1967;21:163–184.
18. **Sandritter W, Jestädt T.** Triphenyl tetrazolium chloride (TTC) als reduktionsindikator zur makroskopischen diagnose des frischen herzinfarktes. Verh Dtsch Ges Pathol 1958;41:165–171.
19. **Simon LS, Mills JA.** Nonsteroidal antiinflammatory drugs. N Engl J Med 1980;302:1179–1185, 1237–1243.
20. **Hearse DJ, Humphrey SM.** Enzyme release during myocardial anoxia: a study of metabolic protection. J Mol Cell Cardiol 1975;7:463–482.
21. **Hirzel HO, Nelson GR, Sonnenblick EH, Kirk ES.** Redistribution of collateral blood flow from necrotic to surviving myocardium following coronary occlusion in the dog. Circ Res 1976;39:214–222.
22. **Jugdutt BI, Hutchins GM, Bulkley BH, Becker LC.** The loss of radioactive microspheres from canine necrotic myocardium. Circ Res 1979;45: 746–756.
23. **Capurro NL, Goldstein RE, Aamodt R, Smith HF, Epstein SE.** Loss of microspheres from ischemic canine cardiac tissue. Circ Res 1979;44: 223–227.
24. **Jones CE, Scheel KW.** Reduced coronary collateral resistances after chronic ventricular sympathectomy. Am J Physiol 1980;238:H196–H201.
25. **Schaper W.** Experimental coronary artery occlusion. The determinants of collateral blood flow in acute coronary occlusion. Basic Res Cardiol 1978;73:584–594.
26. **Volkonas PS, Malsky PM, Paul SJ, Robbins SL, Hood WB.** Radioautoradiographic studies in experimental myocardial infarction: profiles of ischemic blood flow and quantification of infarct size in relation to magnitude of ischemic zone. Am J Cardiol 1978;42:67–75.
27. **Linder E.** Measurement of normal and collateral coronary blood flow by closed-arterial and intramyocardial injection of krypton$^{85}$ and xenon$^{133}$. Acta Physiol Scand 1966;68:Suppl 272:5–31.
28. **Hirzel HO, Sonnenblick EH, Kirk ES.** Absence of a lateral border zone of intermediate creatine phosphokinase depletion surrounding a central infarct 24 hours after acute coronary occlusions in the dog. Circ Res 1977; 41: 673–683.
29. **Simson MB, Harden W, Barlow C, Harken AH.** Visualization of the distance between perfusion and anoxia along an ischemic border. Circulation 1979;60:1151–1155.
30. **Okun EM, Factor SM, Kirk ES.** End-capillary loops in the heart: an explanation for discrete myocardial infarctions without border zones. Science 1979;206:565–567.
31. **Yellon DM, Hearse DJ, Crome R, Grannell J, Wyse RKH.** Characterization of the lateral interface between normal and ischemic tissue in the canine heart during evolving myocardial infarction. Am J Cardiol 1981;47: 1233–1239.
32. **Russell RE, Chagrasulis RW, Downey JM.** Inhibitory effect of cardiac contraction on coronary collateral blood flow. Am J Physiol 1977;232: H541–H546.
33. **Downey JM, Wilkerson RD, Munch DF.** Inability of isoproterenol or propranolol to alter the lateral dimensions of experimentally induced myocardial infarcts. Basic Res Cardiol 1982;77:486–498.

# Effects of Reduced Coronary Flow on Thallium-201 Accumulation and Release in an In Vitro Rat Heart Preparation

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**To study the relation between myocardial thallium-201 (Tl-201) uptake, Tl-201 release, and reduced coronary flow, isolated Langendorff rat hearts (n = 8) were perfused for 3 hours at constant flows ranging from physiologic (12 ml/min) to severely ischemic (1.5 ml/min); thallium activity was monitored with a scintillation probe. Each heart was perfused for 1 hour with thallium buffer, followed by 2 hours with thallium-free buffer at the same flow rate. Accumulation curves for all 4 flows were monoexponential. However, release curves during the 2 hours of washout with thallium-free buffer demonstrated a biexponential configuration. The early fast release component decreased with reductions in coronary flow, and the later slow release component did not vary significantly with flow. These data show that thallium clearance has at least 2 components: a rapid (possibly extracellular) component related to coronary flow and a slow (possibly intracellular) component independent of coronary flow. These findings should be useful in providing a better understanding of thallium redistribution observed clinically.**

Despite the widespread use of thallium-201 (Tl-201) myocardial imaging, confusion still exists about the kinetic features of Tl-201 release from normal and ischemic myocardium.[1] Yet, the determination of relative myocardial Tl-201 distribution and its change over time is being carried out clinically to evaluate patients with possible coronary artery disease.[2–5] Change in Tl-201 distribution over time after intravenous administration is related both to uptake and release in myocardial tissue. Up to 90% of Tl-201 is extracted during passage through the myocardium.[6] The initial distribution of Tl-201 is related to regional blood flow to viable myocardium.[2] Release of Tl-201 from nonischemic myocardium is directly related to the change in its concentration in the blood after an intravenous injection.[7] However, the impact of ischemia on the release of Tl-201 is not well-understood.

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Gewirtz et al[8] demonstrated no change in the rate of Tl-201 release from ischemic versus nonischemic left ventricular myocardium, using myocardial biopsy evaluation of Tl-201 activity in the canine left anterior descending coronary artery occlusion model after intravenous administration of Tl-201. In a later study, Gewirtz et al[9] substantiated this finding in the same model by evaluating arteriovenous Tl-201 differences in ischemic and nonischemic regions. Recently, Grunwald et al[1] studied the impact of ischemia on myocardial Tl-201 release after administration of an intracoronary dose in order to evaluate its release without the complicating effects of Tl-201 in the systemic arterial blood, as would be the case clinically. These investigators found a slowing of Tl-201 release as blood flow was reduced, which seemed paradoxical, considering the similar behavior of thallium and potassium ions in biological systems[10–14] and the known release of potassium which occurs during myocardial ischemic insult.[15–17]

The present study uses isolated retrograde perfused rat hearts to clarify further the impact of ischemia on myocardial Tl-201 uptake and release. Hearts are perfused at constant flow rates for the 3-hour duration of each experiment. The flow rates vary from 12 ml/min (control) to hypoperfusion rates of 6, 3, or 1.5 ml/min. During the first hour of perfusion, a thallium-labelled buffer was used. In this model, Tl-201 accumulation and retention in the myocardium may be studied without

the complications due to the uptake and release of Tl-201 by other organs or by neurohumoral factors exogenous to the heart. Thus, by monitoring the global retention of Tl-201 by the myocardium during the 2-hour release period, the influence of reduced coronary flow could be investigated. Observations of Tl-201 accumulation and release patterns in this model should be useful in understanding Tl-201 release patterns as they might be measured in patients using new quantitative approaches.[18,19]

## Methods

Male Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, Massachusetts) weighing 320 to 370 g were anesthetized with Nembutal® (10 mg/100 g) administered intraperitoneally. Hearts were isolated and the coronary arteries were perfused retrogradely from the aorta using a modified Langendorff technique (Fig. 1). After transverse incision of the abdominal cavity, the diaphragm was transected and the anterior chest wall was reflected to expose the heart. The heart and proximal aorta were isolated from the distal aorta, pulmonary artery, pulmonary veins, and venae cavae. The heart was then placed in a shallow dish of iced normal saline solution. After exposure of the lumen of the proximal aorta with fine, blunt tweezers, the heart and proximal aorta were lifted and the proximal aorta was placed approximately 3 mm onto an aortic cannula. The proximal aorta was secured around the cannula temporarily with a serrated clip. Retrograde coronary perfusion through the aorta at a nonischemic flow rate of 12 ml/min[20] was then begun immediately with Krebs-Henseleit bicarbonate buffer (pH 7.4) through previously primed tubing. The time required from the initial abdominal incision until retrograde perfusion was no more than 3 minutes. Any pulmonary or thymic tissue adherent to the heart was then removed. The proximal aorta was secured to the cannula with a 3-0 silk suture. An 18 gauge needle was inserted into the left ventricle between the left anterior descending and left circumflex coronary arteries to monitor heart rate and left ventricular pressure.[21] As outlined in Figure 1, the left ventricular cannula was connected to a Statham model P23Db pressure transducer with a 10 cm segment of flexible thick-walled tubing. The pressure transducer's calibration outlet was placed level with the right atrium and the transducer was connected to a B-D Electrodyne CB-124B 4-channel monitor to display a continuous pressure waveform. A B-D Electrodyne WR-4D paper recorder was used. During each experiment, the heart rate and left ventricular peak systolic pressure were recorded at baseline, after 1 hour (at the end of the Tl-201 perfusion period), and after 3 hours (at the end of the period of perfusion with Tl-201–free buffer).

The perfusate, a modified Krebs-Henseleit buffer, consisted of NaCl 118.0 m*M*, KCl 4.7 m*M*; EDTA (2Na+) 0.5 m*M*, $KH_2PO_4$, 1.2 m*M*, $MgSO_4$ 1.2 m*M*, $CaCl_2$ 1.75 m*M*, $NaHCO_3$ 25.0 m*M*, and glucose 11.0 m*M*, with a pH of 7.4. The buffer was warmed to 37°C in a water bath and bubbled with 95% oxygen and 5% carbon dioxide for at least 10 minutes before use and for the duration of each experiment. The perfusate was delivered with a Masterflex roller head 7016 pump and was recirculated during the 1-hour uptake period but was not recirculated during the 2-hour release period.

A gamma scintillation probe (Ludlum model 2200) was positioned 5 cm from the long axis of the heart and was fitted with an 8 mm thick lead collimator that was 3.5 cm in length. The body of the probe was also wrapped in a 2 mm thick sheet of lead. The gamma probe window was set at 60 to 90 keV.

Two perfusates were prepared: 1 with 1 ml of Tl-201 (0.25 to 1.0 mCi/ml) added to 500 ml of buffer and the other without any radionuclide. Experiments were performed with flow held constant at either 12, 6, 3 , or 1.5 ml/min for each 3-hour experiment. During the first hour of each study, the isolated rat heart was perfused with thallium-containing buffer. The Tl-201 buffer was then discontinued and followed with 2 hours of perfusion with buffer free of Tl-201. During the period of perfusion with Tl-201–containing buffer, probe-determined activity was noted at 0.25, 0.5, 1, 1.5, 2, 2.5, 5, 10, 20, 30, 40, 50, and 60 minutes. After 1 hour, perfusion was begun with buffer free of Tl-201 and probe-monitored myocardial activity was expressed as a percentage of the maximal counts per minute achieved during the accumulation phase. Activity was monitored 0.25, 0.5, 1, 1.5, 2, 2.5, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 minutes after initiation of perfusion with Tl-201 free buffer.

The model $u(t) = a_1 + a_0 (1 - e^{-\lambda_u t})$ was fit to the uptake data using the BMDP nonlinear regression program BMDP3R,[22] a commercially available statistics package. Parameters $\lambda_u$, $a_0$, and $a_1$ were estimated, in addition to their standard errors. A separate run of the program was performed for each experimental flow level. BMDP3R was also used to perform tests for a multiexponential uptake-model. Uptake was found to be monoexponential at each of the levels of flow, except for a very fast initial component which could not be resolved at the sampling rate we employed. Therefore, this

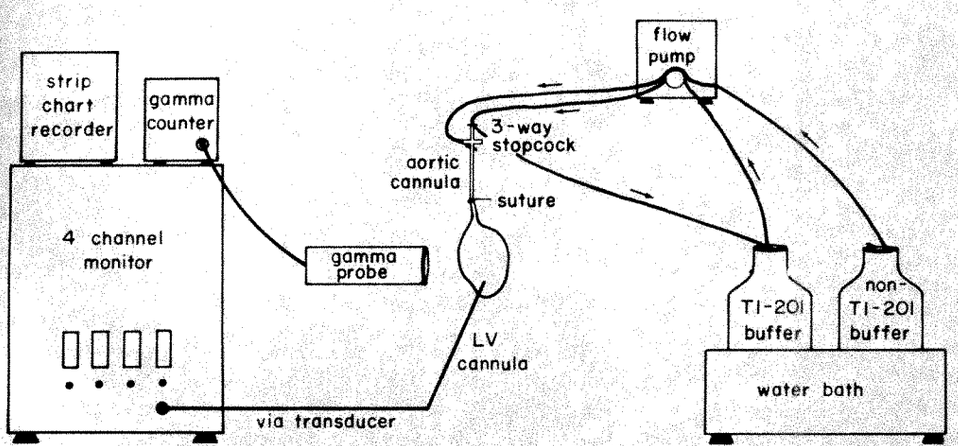



**FIGURE 1.** Schematic diagram of the experimental protocol. LV = left ventricular.

**TABLE I Hemodynamic Variables at Varying Flow Rates and Times (Mean ± Standard Deviation)**

| Flow (ml/min) | Baseline | | 1 Hour | | 3 Hours | |
|---|---|---|---|---|---|---|
| | HR | LVPSP | HR | LVPSP | HR | LVPSP |
| 12 | 260 ± 0 | 64 ± 4 | 235 ± 21 | 66 ± 7 | 250 ± 14 | 84 ± 8 |
| 6 | 220 ± 28 | 28 ± 24 | 240 ± 14 | 28 ± 5 | 220 ± 28 | 31 ± 1 |
| 3 | 165 ± 21 | 26 ± 3 | 122 ± 39 | 25 ± 7 | 138 ± 32 | 29 ± 1 |
| 1.5 | 115 ± 21 | 15 ± 0 | 89 ± 1 | 18 ± 1 | 99 ± 30 | 18 ± 4 |

HR = heart rate (beats/minute); LVPSP = left ventricular peak systolic pressure (mm Hg).

fast, small component was modeled as a constant at time zero (the parameter $a_1$).

For the release data, a multiexponential function was fit to the measured values of percent maximal counts per minute during washout, a(t), where $a(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t}$, where $A_k$ (k = 1 or 2) are the amplitudes of the exponentials $e^{-\lambda_k t}$ and $\lambda_k$ are the respective washout constants. Time, t, is expressed relative to the beginning of the 2-hour washout period. The estimation of parameters $A_1$, $\lambda_1$, $A_2$, $\lambda_2$ and their standard errors was carried out using the computer program BMDP3R in the BMDP package from the University of California at Los Angeles. A separate run of the program was performed for each experimental flow level. The half-life of the washout constants was calculated as follows: $(\text{half-life})_k = \ln 2/\lambda_k$. Linear regressions were used to investigate the relations between flow and the exponential variables of both the uptake and release periods.

## Results

Baseline heart rate and left ventricular peak systolic pressure were significantly lower at 1.5, 3, and 6 ml/min of coronary perfusion than at the control perfusion rate of 12 ml/min (Table I). During the course of each 3-hour experiment, there was no significant change in the hemodynamic parameters at 12 and 6 ml/min of coronary flow (Table I). At 3 and 1.5 ml/min of coronary flow, the heart rate decreased during the first hour of the experimental protocol, but left ventricular peak systolic pressure did not change significantly during the 3-hour duration of each experiment. Reduction in coronary flow rates was correlated with both lower heart rate (r = 0.94) and lower left ventricular peak systolic pressure (r = 0.97).

During the 1-hour period of perfusion with the Tl-201–containing buffer, there was a monoexponential increase in Tl-201 activity (Fig. 2). For uptake, we found that $\lambda_u(\text{flow}) = (0.00766 \pm 0.00075) \times \text{flow} + 0.023 \pm 0.005$ (r = 0.99, p = 0.01), where $\lambda_u$ is the single exponential parameter for uptake. As flow decreased, the uptake constant decreased from $0.117 \pm 0.004$ $\text{min}^{-1}$ at 12 ml/min to $0.034 \pm 0.0004$ $\text{min}^{-1}$ at 1.5 ml/min. Accordingly, the half-life for the uptake constant increased from 6 to 23 minutes as coronary flow was reduced from 12 to 1.5 ml/min (Table II).

During perfusion with Tl-201–free buffer, release of Tl-201 demonstrated a biexponential pattern (Fig. 3). There was a fast release component initially; this was followed by a slow release component at each of the 4 flow rates (Fig. 4). As coronary flow was reduced, the initial fast release rate decreased significantly as assessed by linear regression analysis (r = 0.97, p = 0.03).

**TABLE II Uptake Constants $\lambda_u$ and Half-Life at Varying Flows**

| Flow (ml/min) | Uptake Constant $\lambda_u \pm$ SD ($\text{min}^{-1}$) | Half-Life (min) |
|---|---|---|
| 12 | 0.117 ± 0.004 | 6 |
| 6.0 | 0.067 ± 0.0005 | 10 |
| 3.0 | 0.053 ± 0.001 | 13 |
| 1.5 | 0.03 ± 0.0004 | 23 |

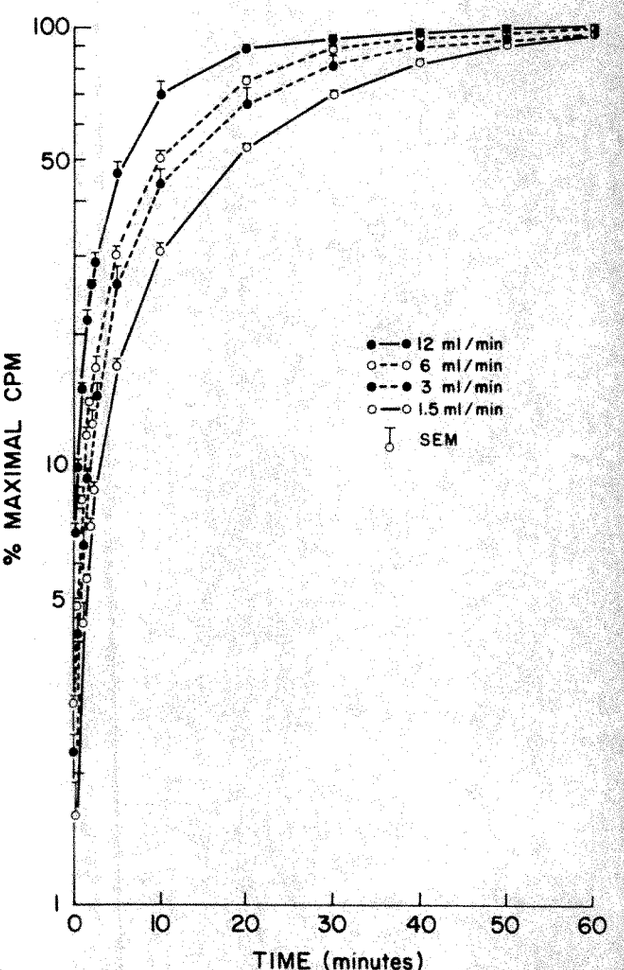



**FIGURE 2.** Net thallium-201 uptake during the 1 hour of Tl-201 loading. Note that even at the lowest coronary flow rate, 1.5 ml/min, 50% of the maximal counts per minute (CPM) have occurred by 20 minutes. SEM = standard error of the mean.

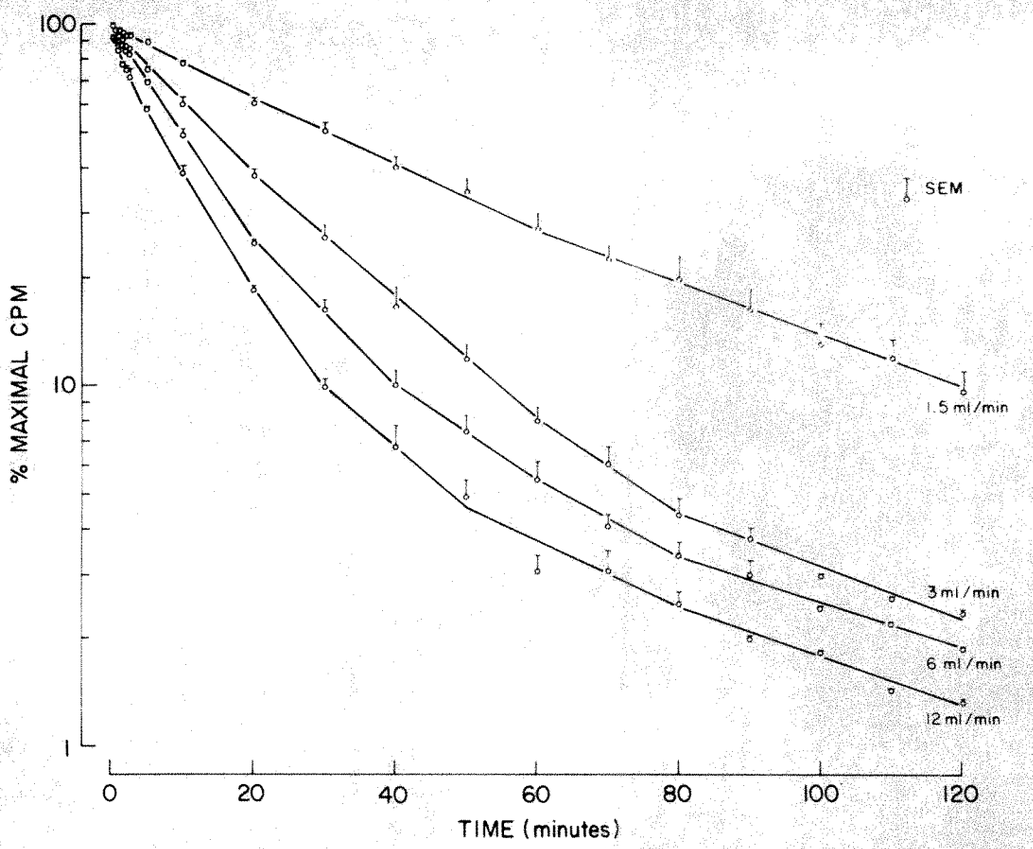



**FIGURE 3.** Thallium-201 release curves are shown at varying coronary flows. A biexponential model fits these release curves. CPM = counts per minute; SEM = standard error of the mean.

Because of the nonlinearity of this relation (Fig. 4), the data were reanalyzed using a linearizing transformation [ln $(0.125 - \lambda_1)$] of the release constants, and the significant monotonic relation between the fast release constant ($\lambda_1$) and flow was confirmed. The value of the fast initial exponential release constant decreased from $0.107 \pm 0.009$ min$^{-1}$ at 12 ml/min to $0.036 \pm 0.015$ min$^{-1}$ at 1.5 ml/min (Fig. 4). Accordingly, the half-time for the fast component of thallium released increased from 6.5 to 19 minutes as flow decreased from 12 to 1.5 ml/min (Table III). Although the value of the slow later exponential release constant decreased from $0.022 \pm 0.006$ min$^{-1}$ at 12 ml/min to $0.015 \pm 0.004$ min$^{-1}$ at 1.5 ml/min (Fig. 4), this change was not significant. The half-time for the slow component of thallium release increased from 32 minutes at 12 ml/min to 46 minutes at 1.5 ml/min, but this increase was not significant (Table III).

## Discussion

The results of this study show that if Tl-201 is delivered continuously using perfusate with a constant concentration, the myocardial uptake rate is monoexponential and decreases as the perfusion rate decreases. After the heart contains Tl-201, during perfusion with thallium-free buffer, 2 distinct exponential release phases are noted: a more rapid early phase and a slower late phase. The earlier more rapid phase showed a distinct and significant slowing as flow decreased, whereas the later and slower phase demonstrated a more subtle and insignificant decrease with decreasing perfusion. The fast release component may be related to myocardial clearance of Tl-201 from an extracellular space, whereas the slow release component may reflect a cellular compartment.

**Kinetic features of thallium-201 uptake:** There is a monoexponential increase in Tl-201 uptake when it is delivered at a constant rate over a 1-hour interval. Studies by our group have demonstrated that even during extreme ischemic-like insult in the fetal mouse heart culture model, thallium accumulates in myocardium during a 4-hour interval, after which net Tl-201 efflux from insulted myocardium occurs.[23] The rate constant of Tl-201 accumulation ($\lambda_u$) in the present model decreased with reduction in perfusion, mainly due to reduced delivery.

**Kinetic features of thallium-201 release:** It is known that ionic potassium is released from ischemic myocardium during ischemic insult.[15–17] Because thallium has been found to behave like potassium in biologic systems,[10–14] it was surprising when Gewirtz et al[8] demonstrated a comparable rate of release of Tl-201 from a region of myocardium made ischemic by ligation of the left anterior descending coronary artery and from a normally perfused region. This study was done using analysis of myocardial biopsy in a canine model, in

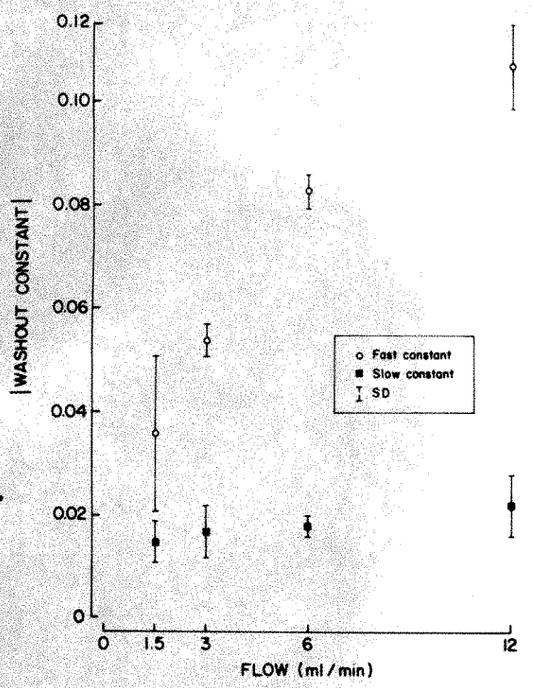



**FIGURE 4.** The absolute values of the slow and fast release constants are shown with varying coronary flow rates. The slow release constant does not change significantly with changes in coronary flow. In contrast, the fast release constant decreases with reduction in coronary flow. SD = standard deviation.

which Tl-201 was given intravenously followed by ligation of the left anterior descending coronary artery. Further studies by Gewirtz et al[9] using measurements of change in coronary arterial-coronary venous Tl-201 difference substantiated the previous observations.

Okada et al[24] examined the clearance of Tl-201 in a canine model with normal myocardial perfusion using implanted myocardial radiation detection probes. After an intravenous dose of thallium, 3 exponential phases of clearance from blood occurred: (1) a very early and relatively rapid component (half-life 2.4 minutes) which was most likely vascular; (2) a second less rapid component (half-life 14.1 minutes) which was probably interstitial; and (3) a third slow component (half-life 446 minutes) which was most likely intracellular. Myocardial activity reached 80% of peak within 1 minute. Afterward, a slow monoexponential myocardial release rate occurred (half-life 437 minutes) which ran parallel to the slowest exponential component of release from the blood. Further studies demonstrated that in zones of myocardium that were supplied by vessels with subnormal blood flow, Tl-201 activity increased more slowly, but that after a peak was achieved myocardial clearance again closely paralleled blood clearance.[7]

In an effort to investigate myocardial release more directly, Krivokapich and Shine[25] studied efflux of Tl-201 under nonischemic conditions with isolated perfused rabbit interventricular septa. Their experiments included a set of conditions similar to our protocol at 12 ml/min flow. Four septa labeled with Tl-201 for at least 40 minutes had washout conducted for ≥90 minutes with a buffer containing 5 m*M* of potassium chloride. The tissue clearance after 40 minutes of washout was 0.013 ± 0.003 $min^{-1}$, not significantly different from our slow release constant at 12 ml/min, 0.015 ± 0.004 $min^{-1}$. These investigators proposed 4 phases of thallium release: vascular, interstitial, rapid cellular, and slow cellular.

Finally, Grunwald et al[1] evaluated the relation between myocardial release and blood flow in the normal and subnormal range after intracoronary Tl-201 administration in a canine model. Tl-201 activity was monitored with an external scintillation detector. These investigators studied Tl-201 release for an interval of 50 minutes and demonstrated a monoexponential release component with a half-life of approximately 70 minutes. When measurements were made using coronary sinus Tl-201 output, 3 exponential components were demonstrated: (1) an early rapid component with a half-life of 2.25 minutes, (2) a slower intermediate component which the investigators did not comment upon (half-life approximately 13 minutes), and (3) a slow component with a half-life of 67 minutes. There is remarkable similarity in the data generated using the dog model of Grunwald and our isolated rat heart model. First, the slow washout phase is of the same order of magnitude (half-life = 67 minutes [dog] versus 32 minutes [isolated rat heart]). Species differences in the normal coronary blood flow/g in dog (1 ml/min/g)[26] versus isolated rat heart (15 ml/min/g)[20] are likely to account in part for this difference. In addition, there may be species differences in the way Tl-201 is handled. Furthermore, we, too, have clearly demonstrated that as coronary blood flow is reduced, the myocardial release rate also decreases.

**Clinical implications:** This report provides further clinically relevant understanding of the relation between the kinetic effects and myocardial perfusion of thallium. Recognizing that several distribution spaces are confounded in a purely exponential model and that specific variables for the mechanisms of transport cannot be estimated in this way,[27] one might view the

**TABLE III Half-Life (in Minutes) of the Fast ($\lambda_1$) and Slow ($\lambda_2$) Release Constants at Varying Flows**

| Flow (ml/min) | Fast Release | | Slow Release | |
|---|---|---|---|---|
| | $\lambda_1$ ± SD ($min^{-1}$) | Half-Life (min) | $\lambda_2$ ± SD ($min^{-1}$) | Half-Life (min) |
| 1.5 | 0.036 ± 0.015 | 19.0 | 0.015 ± 0.004 | 46 |
| 3 | 0.054 ± 0.003 | 13.0 | 0.017 ± 0.005 | 41 |
| 6 | 0.083 ± 0.003 | 8.4 | 0.018 ± 0.002 | 39 |
| 12 | 0.107 ± 0.009 | 6.5 | 0.022 ± 0.006 | 32 |

fast component as being primarily identified with the extracellular distribution space and the slow component as being primarily identified with the intracellular distribution space. Thus, changes in the early exponential component of thallium release after peak uptake are related to changes in blood flow, while later release is not significantly related to blood flow.

Our data should be helpful in interpreting myocardial clearance rates for thallium and in differentiating initial thallium distribution in normally perfused myocardium from tissue undergoing ischemic insult.[18,19] Some patients with initial defects due to chest wall or diaphragmatic attenuation or apical thinning have normal coronary arteries. Clearance rate measurements might allow more accurate definition of those patients with normal myocardial perfusion. From our data, it appears that the clearance rates which predominate during early thallium release provide insight into coronary blood flow. However, the clearance rates which predominate during later thallium release did not provide insight into the severity of myocardial ischemia.

Our previous work in the fetal mouse heart suggests that during ischemic-like injury, thallium efflux exceeds thallium influx only after 4 hours of insult.[23] Therefore, evaluation of very late clearance rates might provide further information on myocardial cellular necrosis. In the present study, observations made on thallium clearance rates during the first 20 minutes are predominantly related to coronary flow and might confound any estimate of cell viability. Our data suggest that observations on thallium release should be extended to identify more precisely the cellular component of thallium release.

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## References

1. **Grunwald AM, Watson DD, Holzgrefe HH Jr, Irving JF, Beller GA.** Myocardial thallium-201 kinetics in normal and ischemic myocardium. Circulation 1981;64:610–618.
2. **Pohost GM, Zir LM, Moore RH, McKusick KA, Guiney TE, Beller GA.** Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. Circulation 1977;55:294–302.
3. **Blood DK, McCarthy DM, Sciacca RR, Cannon PJ.** Comparison of single-dose and double-dose thallium-201 myocardial perfusion scintigraphy for the detection of coronary artery disease and prior myocardial infarction. Circulation 1978;58:777–788.
4. **Berger BC, Watson DD, Burwell LR, Crosby IK, Wellons HA, Teates CD, Beller GA.** Redistribution of thallium at rest in patients with stable and unstable angina and the effect of coronary artery bypass surgery. Circulation 1979;60:1114–1125.
5. **Gewirtz H, Beller GA, Strauss HW, Dinsmore RE, Zir LM, McKusick KA, Pohost GM.** Transient defects of resting thallium scans in patients with coronary artery disease. Circulation 1979;59:707–713.
6. **Welch HF, Strauss HW, Pitt B.** The extraction of thallium-201 by the myocardium. Circulation 1977;188–191.
7. **Okada RD, Leppo JA, Strauss HW, Boucher CA, Pohost GM.** Mechanisms and time course for the disappearance of thallium-201 defects at rest in dogs: relation of time to peak activity to myocardial blood flow. Am J Cardiol 1982;49:699–706.
8. **Gewirtz H, O'Keefe DD, Pohost GM, Strauss HW, McIlduff JB, Daggett WM.** The effect of ischemia on thallium-201 clearance from the myocardium. Circulation 1978;58:215–219.
9. **Gewirtz H, Maksad AK, Most AS, Sullivan MJ, Shearer DR.** The effect of transient ischemia with reperfusion on thallium clearance from the myocardium. Circulation 1980;61:1091–1097.
10. **Mullins LJ, Moore RD.** The movement of thallium ions in muscle. J Gen Physiol 1960;43:759–773.
11. **Gehring PJ, Hammond PB.** The uptake of thallium by rabbit erythrocytes. J Pharmacol Exp Ther 1964;145:215–221.
12. **Britten JS, Blank M.** Thallium activation of the (Na+-K+)-activated ATPase of rabbit kidney. Biochim Biophys Acta Acta 1968;159:160–166.
13. **Skulskii IA, Manninen V, Jarnefelt J.** Interactions of thallous ions with the cation transport mechanism in erythrocytes. Biochim Biophys Acta 1973;298:702–709.
14. **Nitsch J, Steinbeck G, Luderitz B.** Comparison of myocardial potassium and thallium flux as studied by tracer methods. Clin Cardiol 1980;3:188–191.
15. **Burke WM, Asokan SK, Moschos CB, Oldewurtel HA, Regan TJ.** Effects of glucose and non-glucose infusions on myocardial potassium ion transfers and arrhythmias during ischaemia. Am J Cardiol 1969;25:713–722.
16. **Regan TJ, Harman HA, MA, Lehan PH, Burke WM, Oldwurtel HA.** Ventricular arrhythmias and K+ transfer during myocardial ischemia and intervention with procaine amide, insulin or glucose solution. J Clin Invest 1967;46:1657–1668.
17. **Thomas M, Shulman G, Opie L.** Arteriovenous potassium changes and ventricular arrhythmias after coronary artery occlusion. Cardiovasc Res 1970;4:327–333.
18. **Berger BC, Watson DD, Taylor GJ, Cruddock GB, Martin RP, Teates CD, Beller GA.** Quantitative thallium-201 exercise scintigraphy for detection of coronary artery disease. J Nucl Med 1981;22:585–593.
19. **Watson DD, Campbell NP, Read EK, Gibson RS, Teates CD, Beller GA.** Spatial and temporal quantitation of plane thallium myocardial images. J Nucl Med 1981;22:577–584.
20. **Rovetto MJ, Whitmer JT, Neely JR.** Comparison of the effects of anoxia and whole heart ischemia on carbohydrate utilization in isolated working rat hearts. Circ Res 1973;32:699–711.
21. **Neely JR, Rovetto MJ.** Techniques for perfusing isolated rat hearts. In: Hardman JG, O'Malley BW, eds. Methods in Enzymology, vol 39. New York: Academic Press, 1975:43–63.
22. **Dixon WJ, Brown MB, eds.** Biomedical Computer Programs P-Series, Health Science Computing Facility at UCLA. Berkeley: University of California Press, 1979:464–483.
23. **Goldhaber SZ, Newell JB, Alpert NM, Andrews E, Pohost GM, Ingwall JS.** Effects of ischemic-like insult on myocardial thallium-201 accumulation. Circulation 1983;67. In press.
24. **Okada RD, Jacobs ML, Daggett WM, Leppo J, Strauss HW, Newell JB, Moore R, Boucher CA, O'Keefe D, Pohost GM.** Thallium-201 kinetics in nonischemic canine myocardium. Circulation 1982;65:70–77.
25. **Krivokapich J, Shine KI.** Effects of hyperkalemia and glycoside on thallium exchange in rabbit ventricle. Am J Physiol 1981;240:H612–H619.
26. **Kloner RA, Reimer KA, Jennings RB.** Distribution of coronary collateral flow in acute myocardial ischemic injury: effect of propranolol. Cardiovasc Res 1976;10:81–90.
27. **Bassingthwaighte JB.** A concurrent flow model for extraction during transcapillary passage. Circ Res 1974;35:483–503.

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# BASIC THERAPY FOR THE PREVENTION OF ANGINA PECTORIS*

Report from "Step-Care Therapy for Ischemic Heart Disease"
—a special symposium preceding the annual meeting
of the American College of Cardiology, April 24, 1982.

## Synopsis of the Symposium

### Step 1: Nitrates

Since nitrates both reduce myocardial oxygen demand and increase myocardial oxygen supply, their use is warranted as initial therapy for the control of angina pectoris. Dosage needs often vary significantly from patient to patient, and attention should be given to ensure that an adequate dosage level has been established.

### Step 2: Nitrates and beta blockers

For angina refractory to maximum-dose nitrate therapy, the complementary actions of beta blockers and nitrates provide a rational therapeutic modality. At this point a beta blocker should be added to the nitrate regimen.

### Step 3: Nitrates and calcium antagonists

Calcium antagonists have special usefulness in controlling cases where the myocardial oxygen supply is diminished by coronary vasospasm; their use in combination with nitrates is recommended if Step 2 therapy is unsatisfactory (or if the patient has variant or vasospastic angina).

Consensus of the Symposium

**Nitrates are basic in step-care therapy for ischemic heart disease**

**Step 1**
Stable or unstable angina: Nitrates

**Step 2**
If not controlled: Nitrates + beta blockers

**Step 3**
If still not controlled (or in variant angina): Nitrates + calcium antagonists

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"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

**Contraindication:** Idiosyncrasy to this drug.
**Warnings:** Data supporting the use of nitrites and nitrates during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.
**Precautions:** Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.
**Adverse Reactions:** Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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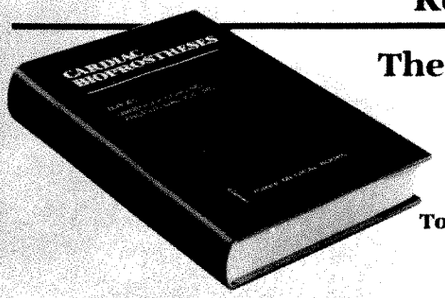
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## Who are the editors?

**Lawrence H. Cohn, MD,** is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

**Vincenzo Gallucci, MD,** is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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**JULIET**

"Wilt thou be gone? It is not yet near day.
It was the nightingale, and not the lark,
That pierced the fearful hollow of thine ear.
Nightly she sings on yond pomegranate tree.
Believe me, love, it was the nightingale.

**ROMEO**

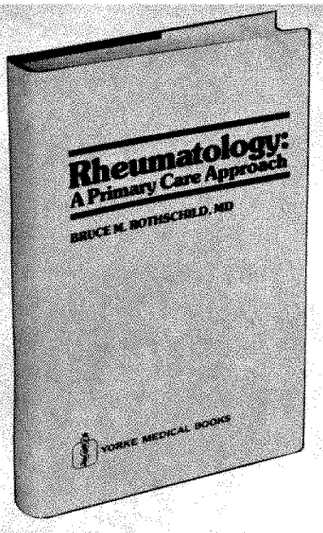
It was the lark, the herald of the morn;
No nightingale. Look, love, what envious streaks
Do lace the severing clouds in yonder East.
Night's candles are burnt out, and jocund day
Stands tiptoe on the misty mountain tops.
I must be gone and live, or stay and die.

**JULIET**

Yond light is not daylight; I know it, I.
It is some meteor that the sun exhales
To be to thee this night a torchbearer
And light thee on thy way to Mantua.
Therefore stay yet; thou need'st not to be gone."

The Dialogue of Romeo and Juliet, Act III, scene V.

**Another Dialog soon to appear—by Siemens.**




# The Diagnosis and Treatment Oriented Approach to Rheumatology with the Primary Care Physician in Mind

# Rheumatology

## A Primary Care Approach

Written by:

**Bruce M. Rothschild, MD**

Director, Division of Rheumatology, University Health Sciences, The Chicago Medical School Chief, Section of Rheumatology, V. A. Medical Center North Chicago, Illinois

**ISBN 0-914316-33-8 430 pp., illus., November 1982, $39.50**

## What is Rheumatology: A Primary Care Approach?

- a succinct (approx. 450 pp.) yet comprehensive presentation of the latest techniques in diagnosis and therapeutic interventions of most use to the primary care physician
- a practical "how-to" desk reference to a difficult but common disease affecting over 35 million patients in the U.S. alone
- a book meant to be used regularly, not read once and stored away on a library shelf
- the primary care physicians' answer to the huge, weighty tomes on Rheumatology which offer too little on diagnosis and treatment and too much on etiology and mechanisms of disease

## Rheumatology: A Primary Care Approach is Not

- a research monograph filled with esoteric information of little use to the practicing primary care physician
- a difficult to follow, badly organized reference tool requiring a thorough knowledge of the subject matter before it can be used effectively
- a massive and verbose dissertation more useful as a door stop than a clinical reference

We know of no other book on rheumatic disease which covers the subject as exhaustively in terms of diagnosis and treatment while avoiding wasting the busy practitioner's time by including information of little interest to the primary care physician. This book emphasizes that information necessary to recognize basic disease processes and their natural history. It provides the reader with the information necessary for making a diagnosis and initiating a plan of treatment. Information on differential diagnosis from the point of view of characteristics which would not fit with a given diagnosis is also provided. It is especially strong on the interpretation of rheumatologic radiology and in its approach to joint examination and assessment of lab results. Rheumatic disease cannot be cured but proper intervention can reduce and sometimes eliminate the attendant disability. This book provides you with the means to diagnose, assess and decide for yourself the necessary intervention.

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**Alfred Soffer, MD**
Chief Editor Archives of Internal Medicine

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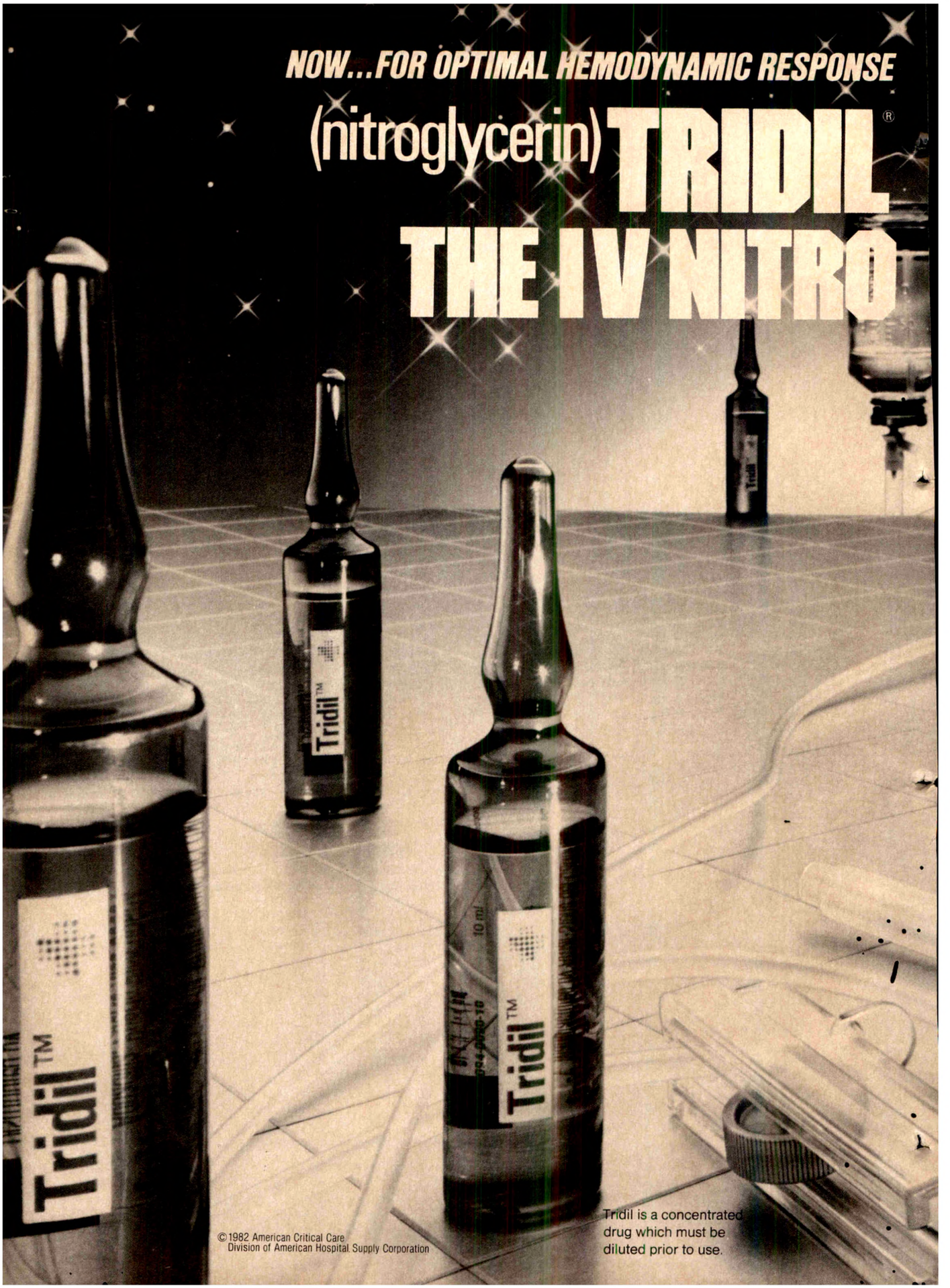
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1. Aronow, W.S., *NEJM* 1973, *289*:516-520. 2. Mehta, J., Pepine, C.J., *Circ* 1978, *58*:803-807. 3. Capurro, N.L., et al. *Am J Card* 1977, *39*:679-683. 4. Baaske, D.M., et al. *Am J Hosp Pharm* 1980, *37*:201-205. 5. Baaske, D.M. et al. *Am J Hosp Pharm* 1982, *39*:121-122.

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**CAUTION**

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1. A known hypersensitivity to nitroglycerin or a known idiosyncratic reaction to organic nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of TRIDIL in such states could produce severe hypotension or shock.
3. Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage).
4. Constrictive pericarditis and pericardial tamponade.

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1. Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of TRIDIL for intravenous infusion should be made only in *glass* parenteral solution bottles.
2. Some filters absorb nitroglycerin; they should be avoided.
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Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of TRIDIL. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

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No long-term studies in animals were performed to evaluate carcinogenic potential of TRIDIL.

**Pregnancy**

Category C. Animal reproduction studies have not been conducted with TRIDIL. It is also not known whether TRIDIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRIDIL should be given to a pregnant woman only if clearly needed.

**Nursing Mothers**

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRIDIL is administered to a nursing woman.

**Pediatric Use**

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**ADVERSE REACTIONS**

The most frequent adverse reaction in patients treated with TRIDIL is headache, which occurs in approximately 2% of patients. Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

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**OVERDOSAGE**

Accidental overdosage of TRIDIL may result in severe hypotension and reflex tachycardia which can be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilizes. Since the duration of the hemodynamic effects following TRIDIL administration is quite short, additional corrective measures are usually not required. However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (e.g., methoxamine or phenylephrine) should be considered.

**DOSAGE AND ADMINISTRATION**

(For complete information, please see Full Prescribing Information)

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TRIDIL IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION. TRIDIL SHOULD NOT BE ADMIXED WITH OTHER DRUGS.

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September 1981

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# THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

**Libi Sherf, MD, FACC**

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Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

*"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."*

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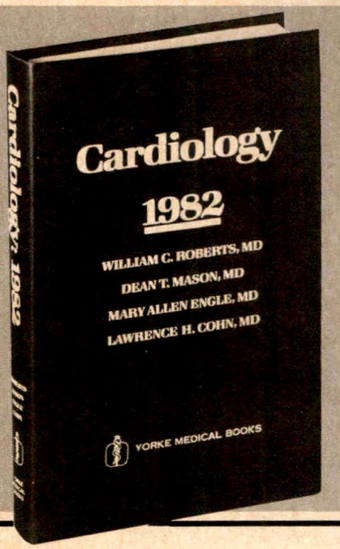
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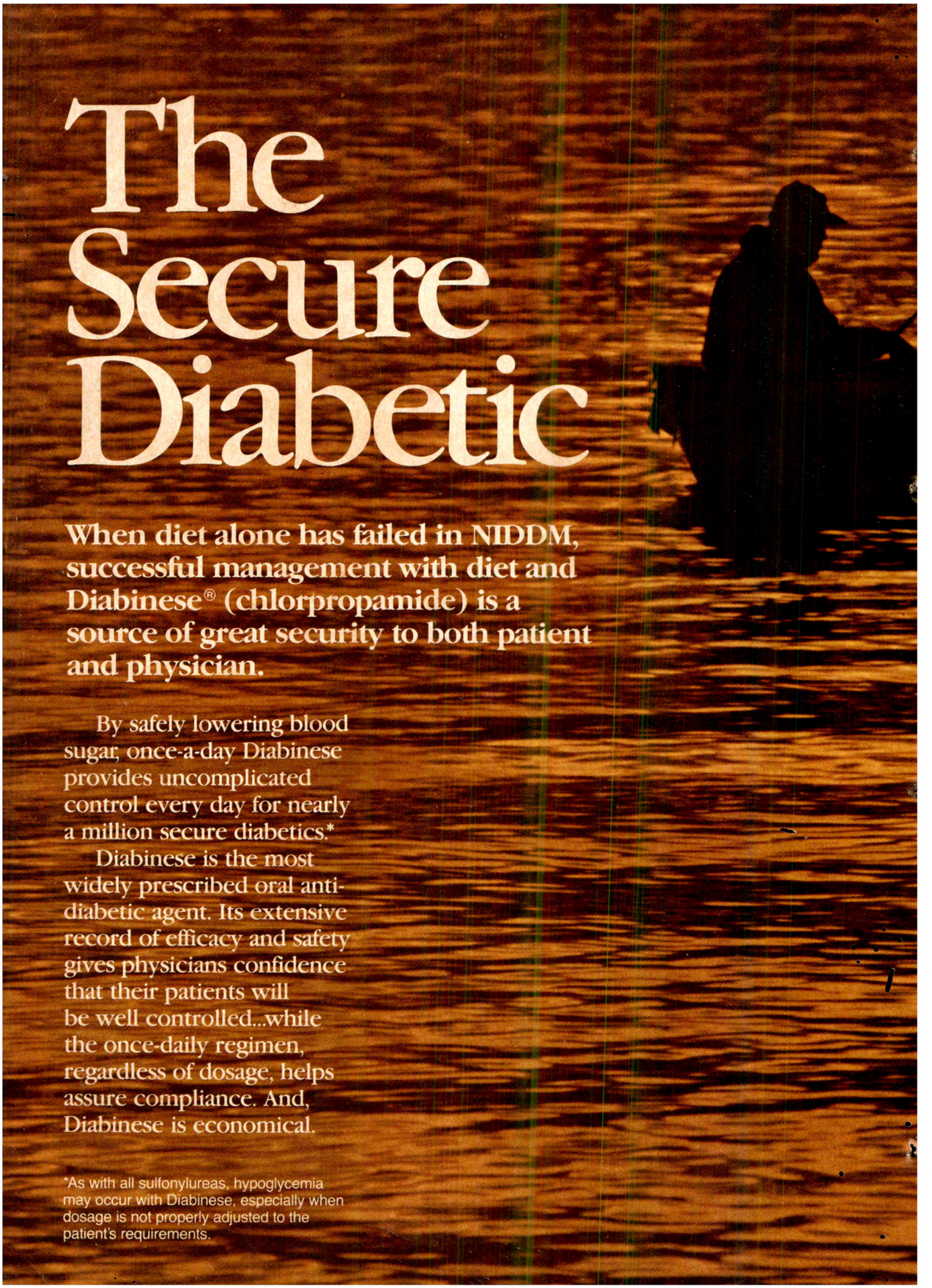
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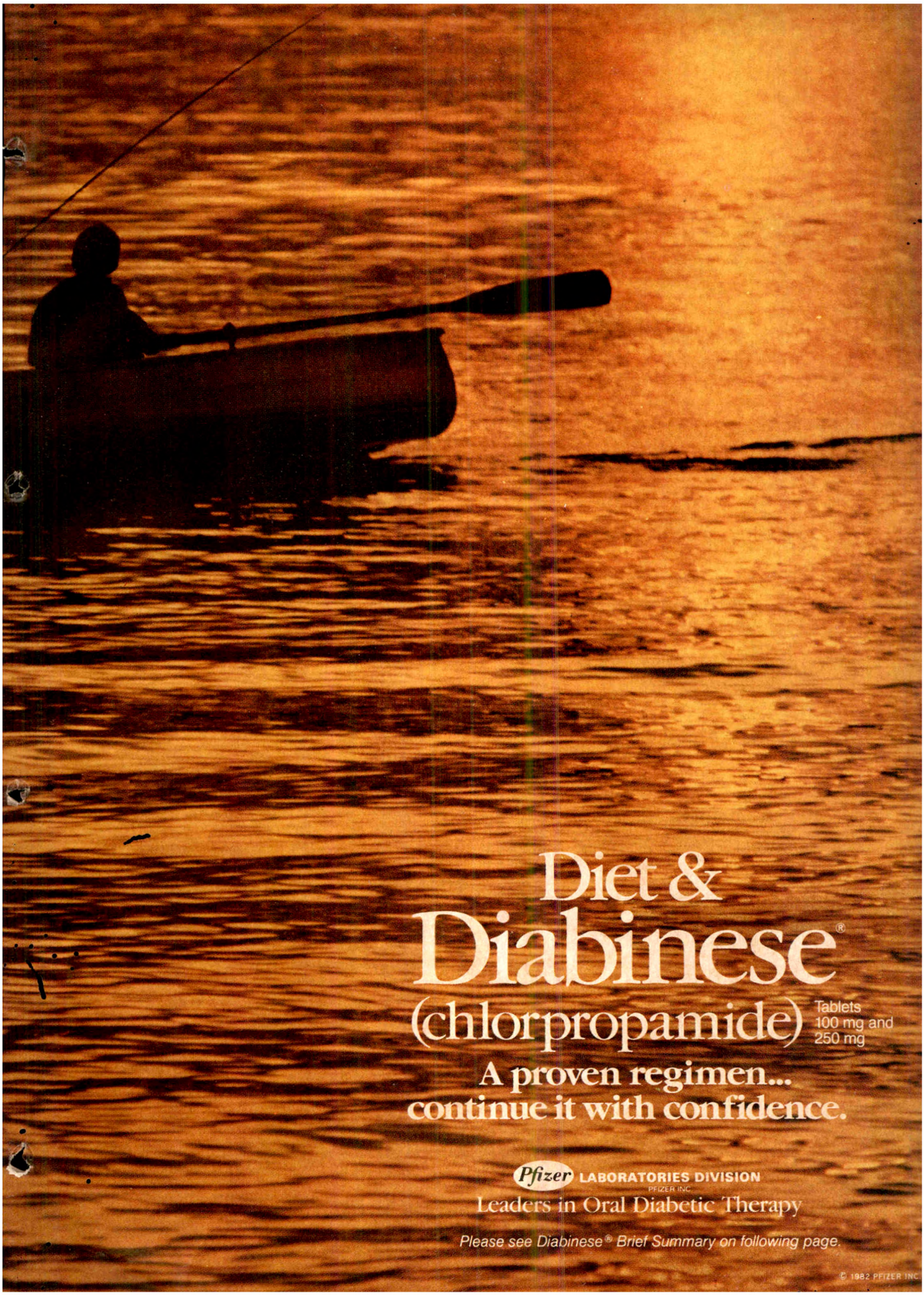
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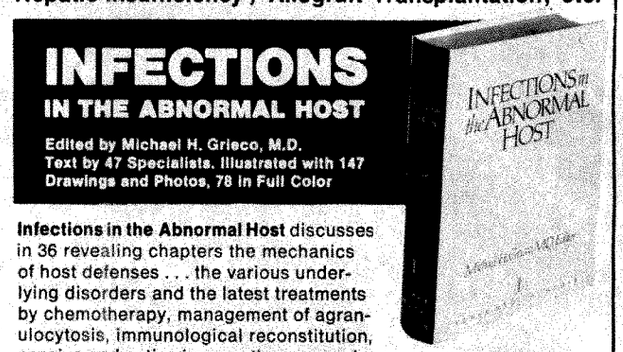
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# Supraventricular Nonreentrant Tachycardia Due to Simultaneous Conduction Through Dual Atrioventricular Nodal Pathways

FREDERICK J. SUTTON, MD and YU-CHEN LEE, MD

Simultaneous conduction of atrial paced beats through dual atrioventricular (AV) nodal pathways was first described by Wu et al[1] in 1975. Subsequently, Csapo[2] reported on a patient with paroxysmal nonreentrant tachycardia due to this mechanism. Recently, Gomes et al[3] performed electrophysiologic studies in 3 patients with supraventricular tachycardia and stated that procainamide altered conduction and refractoriness of the anterograde fast and slow pathways of the AV node so that simultaneous conduction could occur during atrial pacing. The present report describes 2 patients with sustained nonreentrant tachycardia due to simultaneous conduction through dual AV nodal pathways, and discusses various precipitating factors of this unusual arrhythmia.

From the Division of Cardiology, Department of Medicine, University of Maryland Hospital, Baltimore, Maryland. Manuscript received June 7, 1982; revised manuscript received November 25, 1982, accepted November 27, 1982.

*Patient 1: A 33-year-old man was hospitalized for palpitations. A 24-hour Holter tape had previously revealed irregular paroxysmal supraventricular tachycardia which was interpreted as atrial fibrillation (Fig. 1). He received propranolol, 20 mg orally 4 times daily, which aggravated the palpitations. Administration of 50 mg of bethanecol chloride, orally, prolonged the episodes of supraventricular tachycardia, which were terminated by 0.5 mg of atropine sulfate administered intravenously. During tachycardia an intraatrial electrogram showed that most of the P waves were followed by 2 QRS complexes (Fig. 2). When the P wave was followed by a single QRS complex, the P-R interval was markedly prolonged. Administration of procainamide and disopyramide also aggravated the arrhythmia.*

*Pacing techniques included incremental atrial pacing until the development of second degree AV nodal block, programmed atrial extrastimuli scanning diastole during atrial pacing at a cycle length of 700 ms, and programmed single ventricular extrastimulus scanning diastole during sinus rhythm. No discontinuity of $A_1$-$A_2$, $A_2$-$H_2$ could be demonstrated, and no arrhythmia was induced by atrial pacing. During sinus rhythm an interpolated ventricular extrastimulus produced 2 distinct patterns (Fig. 3). When the coupling interval was ≤330 ms, no tachycardia was induced, and there was minimal prolongation of the A-H interval of the first sinus beat which followed the ventricular extrastimuli (Fig. 3 and 4). At longer coupling intervals, most extrastimulus beats had a prolonged A-H interval ranging from 400 to 550 ms (Fig. 3) and were followed by short runs of nonreentrant tachycardia (Fig. 5). The induced tachycardia was similar to the spontaneous tachycardia. A His potential was recorded preceding each QRS complex with the H-V interval constant at 45 ms. No ventriculoatrial conduction was present during ventricular pacing.*

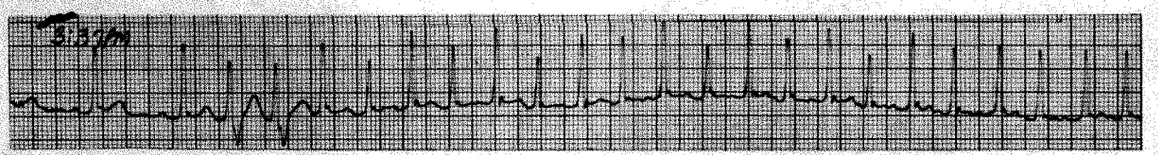


**FIGURE 1.** Patient 1. Holter tracing. After 2 sinus beats a rapid irregular rhythm is seen which was initially interpreted as atrial fibrillation.

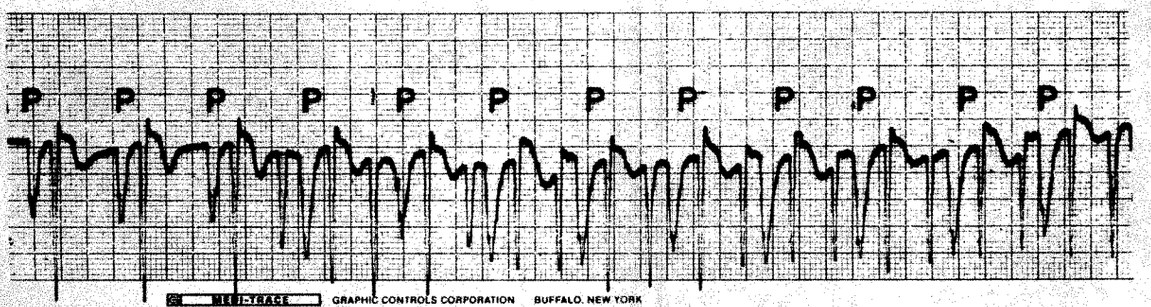



**FIGURE 2.** Patient 1. Intraatrial electrogram after administration of bethanocal chloride. After 2 sinus beats a supraventricular tachycardia is seen. P waves are regular, and each P wave is followed by 2 QRS complexes.

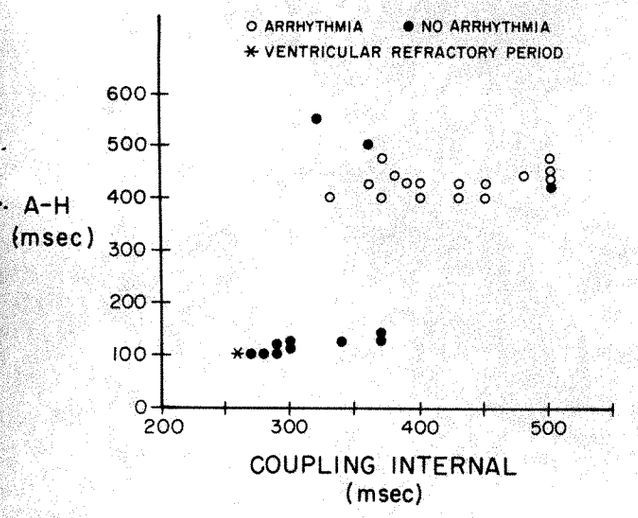



**FIGURE 3.** Patient 1. The relation of the coupling interval of the programmed ventricular extrasystole and the A-H interval of the first sinus beat after the extrasystole. Prolonged A-H interval of the first sinus beat was seen only when the coupling interval was more than 330 ms. The supraventricular tachycardia was induced only when the A-H interval was prolonged.

*Patient 2: A 68-year-old man was referred for evaluation of supraventricular tachycardia, which developed after quinidine treatment for ventricular premature contractions. Procainamide and disopyramide also induced similar supraventricular tachycardia characterized by 1 P wave followed by 2 QRS complexes (Fig. 6).*

The supraventricular tachycardia in these 2 patients is extremely unusual in that the arrhythmia was aggravated by increased vagal tone, propranolol, and type 1 antiarrhythmic drugs. This tachyarrhythmia is most likely due to simultaneous conduction through dual AV nodal pathways. In the first patient, the spontaneous paroxysmal nonreentrant supraventricular tachycardia was repeatedly reproduced by appropriately timed ventricular stimuli during sinus rhythm. The interpolated ventricular beats partly penetrated the distal AV node, which remained refractory for the oncoming sinus impulse traveling through the fast pathway. However, the same sinus impulse traveling down the slow pathway was sufficiently delayed to allow recovery of the distal AV nodal tissue, making ventricular capture possible. The subsequent sinus impulse was conducted simultaneously through both fast and slow AV nodal tracts, resulting in 2 QRS complexes after each P wave (Fig. 7

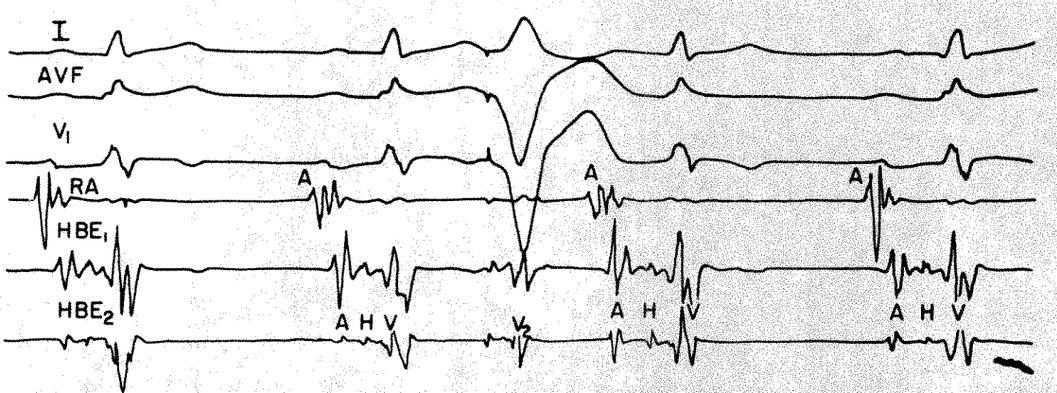



**FIGURE 4.** Patient 1. During sinus rhythm an interpolated ventricular extrastimulus (coupling interval of 320 ms) failed to induce a supraventricular tachycardia and the A-H interval of the following sinus beat prolonged minimally. I, aVF, V = surface electrocardiographic leads; RA = right atrial electrocardiogram; $HBE_1$ and $HBE_2$ = proximal and distal His bundle electrograms, respectively; $V_2$ = programmed ventricular extrasystole.

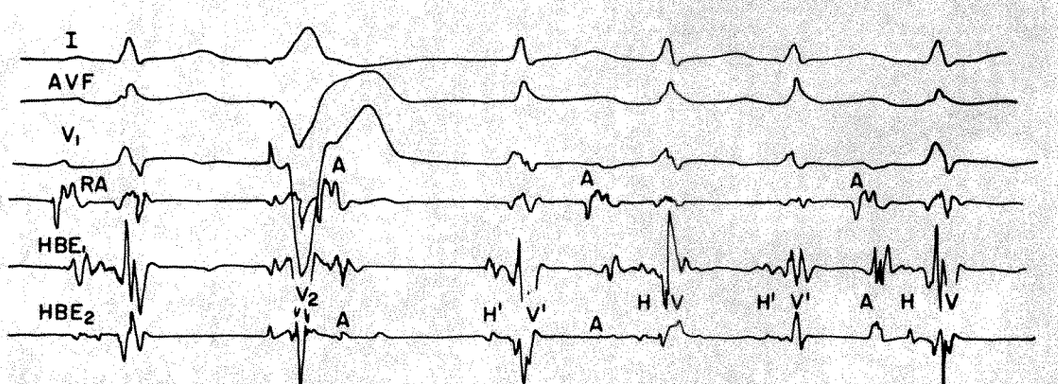



**FIGURE 5.** Patient 1. During sinus rhythm an interpolated ventricular extrastimulus (coupling interval of 460 ms) induced a nonreentrant supraventricular tachycardia. A-H interval of the first sinus beat after the ventricular extrastimulus was markedly prolonged (440 ms).

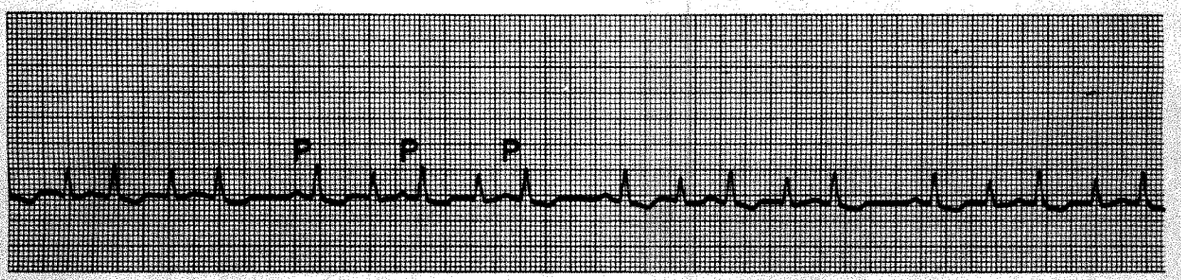



**FIGURE 6.** Patient 2. Lead II surface electrocardiogram. The QRS complexes occur in groups of 5. The first 2 P waves in each group are followed by 2 QRS complexes and the third P wave is followed by a single QRS complex.

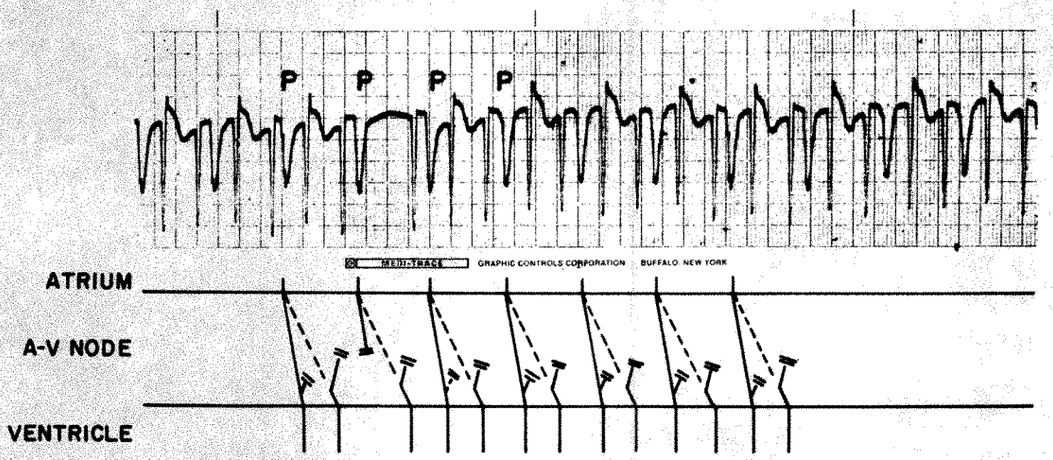



**FIGURE 7.** Patient 1. Laddergram of the proposed mechanism of tachycardia. Presence of retrograde conduction block of both pathways enabled simultaneous anterograde conduction of the sinus P waves. The fourth P wave is conducted through only the slow pathway (**dotted line**) due to deeper retrograde penetration of the fast pathway (**solid line**) which prevented anterograde conduction.

and 8). This rhythm was maintained because the refractory period of the distal common pathway was shorter than the shortest cardiac cycle, and the distal AV nodal pathway of either side was refractory to the retrograde stimuli from the opposite tract (Fig. 8). Shortening of the coupling interval of the ventricular extrastimulus to ≤330 ms allowed sufficient recovery time for the following sinus beat to conduct normally through the fast pathway, and this impulse could then penetrate the slow pathway retrogradely and abort the tachycardia. The presence of 2 distinct patterns of A-H conduction in Figure 3 suggests dual nodal tracts which are not excluded by the failure to document a discontinuous $A_1$-$A_2$, $A_2$-$H_2$ curve in an anterograde fashion.[4]

The supraventricular tachycardia of the first patient was aggravated by increased vagal tone and improved by atropine sulfate. Such paradoxical response has not been reported previously. One possible explanation is that increased vagal tone potentiated the unidirectional

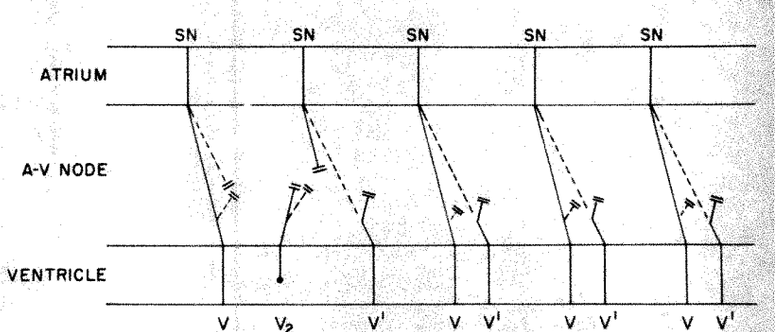



**FIGURE 8.** Mechanism of the programmed ventricular extrastimulus inducing supraventricular tachycardia. The ventricular extrasystole penetrated both pathways retrogradely, and was deep enough to prevent anterograde conduction of the first pathway. However, the slow pathway recovered soon enough to allow anterograde conduction. Presence of retrograde conduction block of both pathways enabled subsequent simultaneous anterograde conduction of the sinus P waves. SN = sinus node; V = QRS conducted through fast pathway; $V^1$ = QRS conducted through slow pathway.

retrograde block that is present in the AV nodal pathway in the basal state. The increased vagal tone insulates both AV nodal pathways and makes anterograde conduction through both AV nodal pathways possible. The supraventricular tachycardia in the second patient probably had the same mechanism as that in the first patient, although electrophysiologic study could not be performed. The episodes manifested by QRS complexes in groups of 5 are explained by the presence of 3 to 2 anterograde AV block through the slow pathway.

Procainamide has been reported to facilitate simultaneous conduction through dual AV nodal pathways by altering conduction and refractoriness of the anterograde fast and slow pathways of the AV node during atrial pacing.[3] However, we believe that the type 1 antiarrhythmic drug in our patients potentiated simultaneous conduction through dual AV nodal pathways by blocking retrograde conduction. Impairment of retrograde conduction of the AV node by these drugs has been reported previously.[5–7]

**Acknowledgment:** We thank Leonard Scherlis, MD, for review of the manuscript, Debbie Trust for secretarial assistance, and Frank Morris, MD, for referring the second case.

### References

1. **Wu D, Denes P, Dhingra R, Pietras RJ, Rosen KM.** New manifestations of dual A-V nodal pathways. Eur J Cardiol 1975;2:456–466.
2. **Csapo G.** Paroxysmal non-reentrant tachycardia due to simultaneous conduction in dual atrioventricular nodal pathways. Am J Cardiol 1979;43: 1033–1045.
3. **Gomes JAC, Kang PS, Kelen G, Khan R, El-Sherif N.** Simultaneous anterograde fast slow atrioventricular nodal pathway conduction after procainamide. Am J Cardiol 1980;46:677–684.
4. **Wu D.** Dual atrioventricular nodal pathways: a reappraisal. PACE 1982;5: 72–89.
5. **Shenasa M, Gilbert CJ, Schmidt DH, Akhtar M.** Procainamide and retrograde atrioventricular nodal conduction in man. Circulation 1982;65:355–362.
6. **Wu D, Hung J, Kuo C, Hsu K, Shieh W.** Effects of quinidine on atrioventricular nodal reentrant paroxysmal tachycardia. Circulation 1981;64:823–831.
7. **Swiryn S, Bauernfeind RA, Wyndham CRC, Dhingra RC, Palileo E, Strasberg B, Rosen KM.** Effects of oral disopyramide phosphate on induction of paroxysmal supraventricular tachycardia. Circulation 1981;64:169–175.

# Survival After Sudden Obstruction of The Left Main Coronary Artery

MOSHE Y. FLUGELMAN, MD, MEIR SHALIT, MD, ARIE SHEFER, MD, YONATHAN HASIN, MD, and MERVYN S. GOTSMAN, MD, FRCP

Left main coronary artery (LMCA) stenosis occurs in 10% of patients undergoing coronary arteriography, but total occlusion is rare.[1] Goldberg et al[2] reported 6 cases of complete obstruction of the LMCA among 2,200 patients studied arteriographically. Sudden obstruction of the LMCA should be lethal,[3] and we found no report describing survival with sudden obstruction of the LMCA. The present report describes such a patient.

*A 55-year-old man, a heavy smoker with no history of ischemic heart disease, had ventricular fibrillation 30 minutes after the onset of severe retrosternal chest pain. Sinus rhythm was restored after 6 direct-current cardioversions combined with lidocaine infusion. After resuscitation, pulmonary edema developed; the patient had a systolic blood pressure of 60 mm Hg, a pulse rate of 120 beats/min and frequent premature ventricular contractions. Electrocardiograms showed sinus tachycardia with frequent ventricular premature contractions and an acute extensive anterior myocardial infarction. The cardiac index, measured with a thermodilution Swan-Ganz catheter, was 1 liter/min/m$^2$. An intraaortic counterpulsation balloon was inserted through the right femoral artery during resuscitation; the blood pressure increased to 110/70 mm Hg and the cardiac index to 1.9 liters/min/m$^2$. Mechanical assistance was combined with intravenous treatment of glucose-potassium-insulin solutions and oral isorbide-dinitrate, digoxin, and diuretic agents. Cardiac catheterization and angiography, performed 15 days later, revealed a left ventricular end-diastolic pressure of 35 mm Hg, a large aneurysm of the anterior and apical regions, and normal contraction of the inferior wall. Coronary arteriography demonstrated complete obstruction of the LMCA (Fig. 1) while the right coronary artery was normal; there was no collateral filling of the left coronary system. The left ventricular ejection fraction was 16% with mechanical assistance and 5% without assistance.*

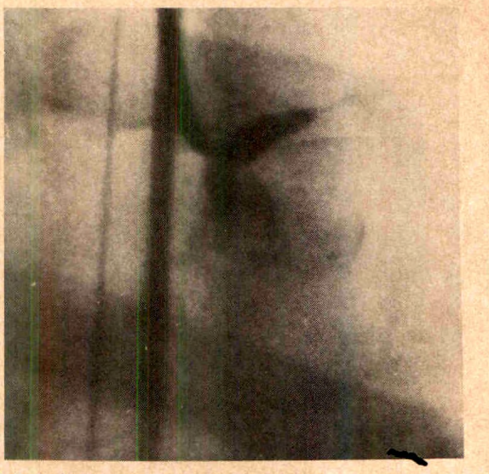


**FIGURE 1.** Left coronary arteriogram (right anterior oblique view) showing complete obstruction of the left main coronary artery.

*After 26 days, the patient developed a shaking chill and the intraaortic counterpulsation balloon was removed. The patient was discharged after 40 days. By this time he had signs of moderate congestive heart failure but no angina pectoris and was in New York Heart Association functional class III. On discharge, the cardiac index was 1.8 liters/*

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*min/m². Radionuclide angiography showed a left ventricular ejection fraction of 10%. A year later he was in functional class III.*

The fulminant course with no previous angina pectoris led us to the conclusion that the obstruction of the LMCA was sudden. The prognosis of severe LMCA narrowing is grave, but early intervention with mechanical support and afterload reduction permitted compensatory mechanisms during the 6 weeks after the infarct and allowed the patient to maintain a cardiac output compatible with life. Ventricular damage was severe, the patient has little cardiac reserve, and he remains severely disabled but alive 12 months later.

**Acknowledgment:** We thank D. R. Rosing, MD for reviewing the article and for his useful remarks.

## References

1. **Helfant RH, Banka VS.** Coronary heart disease. Philadelphia: FA Davis, 1978:66.
2. **Goldberg S, Grossman W, Markis JE, Cohen MV, Baltaxes HA, Levin DC.** Total occlusion of the left main coronary artery. A clinical, hemodynamic and angiographic profile. Am J Med 1978;64:3–8.
3. **Gotsman MS, Lewis BS, Bakst A.** Obstruction of the left main coronary artery—the artery of sudden death. S Afr Med J 1973;47:641–44.

# Hyperkalemia and Cardiac Arrest From Fluoride Exposure During Hemodialysis

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Hyperkalemia as a cause of death after fluoride intoxication has not been appreciated previously. The following report is the first documentation of fluoride-induced hyperkalemia in humans.

*Approximately 1,000 gallons of 22% hydrofluosilicic acid accidentally leaked into a small community's public water supply, raising fluoride levels in tap water samples to 30 ppm. The concentration did not return to acceptable levels (1.6 ppm) for 7 days.[1] Two days after the spill, 8 patients undergoing hemodialysis in an outpatient hemodialysis center developed gastrointestinal symptoms.[2] One patient was found dead at home soon afterward and another patient, the subject of this report, had cardiopulmonary arrest and was found to have marked hyperkalemia after resuscitation.*

*The patient is a 36-year-old white man with chronic renal failure and uremic pericarditis who developed diffuse pruritis 2 hours after the start of hemodialysis. Dialysis was discontinued 30 minutes later because of the development of pressure-like chest pain radiating to the neck, associated with dyspnea, nausea, vomiting, diaphoresis, diarrhea, and numbness in the right arm. After the symptoms abated he went home, but 14 hours later, the dyspnea recurred, and while en route to the hospital via ambulance, he had a cardiopulmonary arrest and was resuscitated.*

*Shortly thereafter he was alert but intubated. The blood pressure was 130/80 mmHg, the pulse 100 beats/min, the respiratory rate 24 breaths/min, and the temperature 96.2°F. Diffuse wheezing and bibasilar rales were present in the lungs, the heart was enlarged, and a grade 2/6 apical systolic crescendo-decrescendo murmur was present. The liver was enlarged and the abdominal cavity contained excessive fluid. The ankles and feet were edematous. The blood hematocrit was 23% and the leukocyte count 11,000/mm³. The serum sodium level was 138, chloride 98, bicarbonate 22, and potassium 10.5 mEq/liter. The blood urea nitrogen and glucose levels were 64 and 141 mg/100 ml. Free fluoride concentration was 0.4 mg/liter (normal 0.01 to 0.20). Arterial blood gas analysis while the patient was breathing 100% oxygen revealed a pH of 7.19, partial pressure of carbon dioxide 51 mm Hg, and partial pressure of oxygen 153 mm Hg. Electrocardiograms recorded sinus arrhythmia with an average rate of 70 beats/min, probable biatrial overload and left ventricular hypertrophy.*

*Cation exchange resin therapy and peritoneal dialysis were instituted, and 4 days later the arterial blood gases and serum electrolyte levels were normal.*

The connection between potassium alterations and death from fluoride poisoning has gone unnoticed in the literature. We previously observed a patient with fatal fluoride ingestion who developed markedly peaked T waves on the electrocardiogram before refractory ventricular fibrillation, were able to reproduce these electrocardiographic changes with fluoride administration in the experimental animal, and showed that they were indeed accompanied by elevated potassium levels.[3]

Fluoride, being the most electronegative element, is well known to lower the levels of cations such as calcium and magnesium because of the tight binding of the fluoride with these cations.[4] The exact mechanism of the hyperkalemia is not known but might be related to the toxic effects of fluoride on the cell membranes,[5] allowing potassium to leak into the blood.

The mode of exposure to the fluoride ion in this case is unusual and has not been previously described as a route of fluoride intoxication. If over 100 gallons of tap water with normal fluoride levels of 1 ppm is used by a patient during dialysis, up to 36 mg of fluoride can be absorbed in a single run. After the contamination of the public water supply, the dialysis patients were subjected to a very high fluoride load and since the elimination of fluoride is almost exclusively renal,[6] a patient with renal failure (undergoing repeated hemodialysis) will have no mechanism for excreting the very high fluoride load.

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### References

1. **Wax CM, Sorley DL, Israel E, Farrell KP, Joseph JM, Caplan YM.** Field investigation report—an outbreak of gastrointestinal illnesses in a dialysis unit as a consequence of overfluoridation in the Annapolis water supply. State of Maryland Department of Health and Mental Hygiene. March 1980.
2. Center For Disease Control. Fluoride intoxication in a dialysis unit. Morbid Mortal Weekly Rep 1980;29:134–136.
3. **Baltazar RF, Mower MM, Reider R, Funk M, Salomon J.** Acute fluoride poisoning leading to fatal hyperkalemia. Chest 1980;78:660–663.
4. **Rabinowitz VM.** Acute fluoride poisoning. Can Med Assoc J 1945;52:345.
5. **McIvor MC, Mower MM, Baltazar RF, Wenk RE, Lustgarten JA, Salomon J.** Biochemical implications in treatment of fluoride induced hyperkalemia. Clin Res 1982;30:703A.
6. **Buttner W, Karle E.** Chronic toxicity and retention of fluoride in the unilaterally nephrectomized rat. Caries Resp 1974;8:359–367.


# Coronary Arterial Rupture During Coronary Angioplasty


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and WILLIAM C. ROBERTS, MD


Although percutaneous transluminal coronary angioplasty (PTCA) appears to be a relatively safe and effective procedure, reported complications include coronary occlusion and dissection with or without acute myocardial infarction.[1,2] Herein, a hitherto unreported complication of PTCA is described.


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*A 77-year-old man with unstable angina pectoris by coronary angiography had focal severe stenosis of a dominant right coronary artery (Fig. 1a), a normal left coronary system, and normal left ventricular function. PTCA of the right coronary artery was performed. The tight stenosis prevented appropriate placement of a 2-mm Gruntzig catheter; therefore, the narrowing was dilated initially by multiple inflations of a Simpson catheter advanced across a guide wire, and subsequently by a 3-mm Gruntzig catheter at 4 atm (Fig. 1b). Post-PTCA angiograms demonstrated mild residual stenosis (Fig. 1c). Coronary angiography 3 months later disclosed significant stenosis again at the site of the previous dilatation procedure (Fig. 1d). Repeat PTCA was performed. Multiple inflations of a 3-mm Gruntzig catheter at a maximal pressure of 9 atm reduced the stenosis to about 60% diameter reduction. A 3.7-mm Gruntzig catheter was then positioned and inflated 5 times at a maximal pressure of 10*

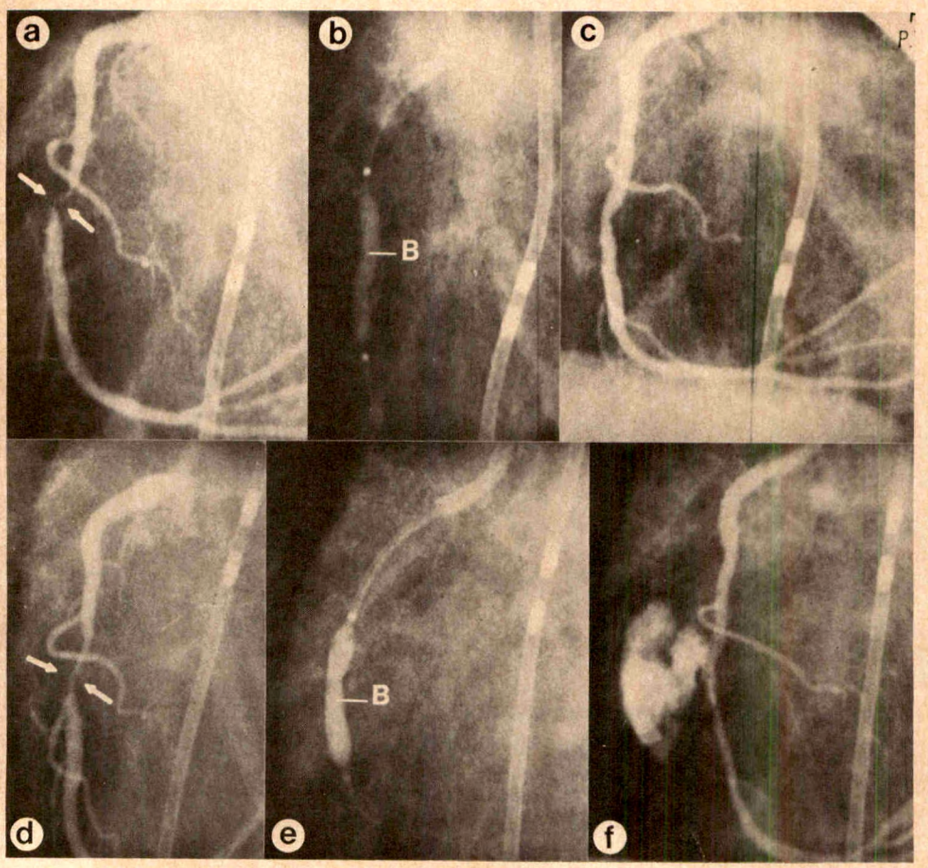



**FIGURE 1.** Right coronary arteriograms before (**a** and **d**), during (**b** and **e**), and after (**c** and **f**) percutaneous transluminal coronary angioplasty (PTCA). **a,** a discrete severe narrowing is present (**arrows**). **b,** the stenosis was dilated by a 3-mm Gruntzig balloon (B) catheter. **c,** mild residual narrowing remained after the first PTCA procedure. **d,** the previously dilated area was again severely narrowed (**arrows**) 3 months after the first PTCA procedure. **e,** the narrowing was dilated by a 3.7-mm Gruntzig balloon (B) catheter. **f,** arteriography after PTCA showed leakage of contrast material into the epicardial tissues. The luminal diameter immediately proximal and distal to the narrowing is approximately equal to that of the pacing catheter (**d**). The diameter of the inflated balloon (**e**) is larger than that of the pacing catheter and thus exceeds the diameter of the nonstenotic arterial lumen.

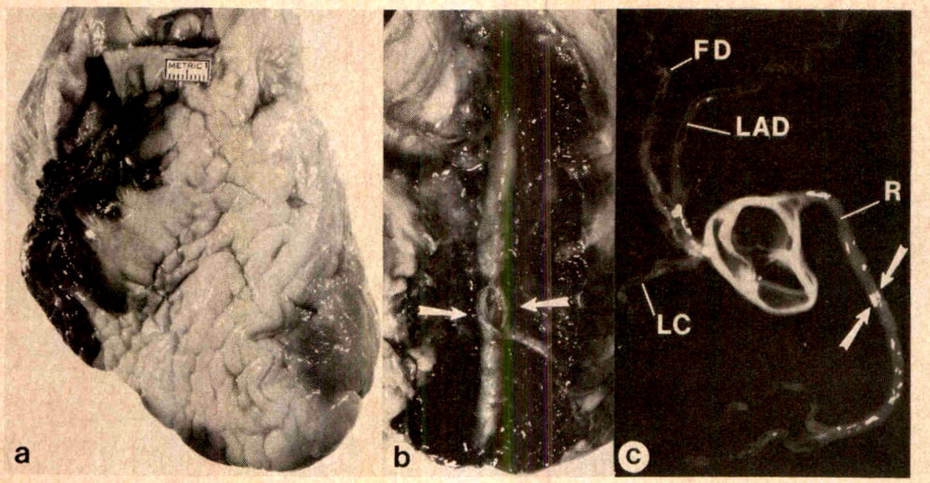



**FIGURE 2. a,** Photograph of heart showing hemorrhage in the right atrioventricular sulcus which contains the right coronary artery. **b,** a rupture site (**arrows**) in the right coronary artery 3.5 cm from the aortic ostium. **c,** radiograph of the major epicardial coronary arteries demonstrating focal calcific deposits. **Arrows** designate the site of rupture of the right (R) coronary artery. FD = first diagonal; LAD = left anterior descending; LC = left circumflex. (Photographs by M. M. M. Moore.)

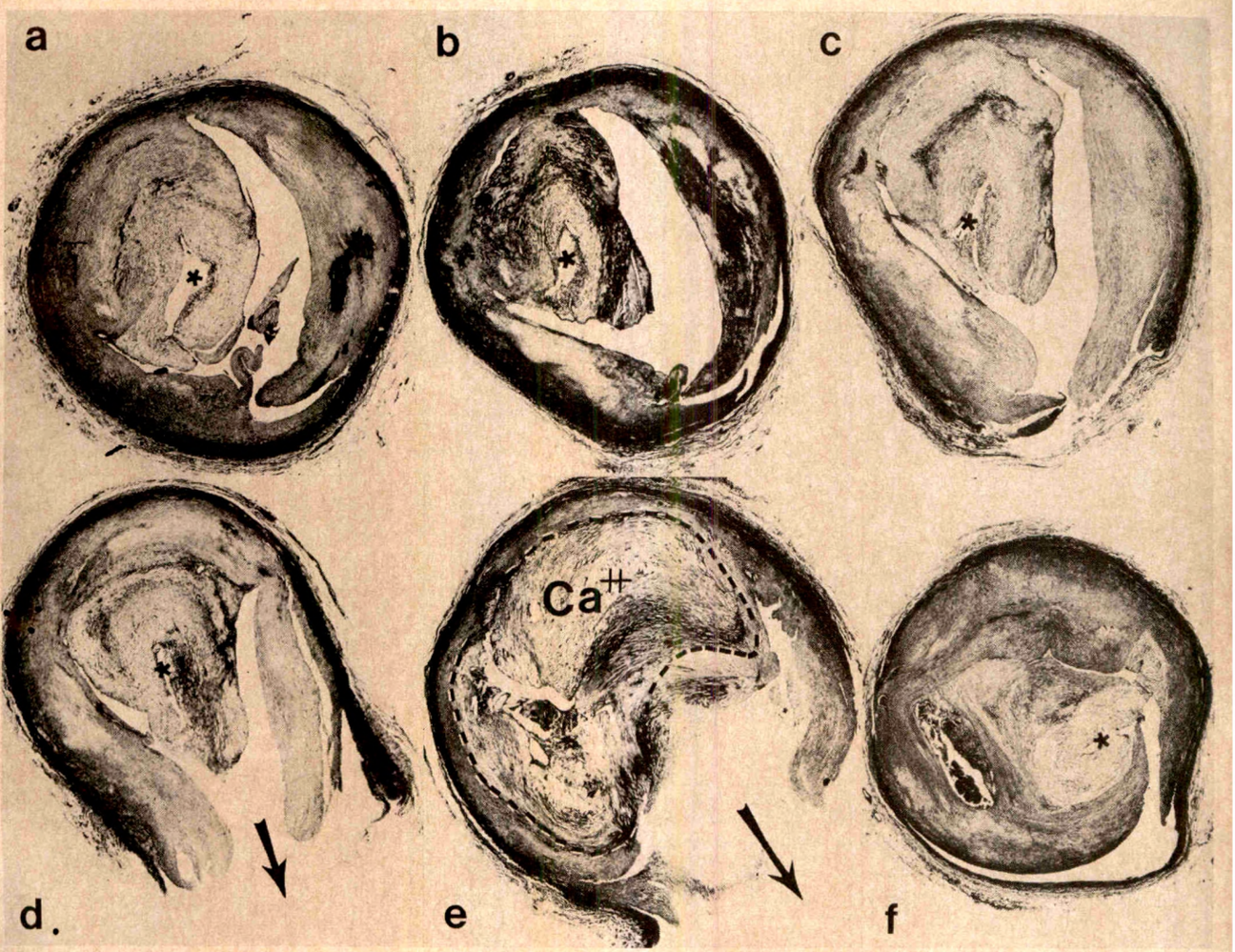



**FIGURE 3.** Photomicrographs of cross-sections of the right coronary artery in the vicinity of the rupture site. Proximal to the rupture site (**a**) the atherosclerotic plaque is split. This split communicates with the original lumen, indicated by the **asterisks.** The split extends through the media (**b**) and adventitia (**c**) until through-and-through rupture (**arrows**) occurs (**d,e**). Rupture occurred opposite a large calcified ($Ca^{++}$) plaque (outlined by **dashed line**). Distal to the rupture site (**f**), additional splitting of the intimal plaque is seen communicating with the original lumen.

**TABLE I Number of 5-mm Segments of the 4 Major Epicardial Coronary Arteries Showing the 4 Grades of Cross-Sectional Area Narrowing**

| Coronary Artery | Length (cm) | 5-mm Segments (n) | 5-mm Segments (n) Narrowed to Each of 4 Categories of Cross-Sectional Area Narrowing | | | |
|---|---|---|---|---|---|---|
| | | | 0–25% | 26–50% | 51–75% | 76–100% |
| R | 8.5 | 17 | 1 | ... | 9 | 7 |
| LM | 0.5 | 1 | ... | 1 | ... | ... |
| LAD | 9.0 | 18 | 2 | 11 | 5 | ... |
| LC | 4.5 | 9 | 3 | 6 | ... | ... |
| Totals | 22.5 | 45 | 6 (13%) | 18 (40%) | 14 (31%) | 7 (16%) |

LAD = left anterior descending, LC = left circumflex, LM = left main, and R = right coronary artery.

*atm (Fig. 1e). On the fifth inflation, the proximal end of the balloon ruptured. Angiography then demonstrated extravasation of contrast material into the epicardial tissue plus run-off into the distal right coronary artery (Fig. 1f). The heart rate and arterial blood pressure quickly decreased; blood was drained from the pericardial sac, but fatal cardiac arrest ensued.*

*At necropsy, the heart weighed 265 g. The epicardial adipose tissue surrounding the right coronary artery was hemorrhagic (Fig. 2a) and an elliptical rupture site measuring 0.6 cm in the long axis was present in the right coronary artery 3.5 cm from the ostium (Fig. 2b). Radiographs of the major epicardial coronary arteries (Fig. 2c) disclosed focal calcific deposits. The results of histologic examination of 5-mm segments of the major epicardial coronary arteries are shown in Table I. A 1.7-cm segment of right coronary artery containing the rupture site was subserially sectioned and photomicrographs of several sections are illustrated in Figure 3.*

It is clear that the right coronary artery in the patient just described ruptured during the PTCA procedure. At the site of the arterial rupture, the lumen of the artery was extremely small and a large amount of calcium was present in the atherosclerotic plaque. In addition, the artery itself was quite small. (The patient weighed only 105 pounds and the heart weighed only 265 g.) The presence of a *small, rigid (calcified) artery* and the use of a *balloon larger than the artery* itself caused the arterial rupture in this patient. Balloon dilatation was successful in enlarging the lumen by splitting the plaque. However, the splitting was not limited to plaque but extended into the media and adventitia, resulting in fatal rupture.

To our knowledge, rupture of a coronary artery during PTCA has not been reported previously. The lesson of this case is that angioplasty balloons larger than the artery to be dilated should not be employed.

### References

1. **Dorros G, Cowley M, Simpson J.** Members of Executive Committee of NHLBI-PTCA Registry. National Heart, Lung, and Blood Institute registry report of complication of percutaneous transluminal angioplasty (abstr). Am J Cardiol 1981;47:396.
2. **Bourassa MG.** Percutaneous transluminal coronary angioplasty—still an investigational procedure. Mayo Clin Proc 1981;56:334–335.

# Q-T Prolongation and Torsades de Pointes Ventricular Tachycardia Produced by the Tetracyclic Antidepressant Agent Maprotiline

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Tricyclic antidepressant drugs such as imipramine and desipramine have long been known to produce cardiovascular side effects including sinus tachycardia, prolongation of the P-R, QRS, and Q-T intervals, and decreased T-wave amplitude.[1,2] Life-threatening ventricular ectopic activity has occurred after tricyclic drug overdose.[3] Recently, maprotiline (Ludiomil®), a tetracyclic anthracene-derivative antidepressant, has become available for the treatment of affective disorders. It appears as effective as the tricyclic drugs in relieving unipolar depression.[4–6] Although several studies have reported a low incidence of cardiovascular side effects,[4,6] others show little difference between the tetracyclic and tricyclic drugs.[2,4,5] This report describes a patient in whom maprotiline treatment caused Q-T prolongation and life-threatening torsades de pointes ventricular tachycardia (VT).

From the Medical Services, Massachusetts General Hospital, Boston, Massachusetts. Manuscript received October 18, 1982; revised manuscript received December 3, 1982, accepted December 6, 1982.

*An 81-year-old woman was hospitalized after falling from a chair. She had previously been treated for recurrent depression with imipramine, desipramine, doxepin, and methylphenidate, which were discontinued because of anticholinergic side effects or poor compliance. Treatment with maprotiline (25 mg daily) was begun 10 months before admission. The dosage was increased to 50 mg daily 1 month before admission and then to 62.5 mg 8 days before her fall. The patient was also taking levothyroxine (0.125 mg), tol-*

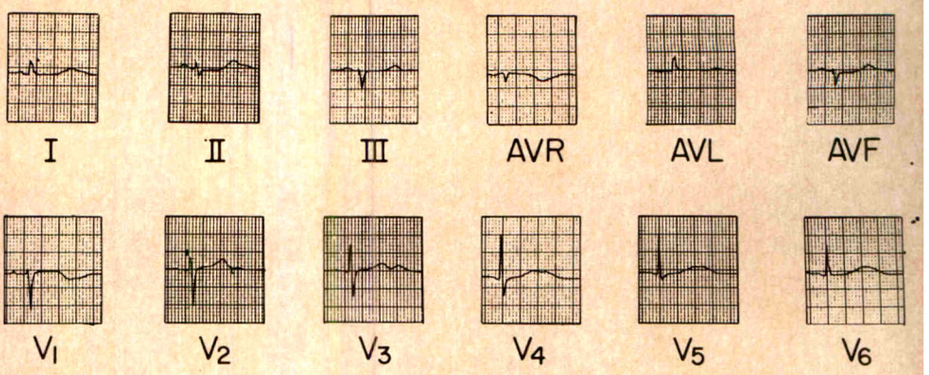



**FIGURE 1.** Admission electrocardiogram.

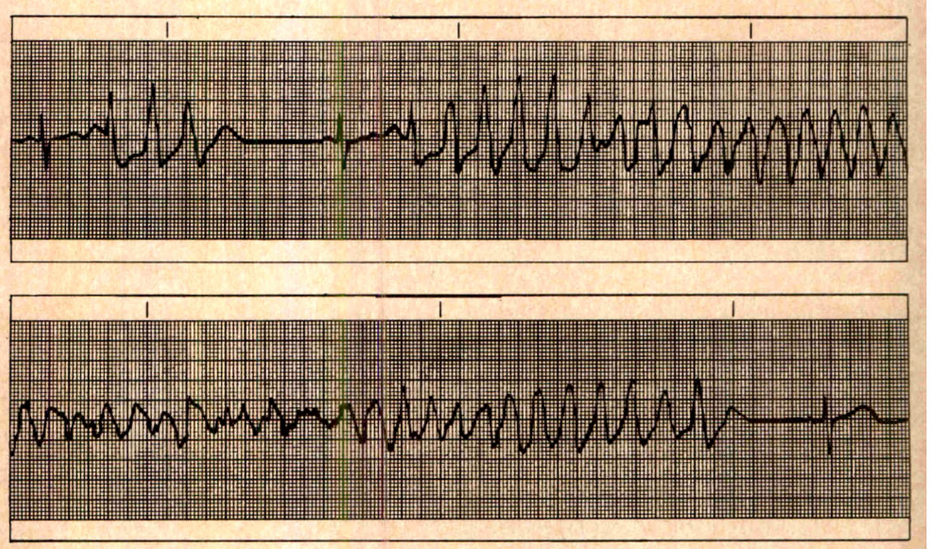


**FIGURE 2.** Ventricular ectopy with torsades de pointes.

*butamide (500 mg), hydrochlorothiazide (25 mg), and spironolactone (25 mg).*

*On arrival at the hospital, the patient had a regular pulse and was normotensive. She had no precordial murmurs and no neurologic abnormalities. Electrolyte and thyroid function tests gave normal results; the electrocardiogram revealed a prolonged Q-T interval of 0.64 second at a rate of 75 beats/min (Fig. 1). In the emergency room, ventricular bigeminy and runs of VT developed which were suppressed with intravenous lidocaine. All medications were discontinued and she received 1 dose of oral propranolol which was then stopped because of sinus bradycardia. Because of recurring VT, her antiarrhythmic regimen was changed to intravenous bretylium (300 mg bolus and infusion at 2 mg/min). A prolonged episode of torsades de pointes configuration VT causing hypotension and loss of consciousness occurred 30 hours after admission (Fig. 2). At that time, she was still receiving bretylium and had a serum potassium level of 4.1 mEq/liter (normal range 3.5 to 5.0). Dilantin was begun and over the ensuing 4 days, no further ectopy occurred and all antiarrhythmic drugs were gradually withdrawn and discontinued. The Q-T interval gradually shortened in association with a measured decrease in serum maprotiline level (Table I). A 24-hour ambulatory electrocardiogram, recorded just before discharge while the patient was taking her original medications (except maprotiline) and no antiarrhythmic drugs, disclosed a Q-T interval of 0.42 second ($Q\text{-}T_c$ = 0.43). No ventricular ectopic activity was recorded.*

We report the occurrence of a prolonged Q-T interval resulting in VT and torsades de pointes in a patient taking the tetracyclic antidepressant, maprotiline. Prolongation of the Q-T interval predisposes to reentrant arrhythmias probably by increasing the disparity in ventricular repolarization. In our patient, Q-T prolongation and consequent torsades de pointes occurred coincident with a recent increase in maprotiline dosage and resolved after discontinuation of the drug and a decrease in the serum maprotiline level. The increased Q-T interval observed 24 to 36 hours after the last dose was taken may be due to a cardioactive metabolite of maprotiline or a drug interaction, as with levothyroxine. Thus, the tetracyclic antidepressant drug maprotiline may cause Q-T prolongation similar to that seen with the closely related tricyclic antidepressants, and this effect can occur at a therapeutic serum concentration. We recommend that physicians prescribing maprotiline maintain the same vigilance for cardiovascular side effects as that currently accorded tricyclic antidepressant drugs.

**TABLE I Serum Maprotiline Levels and Q-T Intervals With Time**

| Time After Last Dose (days) | Maprotiline Level (ng/ml)* | Q-T Interval (s) | Q-$T_c$† (s) |
|---|---|---|---|
| 1 (A.M.) | 169 | 0.68 | 0.683 |
| (P.M.) | 118 | ... | ... |
| 2 (A.M.)‡ | 82 | 0.84 | 0.808 |
| (P.M.) | ... | 0.77 | 0.794 |
| 3 | 69 | 0.76 | 0.700 |
| 4 | 54 | 0.60 | 0.588 |
| 5 | 31 | 0.55 | 0.545 |
| 6 | 55 | 0.48 | 0.500 |

* Therapeutic level = 100 to 300 ng/ml[4]; reported half-life = 43 to 48 hours.[6]

† Q-$T_c$ = Q-T interval (including U wave)/$\sqrt{\text{R-R interval}}$ (upper limit of normal for adult woman = 0.43 second).

‡ Occurrence of torsades VT.

**Acknowledgment:** We thank Mark Fishman, MD, for his support and Sibylle Barlow for typing the manuscript.

## References

1. **Giardina E, Bigger JT, Glassman AH, Perel JM, Kantor SJ.** The electrocardiographic and antiarrhythmic effects of imipramine hydrochloride at therapeutic plasma concentrations. Circulation 1979;60:1045–1052.
2. **Burckhardt D, Raeder E, Miller V, Imhol P, Nebauer H.** Cardiovascular effects of tricyclic and tetracyclic anti-depressants. JAMA 1978;239:213–216.
3. **Fasoli RA, Glaiser FL.** Cardiac arrhythmias and ECG abnormalities in tricyclic antidepressant overdose. Clin Tox 1981;18:155–163.
4. **Pinder RM, Brogden RN, Speight TM, Avery GS.** Maprotiline: a review of its pharmacologic properties and therapeutic efficacy in mental depressive states. Drugs 1977;13:321–352.
5. **Sims ACP.** Comparison of the efficacy of sustained-release amitryptiline with maprotiline in the treatment of depressive illness. Curr Med Res Opinion 1980;6:534–539.
6. **Forrest WA.** Maprotiline in depression: a report of a monitored release study of 10,000 patients in general practice. J Int Med Res 1977;5:42–47.

# Angiographic Evidence of Hemorrhagic Myocardial Infarction After Intracoronary Thrombolysis With Streptokinase

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The reperfusion of acutely ischemic myocardium by intracoronary streptokinase thrombolysis is an exciting new therapy for acute myocardial infarction (MI).[1] It appears that successful thrombolysis and reperfusion in the first few hours after acute coronary occlusion may salvage myocardium and possibly improve prognosis. A potential adverse effect of reperfusion is the production of hemorrhage in the area of myocardial necrosis.[2–4] We report on a patient with prompt, successful coronary thrombolysis by streptokinase infusion who showed angiographic evidence of a hemorrhagic MI.

*A previously well 72-year-old man was admitted with chest pain of 1 hour's duration. An electrocardiogram showed an acute inferior wall MI (Fig. 1). Immediate coronary angiography demonstrated no significant narrowing of the left coronary system but complete occlusion of the proximal portion of the right coronary artery (Fig. 2, left). The angiogram was unchanged after intracoronary administration of 200 μg of nitroglycerin. The intracoronary administration of a 10,000 unit bolus of streptokinase followed by an infusion of 2,500 units/min for 30 minutes produced no change. A 0.035 inch flexible tipped guidewire was passed through the occlusion in the right coronary artery, and streptokinase was infused for another 15 minutes. Repeat angiography (approximately 2.5 hours after the onset of chest pain) demonstrated that the right coronary artery was patent with a residual high-grade stenosis of the proximal and middle portions (Fig. 2, right). A nonopacified lucency probably represented thrombus was seen to move from the area of previous occlusion in the proximal right coronary and lodge in the midportion of the posterior descending artery. After injection of the right coronary artery, contrast material was seen in the wall of the left ventricle (Fig. 3, left). On the subsequent left ventriculogram, the intramyocardial contrast material was seen in the endocardium of the posterior basilar segment of the left ventricle, in an area of localized akinesia (Fig. 3, right). A resting thallium scan immediately after reperfusion showed a large area of markedly decreased thallium uptake in the inferior wall (Fig. 4). Twenty-four hours after reperfusion, the subendocardial contrast material was again visualized fluoroscopically and repeat angiography demonstrated that the right coronary artery remained patent. The filling defect in the mid-posterior descending coronary artery had resolved. A 2-dimensional echocardiogram demonstrated inferoposterior hypokinesia before reperfusion. After reperfusion, the inferoposterior wall had become akinetic and the apex was hypokinetic. Initially, the electrocardiograms (Fig. 1) demonstrated an evolving inferior*

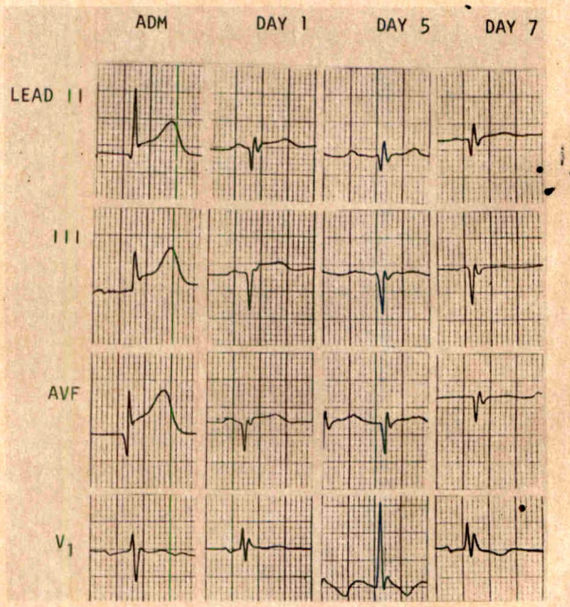



**FIGURE 1.** Serial electrocardiograms.

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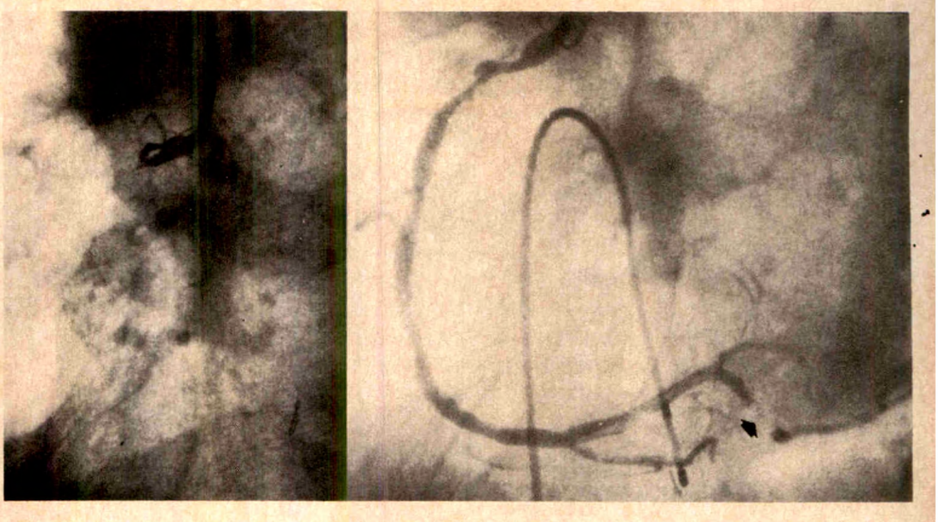


**FIGURE 2. Left,** right coronary angiogram demonstrating complete occlusion in its proximal portion. **Right,** after guide wire probing and intracoronary streptokinase, the right coronary artery was patent with residual stenosis. A filling defect thought to represent the occluding thrombus was seen to move from the area of initial occlusion and lodge in the mid-posterior descending coronary artery (**arrow**).

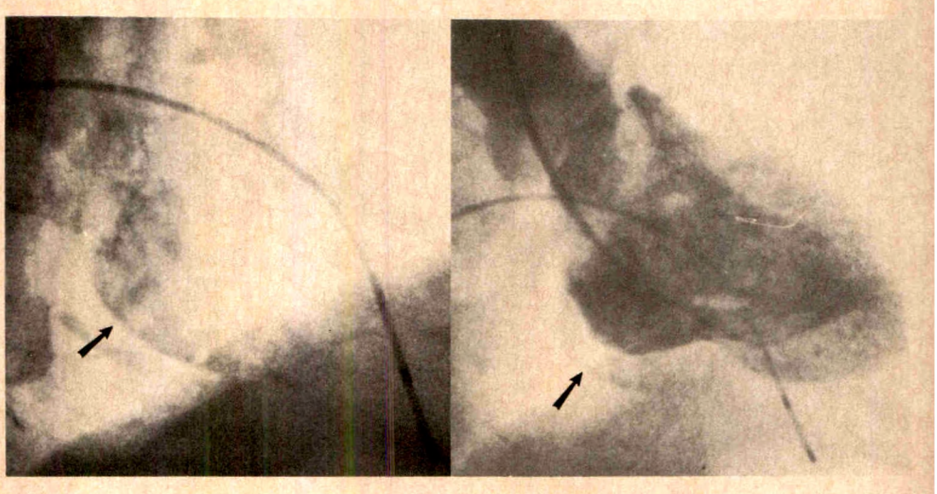


**FIGURE 3.** After the coronary angiogram (Fig. 2, right), contrast medium was seen in the myocardium (**left, arrow**). This intramyocardial contrast medium in the ensuing left ventriculogram (**right, arrow**) was in the subendocardium of the inferobasilar left ventricle in an area of localized akinesia.

*MI, but despite continued patency of the right coronary artery, they subsequently showed incomplete right bundle branch block and suggested posterior extension of the MI.*

*The patient was placed on heparin infusion for 7 days after thrombolysis, and his subsequent hospital course was complicated by a femoral hematoma and transient pericarditis. He was discharged on the 14th hospital day and his subsequent convalescence was uneventful.*

In this patient, who presented with symptoms and electrocardiographic changes of an acute transmural inferior MI, prompt recanalization of the occluded right coronary artery was associated with extravasation of angiographic contrast medium from the reopened right coronary artery into the subendocardium of the posterior basilar left ventricular wall. This subendocardial contrast persisted at least 24 hours.

Experimentally, hemorrhagic MI has been produced by coronary reperfusion after transient occlusion.[3,4] Experimentally, such hemorrhage occurs in areas of the most severe myocardial ischemia where cell injury is already irreversible.[3] In our patient, extravasation of contrast medium was limited to the subendocardium where ischemia would be most severe. It is possible that hemorrhage into already necrotic myocardium may jeopardize adjacent islands of potentially viable myocardium.[4] We are unable to determine whether the production of hemorrhagic MI adversely affected our patient; however, several observations suggest that it did. The inferoposterior left ventricular wall which was

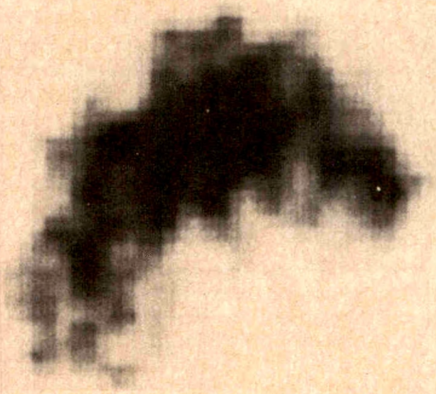


**FIGURE 4.** Resting thallium scan (lateral view) obtained after thrombolysis showing markedly decreased uptake in the inferior left ventricular wall.

hypokinetic as visualized on 2-dimensional echocardiography before reperfusion was akinetic on both echocardiography and angiography after reperfusion. In addition, the apex became hypokinetic despite reperfusion. There was no thallium uptake in the inferior wall after thrombolysis, and the serial electrocardiogram suggested extension of the initial inferior MI to the posterior wall. These observations suggesting no benefit from reperfusion and possible deterioration after thrombolysis did not result from either an inordinate delay in reperfusion or early reocclusion of the artery.

The finding of postreperfusion extravasation of contrast medium into the myocardium may be a useful angiographic sign of the production of hemorrhagic MI by coronary thrombolysis that merits further observation and study.

### References


1. **Rentrop P, Blanke H, Karsch KR, Kaiser H, Kostering H, Leitz K.** Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. Circulation 1981;63:307–317.
2. **Mathey DG, Kloppel G, Kuck K, Feil U, Schofer J.** Transmural, hemorrhagic infarction following intracoronary streptokinase: clinical, angiographic and autotopical findings (abstr). Circulation 1981;64:Suppl-IV:IV-731.
3. **Fishbein MC, Rit RY, Lando U, Kanmatsuse K, Mercier JC, Ganz W.** The relationship of vascular injury and myocardial hemorrhage to necrosis after reperfusion. Circulation 1980;62:1274–1279.
4. **Bresnahan GF, Roberts R, Shell WE, Ross J Jr, Sobel BE.** Deleterious effects due to hemorrhage after myocardial reperfusion. Am J Cardiol 1974;33: 82–86.


# Real-Time 2-Dimensional Echocardiographic Visualization of Thrombus on a Björk-Shiley Mitral Valve Prosthesis

## Emergency Cesarean Section and Mitral Valve Replacement in Late Pregnancy

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Echocardiography is invaluable in the assessment of cardiac valves, but the signs of prosthetic valve dysfunction may be difficult to interpret, especially in patients with metallic valve prostheses.[1–4]

*A 25-year-old woman underwent mitral valve replacement with a 29 mm Björk-Shiley prosthesis. On routine examination 5 years later, she was well and the prosthesis appeared to be functioning normally. She was receiving warfarin (prothrombin index 32%), but because she was then 38 weeks pregnant, warfarin was replaced by intravenous heparin. Five days later the patient had left anterior chest pain and an episode of hypotension. Examination revealed muffling of the prosthetic valve sounds. However, blood pressure soon returned to normal, and on cinefluoroscopy the disc moved normally. Real-time 2-dimensional echocardiography showed a large mass on the ventricular surface of the prosthetic valve disk (Fig. 1). Disc excursion was normal. The left ventricle contracted well, and the left atrium was enlarged 2.5 times the diameter of the aortic root. The diagnosis of prosthetic valve thrombosis with intermittent mitral valve obstruction was made.*

*The clinical state deteriorated. Emergency Cesarean section was performed and a healthy boy was delivered. The chest was opened and cardiopulmonary bypass established. A large, fresh thrombus was present on the ventricular surface of the prosthesis (Fig. 2). The valve was replaced with*

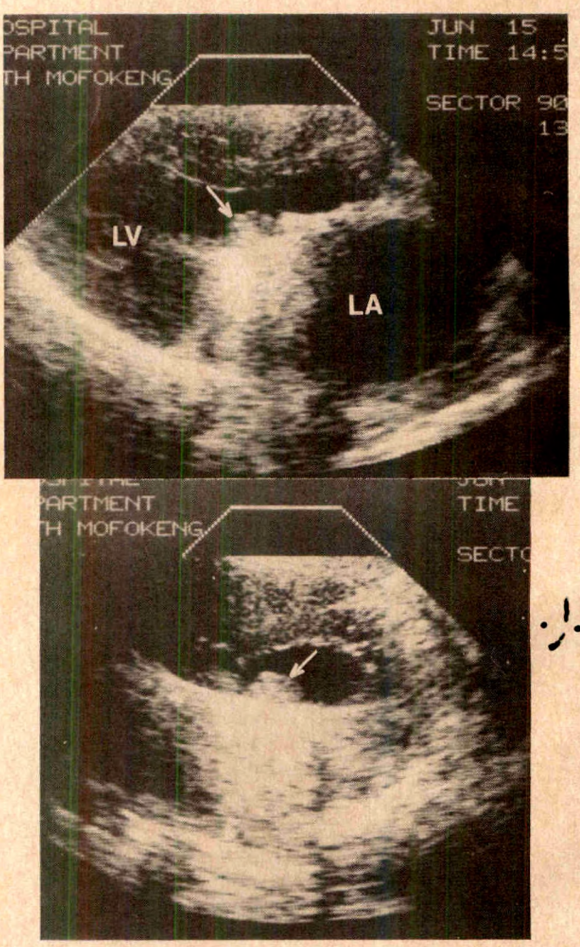



**FIGURE 1. Top,** real-time 2-dimensional echocardiogram (parasternal long-axis view in diastole) showing a mass (**arrow**) on the ventricular surface of the Björk-Shiley disc. LA = left atrium; LV = left ventricle. **Bottom,** parasternal short-axis view (diastolic frame) showing the thrombus (**arrow**) in the left ventricular outflow tract.

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*a Hall-Kaster prosthesis, the patient made an uneventful recovery, and both mother and child were discharged well 2 weeks later.*

Two-dimensional echocardiography is useful in identifying masses on bioprosthetic valves,[5] but it is difficult to demonstrate thrombus on the disc of a Björk-Shiley prosthesis because of bright echocardiographic reflections from the valve itself. Serial studies may show changes in the amplitude, velocity, pattern, or timing of disc motion,[2–4,6–8] whereas abnormal left ventricular filling rate[9] may indicate impaired mitral blood flow. In our patient, the major part of the thrombus formed on the ventricular surface of the disc. The echocardiographic beam reached the thrombus before the valve, and we recorded high quality images of the mass, corresponding exactly to the findings at operation. Direct visualization of the thrombus was invaluable because obstruction to blood flow was intermittent. At echocardiography the patient was asymptomatic and cinefluoroscopy gave normal results.

The diagnosis of a clotted mitral valve prosthesis at 38 weeks of pregnancy posed interesting problems in management. The transfer from warfarin to heparin is routine, but we urge great vigilance because thrombosis of the mitral Björk-Shiley prosthesis is not rare.[10] Clinical deterioration in our patient's condition necessitated immediate obstetric and cardiac intervention which were performed successfully at the same operating session.



**FIGURE 2.** Excised Björk-Shiley mitral valve showing extensive tissue ingrowth and a large mound of thrombus on the ventricular surface of the disk.

### References


1. **Feigenbaum H.** Echocardiography. 3rd ed. Philadelphia: Lea & Febiger, 1980.
2. **Brodie BR, Grossman W, McLaurin L, Starek PJK, Craige E.** Diagnosis of prosthetic mitral valve malfunction with combined echo-phonocardiography. Circulation 1976;53:93–100.
3. **Cunha CLP, Giuliani ER, Callahan JA, Pluth JR.** Echophonocardiographic findings in patients with prosthetic heart valve malfunction. Mayo Clin Proc 1980;55:231–242.
4. **Mintz GS, Carlson EB, Kotler MN.** Comparison of non-invasive techniques in evaluation of the non-tissue cardiac valve prosthesis. Am J Cardiol 1982;49:39–44.
5. **Schapira JN, Martin RP, Fowles RE, Rakowski H, Stinson EB, French JW, Shumway NE, Popp RL.** Two-dimensional echocardiographic assessment of patients with bioprosthetic valves. Am J Cardiol 1979;43:510–519.
6. **Douglas JE, Williams GD.** Echocardiographic evaluation of the Björk-Shiley prosthetic valve. Circulation 1974;50:52–57.
7. **Escarous A.** The Björk-Shiley tilting disc valve prosthesis. Echocardiographic findings. Scand J Thorac Cardiovasc Surg 1975;9:192–196.
8. **Barnal-Ramirez JA, Phillips JH.** Echocardiographic study of malfunction of the Björk-Shiley prosthetic heart valve in the mitral position. Am J Cardiol 1977;40:449–453.
9. **Upton MT, Gibson DG.** The study of left ventricular function from digitized echocardiograms. Prog Cardiovasc Dis 1978;20:359–384.
10. **Copans H, Lakier JB, Kinsley RH, Colsen PR, Fritz VU, Barlow JB.** Thrombosed Björk-Shiley mitral prostheses. Circulation 1980;61:169–174.


# Cardiac Rhabdomyosarcoma Presenting as Hypereosinophilic Syndrome

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We report herein the first patient with intracardiac rhabdomyosarcoma presenting with a clinical syndrome mimicking Löffler's endocarditis[1–4] with profound eosinophilia and refractory congestive heart failure.

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*A 59-year-old white man was well until 4 months before death when fatigue, fever, and the onset of a 35-pound weight loss developed. Electrocardiograms (Fig. 1) 5 days before death showed acute anterior wall injury, right axis deviation, probable right ventricular hypertrophy, nonspecific T-wave changes, and right intraventricular conduction delay. The white blood cell count was 90,000 cells/mm$^3$ with 57% eosinophils. Serial electrocardiograms showed no changes and serial creatine phosphokinase enzymes were normal. Examination 24 hours before death disclosed a supine blood pressure of 80/50 mm Hg, without pulses paradoxicus and sinus rhythm. The neck veins were distended to the angle of the mandible at 90°. The heart sounds were reduced and no murmurs were heard. The patient was transferred to the Ohio State University Hospitals.*

*The electrocardiogram was unchanged and the chest radiograph showed borderline cardiomegaly with clear lung fields. Serum lactate dehydrogenase was 3,010 U/ml (normal up to 440), and creatine phosphokinase was 7 U/ml (normal up to 12 U/ml), increasing 12 hours later to 13 U/ml with 7% MB band. The serum immunoglobulin E (IgE) level was 193 U/ml (normal up to 455). The total eosinophil count was 14,200 cells/mm$^3$. A bone marrow aspirate showed 30% eosinophils with a predominance of mature forms. Right-sided*

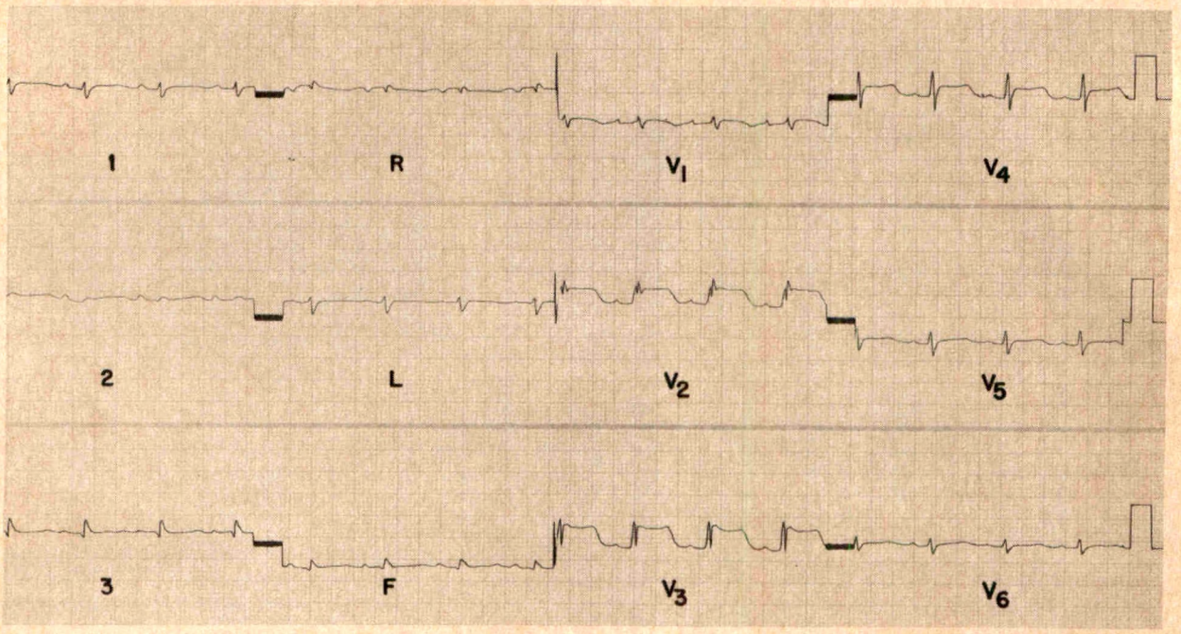



**FIGURE 1.** Twelve-lead electrocardiogram. The unusual, localized anterior epicardial injury pattern is demonstrated.

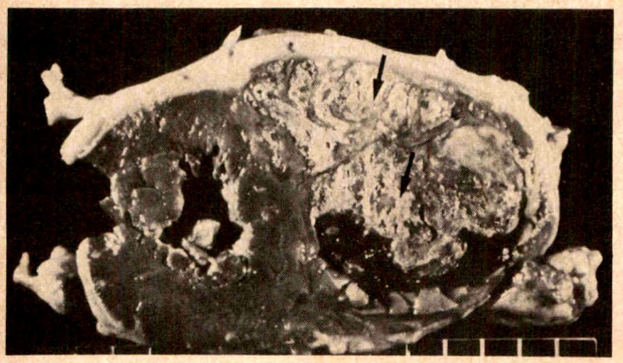


**FIGURE 2.** Gross pathology specimen of the sectioned heart. Extensive infiltration by the cardiacc rhabdomyosarcoma into the right ventricular cavity is evident.

*cardiac catheterization disclosed a right atrial mean pressure of 22 mm Hg and a right ventricular pressure of 33/20 mm Hg with unusual sinusoidal appearing wave forms. The pulmonary trunk could not be entered. A 2-dimensional echocardiogram was of poor quality and showed only right atrial enlargement. The patient died within 24 hours after hospitalization.*

*At autopsy, the heart weighed 910 g. Necrotic tumor arose from the right ventricular free wall and virtually filled the entire right ventricular cavity, with extensive invasion of the right ventricular myocardium and ventricular septum (Fig. 2). Several tumor nodules up to 0.5 cm in diameter were found in the left ventricular wall and hilar lymph nodes. Histologically, the tumor was composed of large cells with irregularly shaped nuclei and prominent nucleoli. Multinucleation and strap cells were present. Special staining with phosphotungstic acid hematoxylin and for nicotinamide adenine dinucleotide in reduced form (NADH) revealed striations characteristic of rhabdomyosarcoma.*

To our knowledge, eosinophilia and rapidly progressive congestive heart failure have never been reported with a primary intracardiac tumor. As the course of these unusual neoplasms might be altered favorably by surgical intervention,[5] the diagnosis should be suspected in patients with eosinophila and profound congestive heart failure, especially when intracardiac mass lesions are identified.

## References

1. **Chusid MJ, Dale DC, West BC, Wolff SM.** The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine 1975;51: 1–27.
2. **Parillo JE, Borer JS, Henry WL, Wolff SM, Fauci AS.** The cardiovascular manifestations of the hypereosinophilic syndrome. Am J Med 1979;67: 572–582.
3. **Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH.** The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic and therapeutic considerations. Ann Intern Med 1982;97:78–92.
4. **Hall SW, Theologides A, From AHL, Gobel FL, Fortuny IE, Lawrence CJ, Edwards JE.** Hypereosinophilic syndrome with biventricular involvement. Circulation 1977;55:217–223.
5. **McAllister HA.** Primary tumors and cysts of the heart and pericardium. In: Harvey WP, ed. Curr Probl Cardiol 1979;4:1–51.

POINT OF VIEW

# How Should We Describe Hearts in Which the Aorta Is Connected to the Right Ventricle and the Pulmonary Trunk to the Left Ventricle?

## A Matter for Reason and Logic

ANTON E. BECKER, MD and ROBERT H. ANDERSON, MD, BSc

There is undoubtedly a need for cataloguing succinctly anomalous hearts in which the aorta is connected to the morphologic right ventricle and the pulmonary trunk to the morphologic left ventricle. Excluding more complex cases in which either the atrial chambers are deformed (splenic syndromes) or the atrial chambers are connected to only 1 ventricular chamber (tricuspid atresia and single ventricle), there are 2 basic chamber arrangements that exist with this discordant ventriculoarterial connection. In the most common pattern the atrial chambers connect concordantly with their appropriate ventricles. In the less common type, a discordant connection is present at both atrioventricular and ventriculoarterial junctions. The need exists for terms that describe precisely these chamber combinations and only these combinations. They previously were termed *complete* and *congenitally corrected transposition*, respectively. Nowadays it is much more usual to see the terms *d*- and *l-transposition* employed for cataloguing these general segmental combinations. We question the latter practice on grounds of necessity and scientific inaccuracy. The old terms *complete* and *congenitally corrected* seemed to us sufficiently precise to negate the need for new ones, particularly when the newer terms, describing relationships, are poorly suited to describe segmental connections. Moreover, this use of relationship terms in a connections fashion was not initially intended by Van Praagh and his colleagues.[1,2]

There is one justifiable criticism of the use of *complete* to qualify transposition. When introduced, the adjective distinguished that variety in which both arteries arose from inappropriate ventricles from another arrangement in which only the aorta was connected to its wrong ventricle ("partial transposition"). If this system were still employed, it could be argued that the ventriculoarterial connection in congenitally corrected transposition was also that of "complete" transposition in the sense that both arteries are connected to inappropriate ventricles. However, we know of no center that now uses this system in its clinical practice. Nowadays, hearts in which both great arteries are connected to the same ventricle are almost invariably known as *double outlet*. The term *complete transposition* is then free to be used specifically and solely to describe those hearts in which the right atrium is connected to the morphologic right ventricle and then to the aorta, whereas the left atrium is connected to the morphologic left ventricle and then the pulmonary trunk. Similarly, congenitally corrected transposition can then be used with scientific precision to describe only those hearts in which the right atrium connects to the morphologic left ventricle and the pulmonary trunk, whereas the left atrium connects to the morphologic right ventricle and the aorta. In these entities, delineated because of abnormal chamber connections, the relations may not always be as anticipated. Ventricular architecture may be unusual; however, these features can then be described in a subsidiary fashion without in any way affecting the basic definition of complete and congenitally corrected transposition.

When we consider the terms *d*- and *l-transposition*, we encounter many more problems, but only when the terms are used inappropriately to describe anomalies defined on the basis of segmental connections. When Van Praagh and colleagues[1,2] introduced the terms, they were meant to describe relations of the great arteries in which the aorta was anterior to the pulmonary trunk and either to its right (d) or its left (l). The terms were not used in isolation but were part of a full segmental description of the heart: for example, *transposition* {*s*, *d*, *d*} or *transposition* {*s*, *l*, *l*}. It so happens that these particular segmental combinations are what could alternatively be called *complete* and *corrected transposition*, respectively. It is a fact that in persons with

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usually arranged atrial chambers (solitus), in most cases there is a right-sided aorta in complete transposition and a left-sided aorta in congenitally corrected transposition. But most cases is not all cases. In patients with mirror-image atria (situs inversus), it is the rule to find a left-sided aorta with complete transposition and a right-sided aorta with congenitally corrected transposition. In patients with the usual atrial arrangement, complete transposition is frequently found with a left-sided aorta[3] and congenitally corrected transposition occasionally found with a right-sided aorta.[4] These variations present no problems for description in the system that uses *complete* or *congenitally corrected* as adjectives to qualify the presence of ventriculoarterial discordance. Full segmental notation also copes with them adequately, providing it is assumed that more complex lesions such as tricuspid atresia or double inlet are not present. Thus, complete transposition with usual atrial chambers and left-sided aorta can be described as *transposition* {*s*, *d*, *l*} or congenitally corrected transposition with usual atrial arrangement and right-sided aorta as *transposition* {*s*, *l*, *d*}. What is clear is that such variants as complete transposition with usual atria and left-sided aorta, or complete transposition with mirror-image atria and left-sided aorta, cannot sensibly be described as *d-transposition*. Similarly, congenitally corrected transposition with either mirror-image atria or usual atria and right-sided aorta cannot adequately be catalogued as *l-transposition*. Yet, this is now the approach advocated by some highly respected authorities.[5,6] We suggest that the time has come to pause and take a good and hard look at this increasing habit of using *d-* and *l-transposition* inappropriately. The anomalies to which the terms are applied are described simply and accurately as complete and congenitally corrected transposition, respectively. They also can be accounted for using full symbolic segmental notation as suggested by Van Praagh et al.[7] There is no need to describe them using the terms *d* and *l-transposition in isolation*. It is not a matter of semantic pedantry. It is a matter of introducing precision to and removing ambiguity from the terminology of congenital heart disease. This will ultimately improve the understanding of practitioners and subsequently benefit their patients.

## References


1. **Van Praagh R, Ongley PA, Swan HJC.** Anatomic types of single or common ventricle in man: morphologic and geometric aspects of sixty necropsied cases. Am J Cardiol 1964;13:367–386.
2. **Van Praagh R, Van Praagh S, Vlad P, Keith JD.** Anatomic types of congenital dextrocardia. Diagnostic and embryologic implications. Am J Cardiol 1964;13:510–531.
3. **Carr I, Tynan MJ, Aberdeen E, Bonham-Carter RE, Graham G, Waterson DJ.** Predictive accuracy of the loop rule in 109 children with classical complete transposition of the great arteries (abstr). Circulation 1968;38:VI-52.
4. **Allwork SP, Bentall HH, Becker AE, Cameron H, Gerlis LM, Wilkinson JL, Anderson RH.** Congenitally corrected transposition of the great arteries: morphologic study of 32 cases. Am J Cardiol 1976;38:910–923.
5. **Aziz KU, Paul MH, Bharati S, Cole RB, Muster AJ, Lev M, Idriss FS.** Two dimensional echocardiographic evaluation of Mustard operation for d-transposition of the great arteries. Am J Cardiol 1981;47:654–664.
6. **Ruttenberg HD.** Corrected transposition (L-transposition) of the great arteries: splenic syndromes (asplenia, polysplenia). In: Moss AJ, Adams FH, Emmanouilides GC, eds. Heart Disease in Infants, Children and Adolescents. 2nd ed. Baltimore: Williams & Wilkins, 1977:338–354.
7. **Van Praagh R, Layton WM, Van Praagh S.** The morphogenesis of normal and abnormal relationships between the great arteries and the ventricles. In: Van Praagh R, Takao A, eds. Etiology and Morphogenesis of Congenital Heart Disease. Mount Kisco, NY: Futura Publishing, 1980:271–316.

# Q-Wave Infarction Versus S-T Infarction

## Nonspecificity of Electrocardiographic Criteria for Differentiating Transmural and Nontransmural Lesions

DAVID H. SPODICK, MD, DSc

### Nonspecificity of the Electrocardiogram

For several decades cardiologists have considered abnormal Q waves synonymous with transmural myocardial infarction, as distinguished from infarcts characterized only by ST-T abnormalities, labelled "nontransmural" or "subendocardial." Curiously, journal reviewers have not vetoed these misnomers despite repeated marshalling of evidence demonstrating at autopsy that abnormal Q waves occur frequently with anatomically nontransmural infarction and may be absent with transmural infarcts.[1–3] This evidence first appeared about 40 years ago and has consistently been substantiated.[4–19] Indeed, early investigators who reported an electrocardiographic distinction between the 2 anatomic types of infarct failed to prove it on examination of their own illustrations: among 4 electrocardiograms illustrating nontransmural infarcts, 1 shows incomplete left bundle branch block and 3 clearly have pathologic Q waves[15]; among 6 subendocardial infarcts demonstrated pathologically, 2 electrocardiograms show incomplete left bundle branch block, 2 have abnormal (≥0.04 second) Q waves in lead aVF, and 2 were too poorly reproduced to decipher.[5] (This is especially surprising considering that illustrations invariably put the author's "best foot forward.") More recently, among 12 of 24 autopsied subjects with nontransmural infarcts, 10 had QRS changes, 8 with abnormal Q waves (including anatomically small infarcts); the other 12 patients had transmural infarcts, but 5 had no abnormal Q waves.[8] Another recent report confirms postmortem documentation of transmural infarcts with only ST-T changes.[11] In a series of 154 autopsy subjects, most of those with nontransmural infarction had typical QRS changes and many with transmural infarcts lacked pathologic Q waves.[7]

It is possible that some earlier work may have established an *idée fixe* in the mind of cardiologists, despite the early availability of a mass of contrary evidence.[4–6,17,19] Indeed, Wilson, a pioneer in cardiology, and his colleagues[19] demonstrated abnormal Q waves in nontransmural infarction both experimentally and clinically. The perceptive observations of Pipberger and Lopez[20] suggest that the erroneous criteria may have been reinforced by Prinzmetal's experiments of 1954, subsequently invalidated by the same investigator in 1957.

### Conceptual Errors Inhibit Investigation

Whatever the reason for continued confusion regarding their anatomic extent, the pseudospecificity of Q and S-T myocardial infarctions remains a lasting myth. Indeed, investigators of the highest intellect and skill—despite explicitly acknowledging the material cited in References 1 to 3,[21]—write "regardless of the terms used. . . ,"[21] implying that slipshod terminology is unimportant. Such disregard by distinguished colleagues is disturbing. We are not dealing with minor matters such as "ECG" (English) versus "EKG" (Dutch and German). Arguments over terminology would be mindless quibbles if misleading labels did not perpetuate misleading concepts. False terminology does more than semantic damage: it does conceptual damage. If we continue to accept a Q infarct as dependably indicating a transmural lesion, we can inhibit consideration of what it really does mean. Indeed, do Q infarcts and S-T infarcts have distinctive gross anatomy? Given the ultimate nonspecificity of many electrocardiographic findings it should not be surprising that they overlap to such a degree that "transmural" and "nontransmural" are gross misnomers.

### Q Infarcts Versus S-T Infarcts: Differences and Similarities

Although their gross anatomy cannot yet be predicted electrocardiographically, Q-wave and S-T infarcts differ clinically and physiologically. Prodromal symptoms are more frequent with S-T infarcts[22]; vomiting is more frequent with Q-wave infarcts.[18] Q-wave infarction implies more damage as measured by peak creatine phosphokinase levels,[23] with a greater tendency to undergo expansion.[34] Positron emission tomography[25] shows defects with homogeneous depression of tracer

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**TABLE I Q-Wave Infarction Versus S-T Infarction: Differences**

| | Q-Wave Infarct | S-T Infarct* |
|---|---|---|
| Fresh thrombosis | More | Less |
| Collateral vessels | Fewer | More |
| Damage | | |
| ↑Enzyme levels | Higher | Lower |
| ↓Tracer concentration (PET) | Homogeneous | Unequal |
| LV wall abnormality,† | More | Less |
| improved by bypass | Less or none | More |
| Tendency to expand | More | Less |
| Prodromal symptoms | Less | More |
| Vomiting | More | Less |
| Atrioventricular and intraventricular blocks | More | Fewer |
| Congestive failure | More | Less |
| Early mortality | More | Less |
| Recurrent infarction | Less | More |

* Without QRS abnormality. † Some studies differ.
PET = positron emission tomography.

**TABLE II Q-Wave Infarction Versus S-T Infarction: Similarities**

| |
|---|
| Both either transmural or nontransmural |
| Number of diseased vessels |
| Degree of occlusion throughout coronary arteries |
| Ejection fraction* |
| Hypotension |
| Ventricular arrhythmia* |
| Late (>2 year) mortality |

* Some studies differ.

accumulation in all Q-wave infarcts as compared with unequal tracer distribution in 23 of 24 S-T infarcts, with tomographic infarct size greater and residual tracer more depressed in Q-wave infarcts.[28] Two-dimensional echocardiograms showed more (100%) regional wall abnormality during Q-wave than S-T infarction (86%).[26,27] Although total mortality may equalize over 5 to 10 years in the 2 groups, early mortality both in the hospital and after discharge is greater with Q-wave infarcts, whereas recurrent infarction and late mortality are much greater with S-T infarcts.[28,30]

Although the number of diseased coronary arteries and the degree of occlusion throughout the system appear equal in both types,[23] fresh coronary thrombosis may be slightly[31] to moderately[10] more frequent with Q-wave infarction. Collateral vessels were demonstrated in 93% of all patients with S-T infarct and 78% with Q-wave infarct who had postinfarction angina, but in only 35% of patients with Q-wave infarct and no subsequent angina.[31] Coronary bypass tends to improve wall motion in S-T infarcts but only in Q-wave infarcts in which transmural fibrosis is absent.[32,33] Some investigators found reinfarction, angina, and late ventricular arrhythmias to occur equally in Q-wave and S-T infarcts, but more akinesis in patients with anterior Q-wave than with anterior S-T infarcts.[34] Yet, other investigators report comparable ejection fractions and wall motion abnormalities.[23] Finally, in a carefully matched, although retrospective, series S-T infarcts produced less congestive failure, fewer intraventricular conduction defects, and fewer atrial tachyarrhythmias; hypotension and ventricular arrhythmias occurred equally.[21] Yet, the same study also reported a statistically equal occurrence of pericarditis.[21] Because meticulous postmortem examination shows that in fresh infarction acute pericarditis always indicates transmural lesions,[10] those non-Q–wave infarcts with pericarditis, although labelled "nontransmural,"[21] certainly represented transmural infarction—more evidence of the electrocardiogram's anatomic nonspecificity.

## Subdivisions Within Q Infarctions and S-T Infarctions

Investigations pertinent to this analysis correlated anatomically transmural and nontransmural infarcts with electrocardiographically Q-wave and S-T infarcts, irrespective of regional distribution.[4–19] Fresh S-T infarcts usually occur with a normal QRS, but may also occur in patients with previous infarction, ventricular hypertrophy, preexcitation, or conduction disturbances producing QRS changes that mask or cancel processes producing new Q waves. Although most Q-wave infarcts are predominantly either inferior or anterior, it is not established whether either location is more likely to be transmural or nontransmural. Yet, location may have clinical importance: overall mortality in some series is worse with anterior infarcts, perhaps because of their tendency to be larger than inferior infarcts.[35,36] In contrast, in the AMIS Study (4,524 participants) total mortality did not differ among infarct locations, including patients who lost abnormal Q waves.[37] Yet, ventricular dysfunction tends to be worse with anterior Q waves.[38,39] Finally, both bundle branch block and significant myocardial failure are more frequent with anterior Q-wave infarcts, whereas sinus bradycardia, atrioventricular block, and atrial arrhythmias are more frequent with inferior Q-wave infarcts.[21]

## Q-Wave Infarcts Versus S-T Infarcts

Tables I and II list the similarities and the many differences between Q-wave and S-T infarction. Q-wave infarcts include posterior infarction appearing as a new anterior R wave.

**Conclusions:** The unfortunate practice of mislabelling Q-wave infarction as "transmural" and S-T infarction as "nontransmural" does not correspond to the pathologic evidence. Q-wave infarcts and S-T infarcts differ clinically, physiologically, and prognostically but cannot be anatomically differentiated by electrocardiography. As with a variety of other loose or erroneous terminologies, the absence of precise labelling interferes with clarity of concept and may inhibit further investigation.[40] When a myocardial infarct is characterized strictly by electrocardiography, it should be described by the only accurate terminology—Q-wave infarct or S-T infarct. Confucious tells us:

> If language is not used rightly, then what is said is not what is meant. If what is said is not what is meant, then that which ought to be done is left undone.

## References


1. **Spodick DH.** Transmural vs. nontransmural infarction (letter). Circulation 1980;62:447–448.
2. **Spodick DH.** Anatomic nonspecificity of Q-wave and ST infarcts (letter). Chest 1981;79:245.
3. **Spodick DH.** Left ventricular thrombosis after myocardial infarction (letter). N Engl J Med 1982;305:1416.
4. **Jaffe HL.** Typical and atypical electrocardiograms in myocardial infarction caused by acute coronary occlusion and coronary insufficiency. Dis Chest 1955;27:243–250.
5. **Levine HD, Ford RV.** Subendocardial infarction: report of six cases and critical survey of the literature. Circulation 1950;1:246–262.
6. **Master AM, Gubner R, Dack S, Jaffe HL.** Differentiation of acute coronary insufficiency with myocardial infarction from coronary occlusion. Arch Intern Med 1941;67:647–655.
7. **Raunio H, Rissanen V, Romppanen T, Jokinen Y, Rehnberg S, Helin M, Pyörälä K.** Changes in the QRS complex and ST segment in transmural and subendocardial infarctions. A clinicopathologic study. Am Heart J 1979; 98:176–183.
8. **Savage RM, Wagner GS, Ideker RE, Podolsky SA, Hackel DB.** Correlation of postmortem anatomic findings with electrocardiographic changes in patients with myocardial infarction. Circulation 1977;55:279–285.
9. **Madias JE, Chahine RA, Gorlin R, Blacklow DJ.** A comparison of transmural and nontransmural acute myocardial infarction. Circulation 1974;49: 498–504.
10. **Erhardt LR.** Clinical and pathological observations in different types of acute myocardial infarction. A study of 84 patients deceased after treatment in coronary care unit. Acta Med Scand 1974;Suppl 560:1–78.
11. **Abbott JA, Scheinman MM.** Nondiagnostic electrocardiogram in patients with acute myocardial infarction. Am J Med 1973;55:608–611.
12. **Horan LG, Flowers NC, Johnson JC.** Significance of the diagnostic Q wave of myocardial infarction. Circulation 1971;43:428–432.
13. **Wilkinson RS, Schaefer A, Abildskov JA.** Electrocardiographic and pathologic features of myocardial infarction in man. Am J Cardiol 1963; 11:24–30.
14. **Georas CS, Dahlquist E, Cutts FB.** Subendocardial infarction. Correlation of clinical, electrocardiographic and pathologic data in 17 cases. Arch Intern Med 1963;111:488–492.
15. **Cook RW, Edwards JE, Pruit RD.** Electrocardiographic changes in acute subendocardial infarction. I. Large subendocardial and large nontransmural infarcts. Circulation 1958;18:603–610.
16. **Cook RW, Edwards JE, Pruit RD.** Electrocardiographic changes in acute subendocardial infarction. II. Small subendocardial infarcts. Circulation 1958;18:613–618.
17. **Myers GB, Sears CH, Hiratzka T.** Correlation of electrocardiographic and pathologic findings in ring like subendocardial infarction of left ventricle. Am J Med Sci 1951;222:417–421.
18. **Ingram DA, Fulton RA, Portal RW, Aber CP.** Vomiting as a diagnostic aid in acute ischemic cardiac pain. Br Med J 1980;281:636–637.
19. **Wilson FN, Jonston FD, Rosenbaum FF, Erlanger H, Kossmann CE, Hecht H, Cotrim N, Menezes de Oliveira R, Scarsi R, Barker PS.** The precordial electrocardiogram. Am Heart J 1944;27:19–31.
20. **Pipberger HV, Lopez EA.** "Silent" subendocardial infarcts. Am Heart J 1980;100:597–599.
21. **Hutter AM, DeSanctis RW, Flynn T, Yeatman LA.** Nontransmural myocardial infarction: a comparison of hospital and late clinical course of patients with that of matched patients with transmural anterior and transmural inferior myocardial infarction. Am J Cardiol 1981;48:595–602.
22. **Scheidt S, Wolk M, Killip T.** Unstable angina pectoris. Natural history, hemodynamics, uncertainties of treatment and the ethics of clinical study. Am J Med 1976;60:409–417.
23. **Schulze RA, Pitt B, Griffith LSC, Ducci HH, Achuff SC, Baird MG, Humphries J.** Coronary angiography and left ventriculography in survivors of transmural and nontransmural myocardial infarction. Am J Med 1978; 64:108–113.
24. **Hutchins GM, Bulkley BH.** Infarct expansion versus extension: two different complications of acute myocardial infarction. Am J Cardiol 1978;41: 1127–1132.
25. **Geltman EM, Biello D, Welch MJ, Ter-Pogossian MM, Roberts R, Sobel BE.** Characterization of nontransmural myocardial infarction by positron-emission tomography. Circulation 1982;65:747–755.
26. **Horowitz RS, Morganroth J.** Immediate detection of early high-risk patients with acute myocardial infarction using two-dimensional echocardiography evaluation of left ventricular regional wall motion abnormalities. Am Heart J 1982;103:814–818.
27. **Horowitz RS, Morganroth J, Parrotto C, Chen CC, Soffer J, Pauletto FJ.** Immediate diagnosis of acute myocardial infarction by two-dimensional echocardiography. Circulation 1982;65:323–329.
28. **Marmor A, Sobel BE, Roberts R.** Factors presaging early recurrent myocardial infarction ("extension"). Am J Cardiol 1981;48:603–610.
29. **Cannom DS, Levy W, Cohen LS.** The short- and long-term prognosis of patients with transmural and nontransmural myocardial infarction. Am J Med 1976;61:452–458.
30. **Geltman EM, Ehsani AA, Campbell MK, Schlechtman K, Roberts R, Sobel BE.** The influence of location and extent of myocardial infarction on long-term ventricular dysrhythmia and mortality. Circulation 1979;60:805–814.
31. **Fuster V, Frye RL, Kennedy MA, Connolly DC, Mankin HT.** The role of collateral circulation in the various coronary syndromes. Circulation 1979;59:1137–1142.
32. **Roberts AJ, Moran JM, Sanders JH, Michaelis LL, Spies SM.** Timing of myocardial revascularization following acute myocardial infarction (abstr). Circulation 1980;62:Suppl III:III-94.
33. **Franklin K, Sutton M St. J, Mermelstein LJ, Cohen M, Harken A, Reichet N.** Effect of left anterior descending coronary bypass on anterior wall function (abstr). Circulation 1982;II:II-90.
34. **Taylor GJ, Humphries J, Mellits ED, Pitt B, Schulze RA, Griffith LSC, Achuff SC.** Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction. Circulation 1980;62:960–970.
35. **Goldberg RJ, Kennedy HL, Szklo M, Tonascia J.** Prognosis of anterior myocardial infarction revisited (abstr). Am J Cardiol 1979;43:370.
36. **Geltman EM, Ehsani AA, Campbell MK, Roberts R, Sobel BE.** Determinants of prognosis after initial subendocardial compared to transmural myocardial infarction: the importance of infarct size (abstr). Am J Cardiol 1979;43: 370.
37. **Wasserman AG, Bren GB, Ross AM, Richardson DW, Hutchinson RG, Rios JC.** Prognostic implications of diagnostic Q waves after myocardial infarction. Circulation 1982;65:1451–1455.
38. **Bodenheimer MM, Banka VS, Helfant RH.** Q waves and ventricular asynergy: predictive value and hemodynamic significance of anatomic localization. Am J Cardiol 1975;35:615–618.
39. **Palmeri ST, Harrison DG, Upton MT, Morris KG, Wagner GS.** The electrocardiographic prediction of left ventricular ejection fraction following myocardial infarction (abstr). Circulation 1979;60:II-187.
40. **Spodick DH.** Cardiolocution. Am J Cardiol 1981;48:973–974.

# Randomize the First Patient: Scientific, Ethical, and Behavioral Bases

DAVID H. SPODICK, MD, DSc

With few exceptions,[1] the prospective, randomized controlled trial (RCT) is the optimal test of any therapeutic intervention. Its scientific and practical features and the comparative weaknesses of alternative methods have been analyzed in detail elsewhere.[1,2] Indeed, it has become fashionable to adorn reports of uncontrolled therapeutic trials with explicit (not to say pious) statements declaring the need for an appropriately designed RCT to test the authors' conclusions.[2] Nearly all of these authors never conducted a randomized trial before or since, so that these "escape clauses" may represent less of a victory for principle accepted than for "revision accepted."

Levine[3] recently observed that even distinguished advocates of RCTs could publish an essay insisting on an RCT of a new treatment—lest it gain premature acceptance—and in the very same journal and year report an uncontrolled trial of that treatment. In fairness, their essay had claimed the prior necessity of a "pilot" trial. Since that indeed is traditional practice, the authors undoubtedly were sincere, but were they right? Is a "pilot" trial necessary or even appropriate? Experience shows that it is a diversion that consistently lets the "genie escape from the bottle." Convincing "pilot" trials without appropriate concurrent control series regularly induce enthusiasm for a new cure, producing a pseudoethical compulsion *not* to do an appropriate RCT.[4,5] The traditional stand is, "How can I deny my patients a treatment I *know* (read: "am now convinced") works? In urging randomization ab initio, Chalmers[5] eloquently wrote of the "pernicious influence" of such pilot trials in eliminating or postponing a definitive therapeutic trial.

Randomizing the first patient is supported by 3 cases: scientific, behavioral, and ethical.

## The Scientific Case

The scientific case for initial randomized trials is the very reason for doing any controlled trial—to demonstrate the value of a treatment by optimal comparison with an alternative treatment or no treatment. The counterargument, implying that a fair comparison compels us to first learn how best to use any new medicine or procedure, ignores the fact that learning to use a treatment is entirely feasible—indeed in no way different—when randomizing from the first patient. The investigators do exactly as they would in an uncontrolled trial, but in an RCT the "learning curve" for a new procedure and the "pilot" trial for a new medicine take approximately twice the time (Fig. 1). Yet, unlike the inadequate trials that rely on the investigators' recollections, literature "controls," or even retrospective historical controls (often massively misleading[1] and demonstrably biased in favor of new treatments[6]), an RCT builds a potentially concurrent (that is, prospective), valid (that is, unbiased), control series. The control patients' baseline characteristics make them equally eligible for the new treatment, with randomization distributing unknown and unmeasurable variables. Blinding, when feasible, further reduces bias and prevents premature termination of the trial.

Let us further examine the objection that during the learning phase changes in treatment methods may occur. Although a valid observation, such changes are entirely compatible with randomizing the first patient (Fig. 1). Until satisfied with the level of one's "learning curve" or "pilot" results, investigators in an RCT must either discard the earlier patients in the treatment series or make them a subset for partial comparison—exactly as they would in an uncontrolled trial—because the definitive RCT would proceed from the time the trial method becomes satisfactory. The only loss might be time, a negligible sacrifice in the search for Truth. In return, we ensure an incontestible standard by which to judge the initial results and avoid unseemly haste in applying an inadequately tested treatment. Moreover, the time "sacrifice" is at worst partial and at best ultimately becomes time-saving: time lost in subsequent argument and agitation for definitive trials could far exceed the extra time needed for initial RCTs (Fig. 1).

## The Ethical Case

In conducting an RCT, investigators implicitly declare reasonable hopes for a new treatment and honestly confess no exact knowledge of its short-term, and especially its long-term, effects in human beings, the precise conditions when Patient 1 is recruited. Without valid control patients, subsequent early success *or failure* tends to bias investigators for *or against* the trial treatment, with successes usually getting published. This leads directly to the ethical case.

Physicians are ethically bound always to offer each patient the best available treatment. Yet, with any new trial treatment we cannot know which alternative is best and cannot so advise Patient 1. Indeed, in recruiting patients for a nonrandomized "pilot" trial, the inves-

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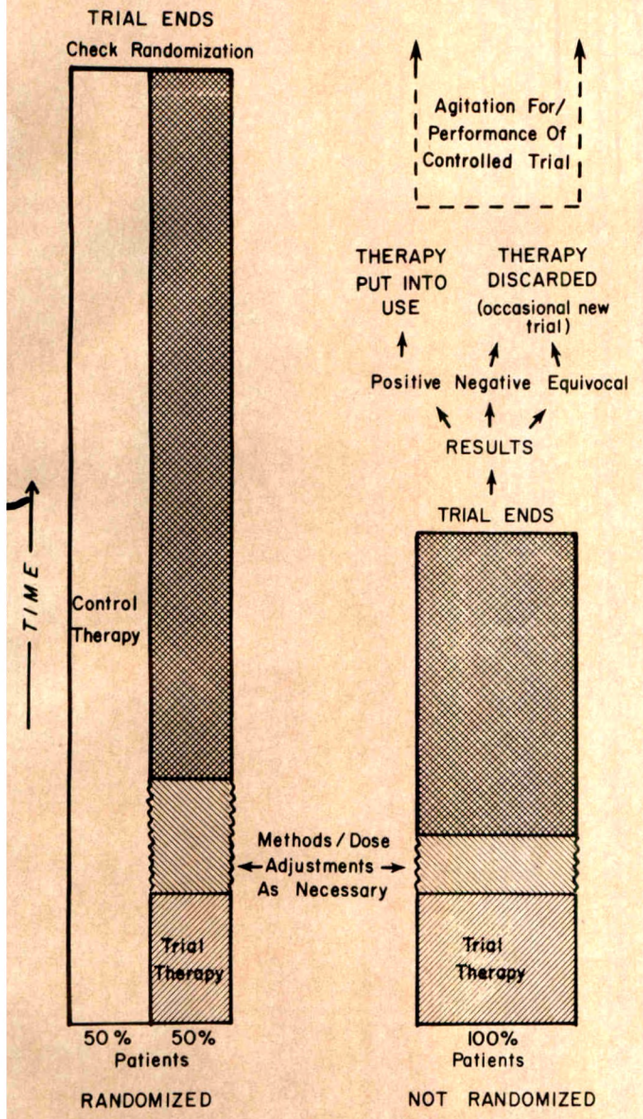



**FIGURE 1.** Concept of controlled trial randomized from the first patient (**left**) versus unrandomized traditional pilot trial (**right**). Time is represented vertically (**arrow**), number of patients horizontally (**width of bars**). The controlled trial includes concurrently randomized control patients (**white half of bar**) absent in the nonrandomized "pilot" trial. Each segment of randomized trial takes twice as long as a "pilot" trial including initiation of therapy, adjustments of methods or dosage, as needed, and continuation of the trial on adjusted therapy. Methods or dose adjustments (**diagonally striped segments**) include the same number of patients, although taking twice as long in randomized trial owing to allocation of 50% of the patients to the control group. The same number of patients are finally studied in each group. At the end of the randomized trial there is a valid control population not available in the unrandomized "pilot" trial. After the "pilot" trial the alternatives are indicated above its endpoint. The randomized trial in theory takes twice as long for the same number of patients, yet the desirability of subsequently performing controlled trials after the "pilot" trial can involve as much or more time.

tigator asks them all to forfeit their right to standard treatment and accept a treatment that he considers not yet sufficiently understood to permit comparison with standard therapy. When uncertain of the precise place of a new treatment, including methodology as well as efficacy and side effects, it seems ethically unjustified to subject every trial patient to it. (Genuinely informed consent would bind honest investigators to state they were "getting the bugs out" and might lose some patients' agreement.) Thus, the RCT is not only scientifically but also ethically superior to nonrandomized "pilot" trials in giving each patient an equal chance to get "best treatment," when we do not know whether "best treatment" will prove to be the new treatment or standard treatment. Once patients are candidly informed that the trial treatment may be better *or worse* than accepted treatment or no treatment, chance alone (that is, random allocation) eliminates bias in allocating them to one or the other.

## The Behavioral Case

Like the scientific case, the behavioral case is intimately bound to the ethical case: if a physician believes what he is doing is best for his patient, he is ethically compelled to do it. Yet this is equally true of witch doctors. Both the witch doctor and the modern physician respond to a personal ethical system when they act on what each considers his best option. Thus, responses to ethical compulsion alone do not ensure valid results. At a recent National Institutes of Health conference on percutaneous transluminal coronary angioplasty, distinguished practitioners of that art, some of whom had published one of the "RCTs are needed" escape clauses (as just cited), stated that they would not in fact do such an RCT because physicians were referring patients to them specifically for the procedure (Spodick DH, commentator. Personal observations, verified by tape transcripts. Bethesda, Maryland, June 11 and 12, 1981). This has been the history of a vast number of new medicines and procedures: early reports, virtually always enthusiastic, from uncontrolled or poorly controlled studies, followed by wide application under pseudoethical barriers to launching a well-controlled trial.

**Conclusions:** The randomized controlled clinical trial is the most powerful and, therefore, the scientifically optimal (hence, ethically optimal) method of demonstrating therapeutic effectiveness and safety. It is feasible to perform appropriately designed randomized prospective investigations beginning with the first trial patient (Fig. 1). This sacrifices only time (later likely to be more than regained) in the search for a real answer, and ensures an ethical approach that gives every patient a 50-50 chance to get best treatment, that is, not to get the new medicine at a time when its precise effects and risk-benefit ratio are not understood. Randomizing the first patient simultaneously avoids unscientific and unethical behavior and prevents premature wholesale application of inadequately tested methods.

## References

1. **Spodick DH.** Revascularization of the heart—numerators in search of denominators. Am Heart J 1971;81:149–157.
2. **Spodick DH.** The randomized controlled clinical trial: scientific and ethical bases. Am J Med 1982;73:420–425.
3. **Levine HJ.** Letter. N Engl J Med 1982;306:301.
4. **Chalmers TC.** Ethical aspects of clinical trials. Am J Ophthalmol 1975;79:753–758.
5. **Chalmers TC.** Randomization of the first patient. Med Clin North Am 1975;59:1035–1038.
6. **Sacks H, Chalmers TC, Smith H Jr.** Randomized versus historical controls for clinical trials. Am J Med 1982;72:233–240.

# LETTERS*

## RESULTS OF MEDICAL VERSUS SURGICAL TREATMENT OF UNSTABLE ANGINA PECTORIS

The recent report of the National Cooperative Study Group to Compare Medical and Surgical Therapy[1] is important, useful, and the result of an enormous amount of very hard work. However, the Study Group evidently did not address (or measure) a variable of supreme importance in the prognosis and management of single-vessel coronary disease (left anterior descending [LAD] or otherwise). Two recent cases illustrate this concept.

*Patient A*, a 64-year-old woman, had previously had exercise angina and recent severe repeated rest pain with transient T-wave changes. Angiography showed a severe (>95%) proximal LAD coronary artery lesion without other important disease. The LAD coronary artery was developmentally small, supplying only a small percentage of the heart. She received a prolonged and systematic in-hospital medical trial with repeated attempts at ambulation. We finally gave up, and she had successful surgery.

*Patient B*, a 45-year-old man, had previously had exercise angina and recent severe repeated rest pain, with transient S-T and T-wave changes. Angiography showed a severe (>95%) proximal LAD coronary artery lesion without other important disease. The LAD coronary artery was very large; its main trunk wrapped around the apex and supplied the entire inferoanterior portion of the heart, and numerous large branches ran to the anterior and lateral left ventricle. We estimated that this vessel alone supplied >60% of the left ventricle. Coronary vein graft surgery was promptly recommended and accomplished.

We are convinced that these patients illustrate a concept that must be considered in trials involving prognosis and therapy. If Patient A had had an infarction of most of her diseased vessel's territory, she would probably have had a small but detectable anterior infarction, with acceptable ventricular function afterwards and an excellent prognosis after recovery. If Patient B had had an infarction of most of his diseased vessel's territory and had survived, he would probably have had an enormous anteroseptal transmural infarction, with dismal immediate prognosis and severely impaired function.

"Single-vessel coronary disease" cannot be understood or effectively analyzed without reference to the percentage of the heart so served or its equivalent. Existing methods for measuring this variable need to be perfected and incorporated into future studies. Studies which, by their design, combine "Patient A and Patient B" may be unwittingly concealing important prognostic information.

**A. Jarrell Raper, MD**
**George W. Vetrovec, MD**
Richmond, Virginia

* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

**REPLY:** Drs. Raper and Vetrovec are probably correct in their consideration of a difference in prognosis for the patient with proximal stenosis of a small or large anterior descending coronary artery. We agree with their request that methods for measuring this variable be perfected and incorporated in future studies. In fact, we argue that in addition to location of stenosis, percentage of stenosis, length of stenosis, and number of stenoses in the same vessel influence prognosis. Interestingly, the ongoing National Heart, Lung, and Blood Institute study (Coronary Artery Surgery Study [CASS]) did make substantial changes in recording coronary artery anatomy for comparison in prospective studies.

The study of LAD disease in the presence of unstable angina as reported by the National Cooperative Study Group[1] did not incorporate the described variation in left anterior anatomy. Certainly we as both investigators and clinicians have urged that our study, which we think has had a profound influence on the early management of unstable angina, be used in context and its findings incorporated into patient management as applicable. Thus, the management of each specific patient must continue to be individualized, although studies such as ours should provide an important point of departure for such management.

**Richard O. Russell, Jr., MD**
**C. Richard Conti, MD**
**Eugene Passamani, MD**
For the National Cooperative Study Group

1. Unstable Angina Pectoris Study Group: National Cooperative Study Group to Compare Medical and Surgical Therapy. IV. Results in patients with left anterior descending disease. Am J Cardiol 1981;48:517–524.

## LEFT VENTRICULAR ANEURYSM BY ANGIOGRAM: A PROBLEM OF DEFINITION

The prognostic significance of left ventricular (LV) aneurysm from the Coronary Artery Surgery Study (CASS) has been described by Faxon et al.[1] However, the study is plagued by the common denominator in all studies attempting to look at LV aneurysm, namely, definition. In their study, the authors define LV aneurysm as a segment of LV wall protruding abnormally "from the expected outline of the LV chamber." The implication is that this entity contrasts in some way to an akinetic segment of left ventricle. This may or may not be true. An aneurysm to 1 observer may in fact be an akinetic segment to another. Therefore, it is not surprising that Faxon et al found no difference in the mortality of patients with LV aneurysm compared with those without aneurysm, but with an equal degree of LV function. The authors may have been comparing the same group with itself.

The second problem with this study is that it evaluates the angiographic analysis of 15 participating institutions in this cooperative trial. Although there was a 93% interobserver agreement within participating institutions in regard to segmental wall motion abnormality, the authors do not tell us what the agreement was in terms of definition of aneurysm.

Third, although the authors use an angiographic definition of aneurysm, they quote several pathologic studies in defining the natural history of this entity. It is probable that there is a certain degree of discrepancy between angiographic and pathologic aneurysms.

Until an adequate method is determined to account for cardiac motion, which may simulate aneurysmal bulging in a patient with an akinetic segment, the definition of LV aneurysm will remain somewhat arbitrary. Any study that attempts to define the natural history of LV aneurysm will, to a certain extent, be misleading in its conclusions. Thus, any results that are drawn from the study of Faxon et al, I believe, should be taken with extreme caution.

**Barry F. Uretsky, MD**
Pittsburgh, Pennsylvania

1. **Faxon DP, Ryan TJ, Davis KB, McCabe CH, Myers W, Lesperance J, Shaw R, Tong TGL.** Prognostic significance of angiographically documented left ventricular aneurysm from the Coronary Artery Surgery Study (CASS). Am J Cardiol 1982;50:157–164.

## KNEE-ELBOW POSITION TO DETECT THE AORTIC DIASTOLIC MURMUR OF AORTIC REGURGITATION

Fifteen years ago one of us (DK) tried to convince a group of medical students that a patient had an aortic diastolic murmur. In the classic sitting-up, leaning-forward position, with the breath held in expiration, I heard the murmur but they did not.

I asked the patient to turn to the knee-elbow position and, pressing the stethoscope from below, on his sternum, the murmur became more audible. The first 2 students could hear the murmur easily, but alas the patient became tired and laid himself on his belly. We continued to press the stethoscope from beneath, on the sternum, and the murmur was even more audible.

Since then, when looking for an aortic diastolic murmur we put the patients on their abdomen, turn the head to the side opposite to our standing position, press the stethoscope blindly between the breasts, choose the most audible point, and ask them to stop breathing in expiration.

We find that this is a much more comfortable way to hear the murmur for the patient and for the inexperienced ear, rather than use of the squatting position or isometric exercise, which accentuates the murmur but is noisy. The patient is better able to remain quiet without much distress.

We have been unable to find this method of auscultation previously described.

**David Kohn**
**Edith Flatau**
**Dan Schiller**
**Omar Daher**
Afula, Israel

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| **Dobutamine/Dobutrex®** Dobutamine HCl | + | + | ++++ | 0 |
| Dopamine Hydrochloride† | ++ | ++ | ++++ | ++++ |
| Isoproterenol Hydrochloride | ++++ | ++++ | ++++ | 0 |
| Norepinephrine Bitartrate† | ++++ | ++++ | ++++ | ++++ |

| Drug | Blood Vessels | | |
|---|---|---|---|
| | $\alpha$ Receptors | $\beta_2$ Receptors | "Dopaminergic" Receptors |
| | Peripheral Vasoconstriction | Peripheral Vasodilation | Dilates Renal Vasculature |
| **Dobutamine/Dobutrex®** Dobutamine HCl | 0 to + | ++ | 0 |
| Dopamine Hydrochloride† | 0 to +++++ | ++ | Yes |
| Isoproterenol Hydrochloride | 0 | +++++ | 0 |
| Norepinephrine Bitartrate† | +++++ | 0 | 0 |


1. Tuttle, R. R., and Mills, J.: Dobutamine: Development of a New Catecholamine to Selectively Increase Cardiac Contractility, Circ. Res., *36*:185, 1975.

2. Goldberg, L. I., Hsieh, Y.-Y., and Resnekov, L.: Newer Catecholamines for Treatment of Heart Failure and Shock: An Update on Dopamine and a First Look at Dobutamine, Prog. Cardiovasc. Dis., *19*:327, 1977.

3. Robie, N. W., Nutter, D. O., Moody, C., and McNay, J. L.: In Vivo Analysis of Adrenergic Receptor Activity of Dobutamine, Circ. Res., *34*:663, 1974.

4. Goldberg, L. I.: Cardiovascular and Renal Actions of Dopamine: Potential Clinical Applications, Pharmacol. Rev., *24*:1, 1972.

5. Innes, I. R., and Nickerson, M.: Norepinephrine, Epinephrine, and the Sympathomimetic Amines, in The Pharmacological Basis of Therapeutics, Ed. 5 (edited by L. S. Goodman and A. Gilman), p. 477. New York: Macmillan Publishing Co., Inc., 1975.


†Action on adrenergic nerve fibers causes release of norepinephrine.

+ = Degree of stimulation
0 = No stimulation

Lilly

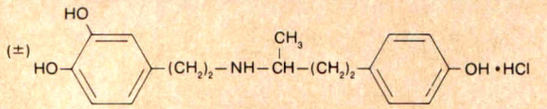
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The clinical formulation is supplied in a sterile lyophilized form for intravenous use only. Each vial contains 250 mg of dobutamine and 250 mg of mannitol. Hydrochloric acid is used to adjust the *p*H. The *p*H of the reconstituted solution is between 2.5 and 5.5.

**Clinical Pharmacology:** Dobutrex is a direct-acting inotropic agent whose primary activity results from stimulation of the beta receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short-term—up to several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas the output of others returned toward base-line values.

The onset of action of Dobutrex is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is two minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

**Indications and Usage:** Dobutrex is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutrex.

**Contraindication:** Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

**Warnings:** 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

**Precautions: 1. During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

*Usage Following Acute Myocardial Infarction*—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

*Usage in Pregnancy*—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

*Pediatric Use*—The safety and effectiveness of Dobutrex for use in children have not been studied.

*Drug Interactions*—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

**Adverse Reactions:** *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

*Miscellaneous Uncommon Effects*—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

*Longer-Term Safety*—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

**Overdosage:** In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

**Administration and Dosage:** *Reconstitution and Stability*—Dobutrex is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add another 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstitution time periods stated above.

*Recommended Dosage*—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

| Drug Delivery Rate (mcg/kg/min) | Infusion Delivery Rate 250 mcg/ml* (ml/kg/min) | 500 mcg/ml† (ml/kg/min) | 1000 mcg/ml‡ (ml/kg/min) |
|---|---|---|---|
| 2.5 | 0.01 | 0.005 | 0.0025 |
| 5 | 0.02 | 0.01 | 0.005 |
| 7.5 | 0.03 | 0.015 | 0.0075 |
| 10 | 0.04 | 0.02 | 0.01 |
| 12.5 | 0.05 | 0.025 | 0.0125 |
| 15 | 0.06 | 0.03 | 0.015 |

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

**How Supplied:** Vials Dobutrex® (dobutamine hydrochloride, Lilly), for Injection (lyophilized), equivalent to 250 mg dobutamine, 20-ml size, rubber-stoppered, in packages of 1. [121979]

*Additional information available to the profession on request.*

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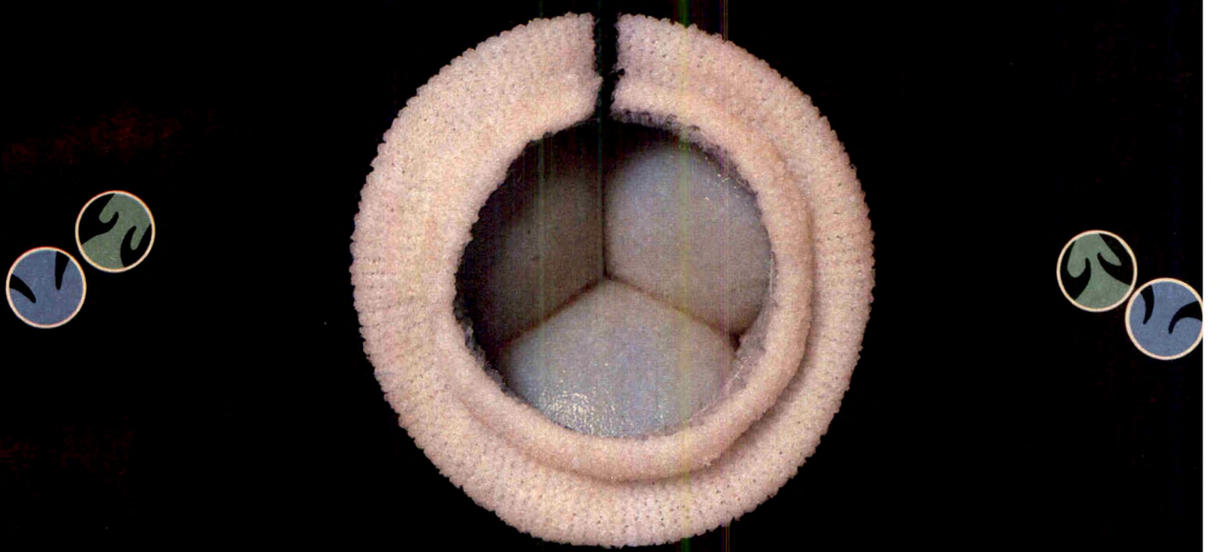
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In Marian Ionescu's ten year clinical experience with the pericardial valve in the mitral position, a low incidence of thromboembolism and no thrombosis have been achieved without the use of longterm anticoagulation.[1] Additional clinical studies from other institutions have now confirmed his findings.[2,3,4] Efficient hemodynamics, excellent thromboresistance and durability are three important reasons why the Ionescu-Shiley Pericardial Xenograft is an effective bioprosthesis for all positions.[5,6]



A film presenting Ionescu-Shiley Pericardial Xenograft implantation techniques, clinical data and comparative in vitro bioprosthetic function is available for your review. To obtain a copy of the film or for further clinical data, please contact Shiley Incorporated or your Shiley technical representative.


1"Clinical Durability of the Pericardial Xenograft Valve: Ten Years' Experience with Mitral Replacement," Marian I. Ionescu, et al. Presented at the Eighteenth Annual Meeting of the Society of Thoracic Surgeons, January 11-13, 1982, New Orleans, Louisiana.

2"The Ionescu-Shiley Pericardial Xenograft Valve," Dr. Denton A. Cooley, et al, Texas Heart Institute, Houston, Texas. **Cardiology Times**, February, 1982.

3"Cardiac Valve Replacement with the Pericardial Xenograft," **Cardiovascular Surgery**, 1980, pps. 640-644. Radu Deac, M.D., et al, Mures Clinic Hospital, Tirgu-Mures, Romania.

4"Clinical Experience with the Ionescu-Shiley Xenograft Valve at Four to Five Years of Follow Up," J. B. Garcia-Bengochea, M.D., et al, University of Santiago School of Medicine; Santiago de Compostela, Spain.

5"Conduit Repair for Complex Congenital Heart Disease with Pulmonary Atresia or Right Ventricular Outflow Tract Obstruction," E.R. de Vivie, et al. **Thoracic Cardiovascular Surgeon**, 1981, pps. 329–336.

6"Tricuspid Valve Replacement," Marian I. Ionescu. **Modern Technics in Surgery, Cardiac/Thoracic Surgery, Installment II.**


For detailed information describing warnings, precautions and contraindications, refer to the instructions provided with each device.

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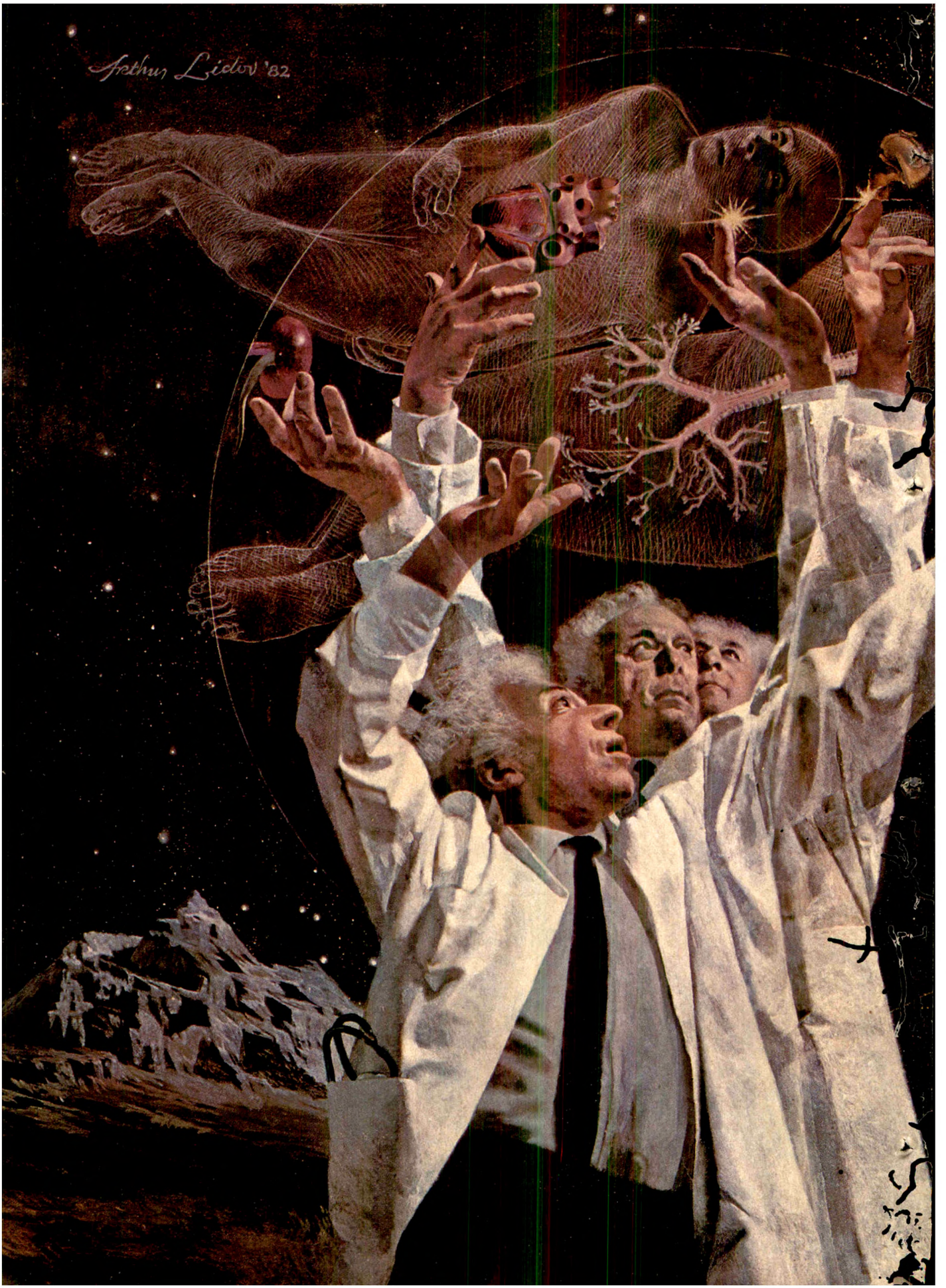
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  Lowers blood pressure without impairing oral antidiabetic effectiveness.
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  Lowers blood pressure without long-term reduction of cardiac output. (Does not reduce renal perfusion or GFR.)
- **Hypertensives with congestive heart failure**
  Does not depress myocardial contractility.
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  Inhibits sympathetic nervous activity centrally and does not elevate plasma catecholamines.
- **Elderly hypertensives**
  Recommended in isolated systolic hypertension in the elderly.[1]

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

**Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

1. Statement on Hypertension in the Elderly, Revised April, 1980. Approved by the National High Blood Pressure Education Program Coordinating Committee.

Tablets of 0.1, 0.2, 0.3 mg

# Catapres®

## (clonidine HCl)

## Hypertension

Please see brief summary of PI for warnings, precautions, and adverse reactions.

# THE ALPHA UNIVERSE

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**Catapres®**
(clonidine HCl)
**Hypertension**



## Catapres®

**(clonidine hydrochloride)**
**Tablets of 0.1, 0.2, 0.3 mg**

**Indication:** The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

**Warnings:** Tolerance may develop in some patients necessitating a reevaluation of therapy.
*Usage in Pregnancy:* In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
*Usage in Children:* No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

**Precautions:** When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

**Adverse Reactions:** The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

**Overdosage:** Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

**How Supplied:** Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000 and unit dose package of 100.. Also available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.
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*The Alpha Universe*, a painting by Arthur Lidov, commissioned by Boehringer Ingelheim Ltd.

Lidov's work, the second in a series on central alpha action, interprets the Alpha Universe on many levels...the universe of patients who can benefit from the central alpha control of Catapres...the special world of patient/clinician interaction... the internal universe within each patient that determines or modifies his therapy...and the universe of medicine itself. Lidov is a painter whose art invites us to share his own fascination with the creativity inherent in science.

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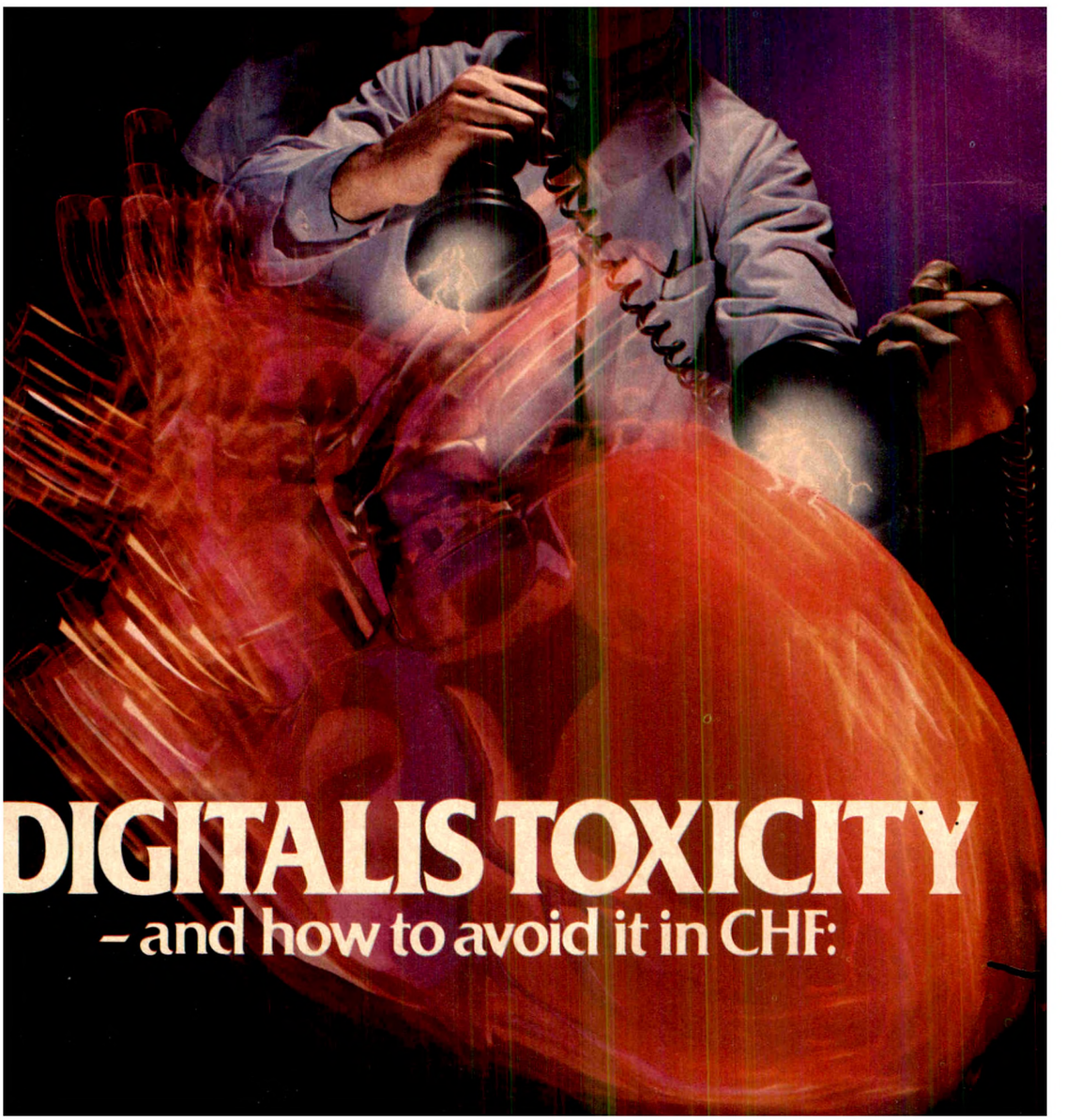
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– and how to avoid it in CHF:

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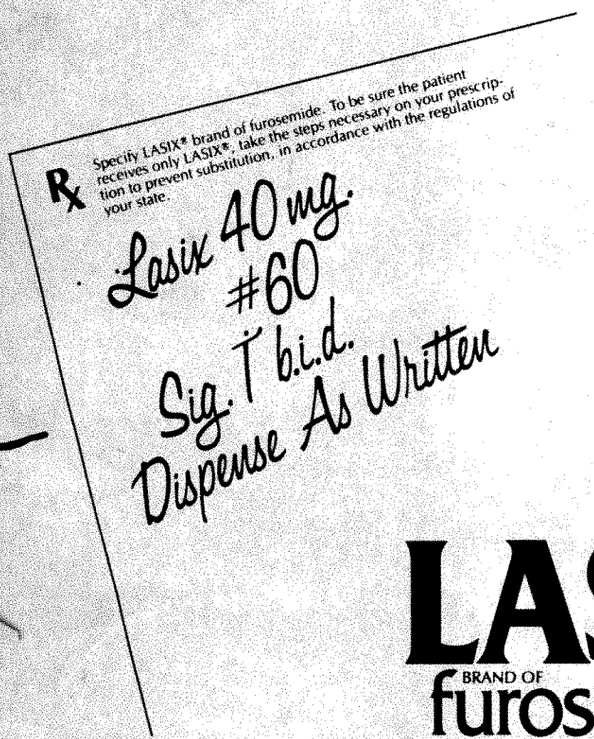
But many patients with impaired renal function are particularly vulnerable because their condition may predispose them to a toxic accumulation of digoxin.

These include the diabetic. The geriatric patient. The patient with renal disease. And the patient with advanced CHF who suffers from hepatic as well as renal complications.

Add to this group the patient on multiple medications with possible drug interactions.

Conditions like these that increase the risk of digitalis toxicity are generally outside the physician's control. But two of the most important *preventive* measures which are not outside the physician's control are precise titration of digitalis, *and the consistent use of one diuretic*.

As to the first, the narrow therapeutic-to-toxic range of digitalis is well known and requires no elaboration.




Naturally, increased renal problems necessitate increased vigilance to any signs of toxicity.

### Why the patient should be maintained on LASIX®

The second precaution is the unvarying use of a single diuretic for a given patient (consistent with proper potassium balance). Thus, if the choice is LASIX®—as it is in most successfully managed CHF cases—the logic behind it is beyond debate. LASIX® is the only diuretic for CHF whose effectiveness has been confirmed in no fewer than 6,000 published papers...which offers the most complete range of dosage forms and strengths for precise titration... and is the most widely available brand of furosemide for filling or refilling your prescription anywhere in the United States. In fact, according to a 1980 nationwide survey,[1] office-based physicians affirmed their confidence in LASIX® by naming it as the medication they prescribe most frequently in office practice.

### Protect your LASIX® prescription: prevent substitution

When you prescribe LASIX®, write the phrase "Do not substitute," or whatever your state requires on the prescription.

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If you are in doubt about a particular generic furosemide, call the offices of the Food and Drug Administration's Bureau of Drugs, Consumer and Professional Relations staff at 301-443-1016.

---

**Reference:** 1. Koch H: Drugs most frequently used in office-based practice: National Ambulatory Medical Care Survey, 1980, Vital and Health Statistics of the Nat Ctr for Health Statistics, No. 78 (May 12) 1982.

**Before prescribing, please consult complete product information, a summary of which appears on the following page.**

# LASIX®

TABLETS: 20, 40 & 80 mg

BRAND OF furosemide

## The diuretic of choice for the digitalized patient.

A159

**Lasix®** (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide) Tablets 20, 40 and 80 mg

**WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.**

**INDICATIONS:** Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

**CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.**

**WARNINGS:** Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, $CO_2$, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

**PRECAUTIONS:** As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

**PREGNANCY:** Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2.4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**ADVERSE REACTIONS:** Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

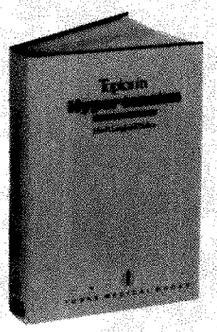
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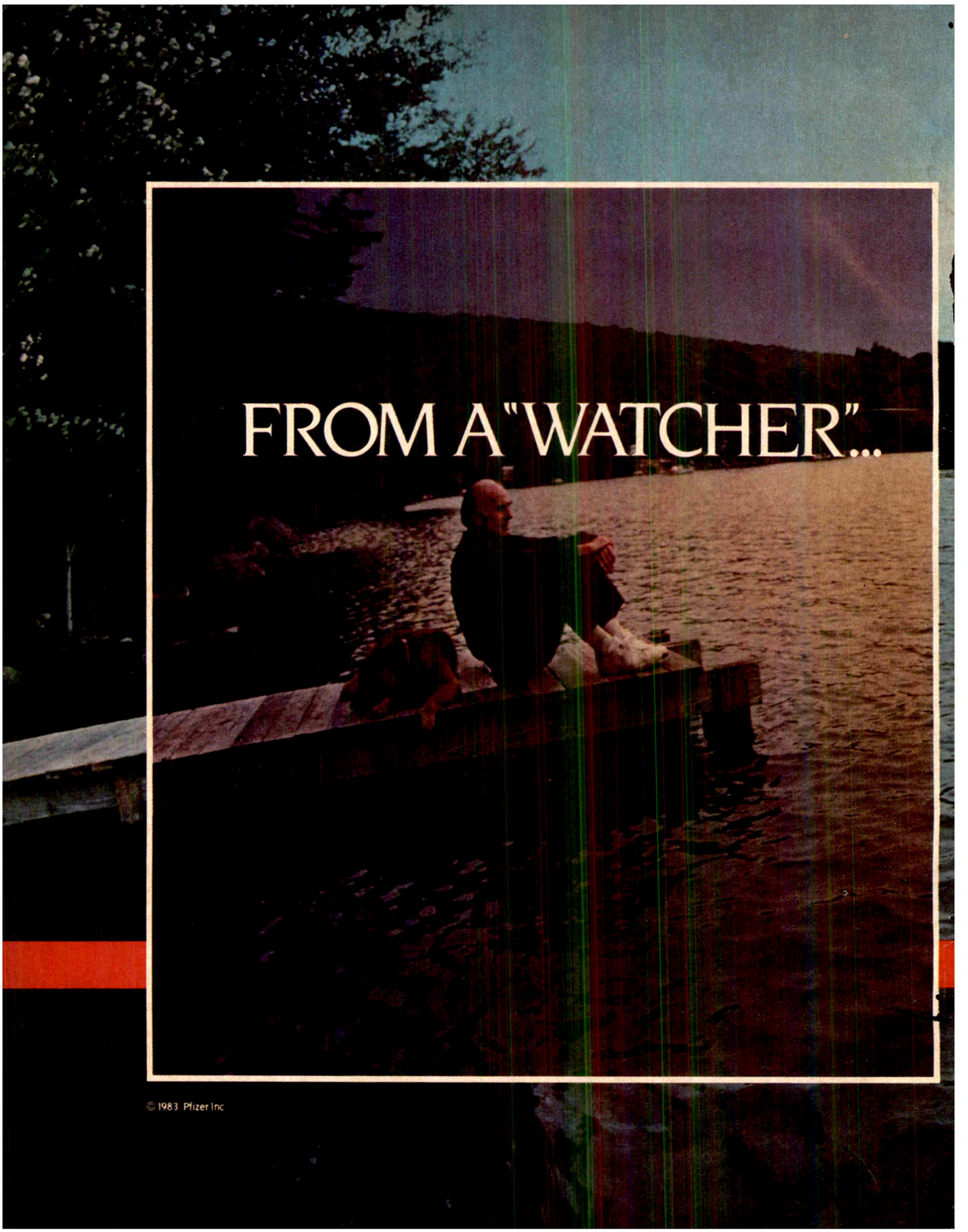
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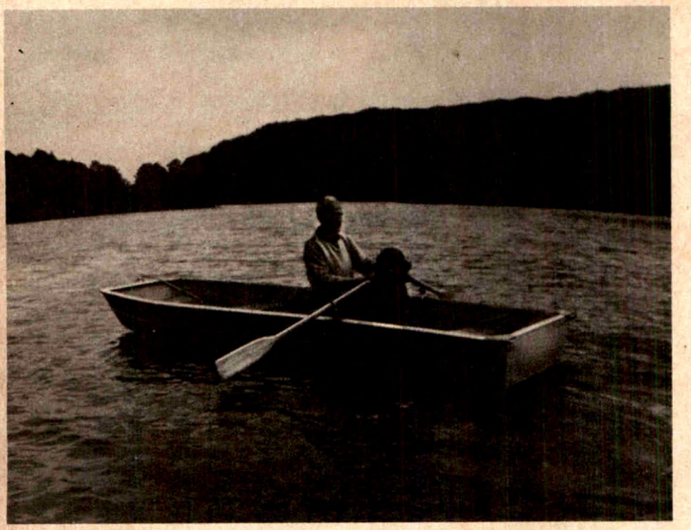
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TO A "DOER"
Your angina patients* can become more active now...with PROCARDIA protection. They'll be pain-free more of the time[1] and find their need for nitroglycerin greatly reduced.[2] They'll be able to work harder, exercise more.[3] And be more active participants in their own lives once again.
feeling better...doing more
PROCARDIA®
(NIFEDIPINE) Capsules 10 mg
*Procardia is indicated for the management of:
• Confirmed vasospastic angina.
• Angina where the clinical presentation suggests a possible vasospastic component.
• Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) Procardia has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.
Please see PROCARDIA® brief summary on next page

*feeling better...doing more*



# PROCARDIA®
## (NIFEDIPINE) *Capsules 10 mg*

## *–Usual effective dosage is 30-60 mg/day*

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because Procardia decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration is suggested. Close observation is especially recommended for patients taking medication known to lower blood pressure.

## *–Offers a favorable safety profile*

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.


**References:**

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Eng J Med* 302:1269-1273, June 5, 1980.
3. De Ponti C, De Biase AM, Pirelli S, et al: Effects of nifedipine, acebutolol, and their association on exercise tolerance in patients with effort angina. *Cardiology* 68 (suppl 2): 195-199, 1981.


**BRIEF SUMMARY**
**PROCARDIA® CAPSULES** For Oral Use
(nifedipine)

**INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA** (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

**II. Chronic Stable Angina (Classical Effort-Associated Angina):** PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

**CONTRAINDICATIONS:** Known hypersensitivity reaction to PROCARDIA.

**WARNINGS: Excessive Hypotension:** Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out.

**Increased Angina:** Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

**Beta Blocker Withdrawal:** Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

**Congestive Heart Failure:** Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

**PRECAUTIONS: General: Hypotension:** Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

**Peripheral edema:** Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

**Drug interactions:** Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

**ADVERSE REACTIONS:** The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

**Laboratory Tests:** Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

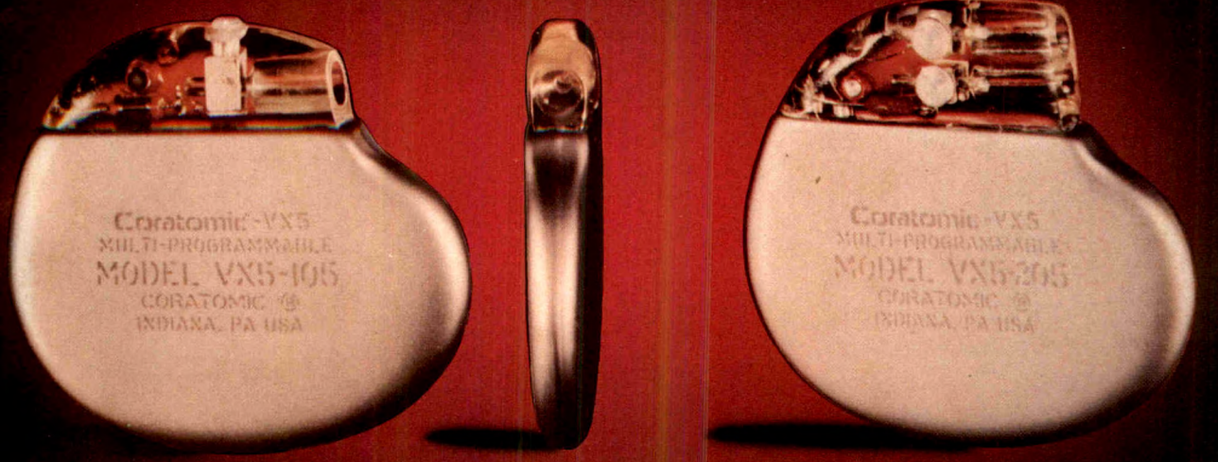
**HOW SUPPLIED:** Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

*More detailed professional information available on request.*


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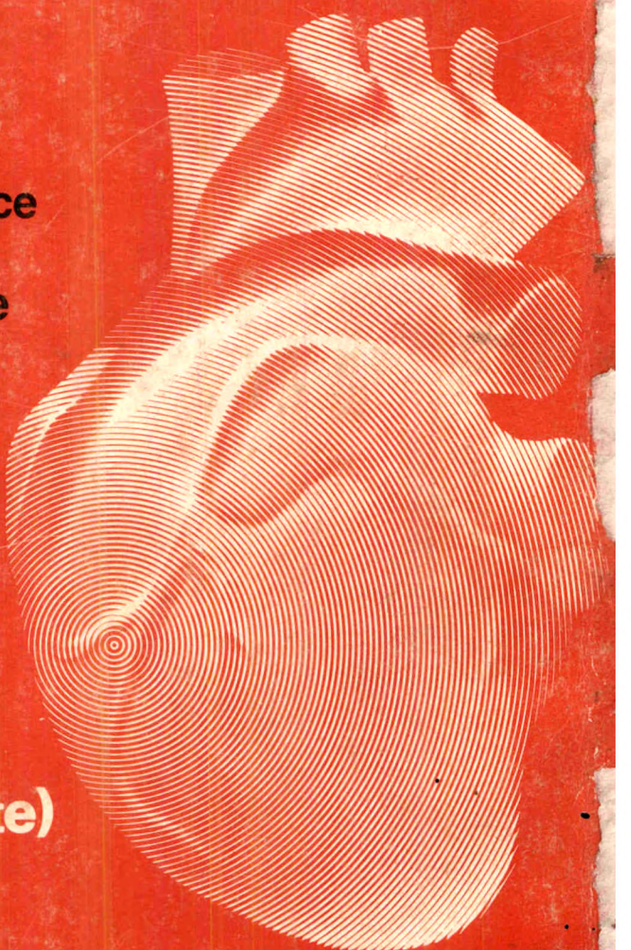
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- Maintains normal sinus rhythm
- Full quinidine cardiodynamics
- Greater gastrointestinal tolerance than with quinidine sulfate*
- Convenient b.i.d. or t.i.d. dosage

*Bibliography available upon request.



# CARDIOQUIN®
## TABLETS
## (quinidine polygalacturonate)

INDICATIONS AND USAGE: CARDIOQUIN Tablets are indicated as maintenance therapy after spontaneous and electrical conversion of atrial tachycardia, flutter or fibrillation and in the treatment of premature atrial and ventricular contractions, paroxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, and paroxysmal ventricular tachycardia when not associated with complete heartblock. CONTRAINDICATIONS: History of hypersensitivity to quinidine, complete A-V block, complete bundle branch block or other severe intraventricular conduction defects, myasthenia gravis, arrhythmias associated with digitalis toxicity. WARNINGS: In the treatment of atrial fibrillation with rapid ventricular response, use digitalis to control ventricular rate prior to administration of quinidine. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine. *Potentially toxic digoxin plasma levels may occur when quinidine is administered concurrently. Consider reducing digoxin dosage and monitoring for digitalis toxicity.* Evidence of quinidine cardiotoxicity (increased P-R and Q-T intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia) mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. NOTE: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia. Quinidine should be used with extreme caution in the presence of incomplete A-V block, since complete block and asystole may result. Quinidine may cause abnormalities of rhythm in digitalized patients; therefore, it should be used with caution in the presence of digitalis intoxication. Caution is also called for in patients exhibiting renal, cardiac or hepatic insufficiency because of potential toxic accumulation of quinidine in plasma. PRECAUTIONS: A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncracy to quinidine. ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered. Periodic blood counts and liver and kidney function tests should be performed during long-term therapy.

DRUG INTERACTIONS OF QUINIDINE:

| DRUG | EFFECT |
|---|---|
| With anticholinergic drugs | Additive vagolytic effect. |
| With cholinergic drugs | Antagonism of cholinergic effects. |
| With carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics | Alkalinization of urine resulting in decreased excretion of quinidine. |
| With coumarin anticoagulants | Reduction of clotting factor concentrations. |
| With tubocurare, succinylcholine and decamethonium | Potentiation of neuromuscular blockade. |
| With phenothiazines and reserpine | Additive cardiac depressive effects. |
| With hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin) | Decreased plasma half-life of quinidine. |
| With digoxin | Increased plasma concentrations of digoxin (see WARNINGS). |

PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: The drug should be used with caution due to excretion of the quinidine in breast milk. ADVERSE REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headaches, and disturbed vision) may appear in sensitive patients after a single dose of the drug. GASTROINTESTINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (including ventricular tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypotension. HEMATOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, delirium, syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis. DERMATOLOGIC: Rash, cutaneous flushing with intense pruritus, urticaria. HYPERSENSITIVITY REACTIONS: Angioedema, acute asthmatic episodes, vascular collapse, respiratory arrest, hepatic toxicity. See package insert for Full Prescribing Information.

**Purdue Frederick**

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